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Glyphosate -
Human Health and Ecological Risk Assessment
Final Report

Prepared for:

USDA, Forest Service
Forest Health Protection

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LIST OF WORKSHEETS

Supplement 1: Glyphosate -WordPerfect Worksheets for Human Health and Ecological Risk Assessments, SERA WPWS 01-43-09-02a, Version 2.04, March 1, 2003.

Supplement 2: Glyphosate -EXCEL Worksheets for Human Health and Ecological Risk Assessments, SERA EXWS 01-43-09-02a, Version 2.04, March 1, 2003.

LIST OF ATTACHMENTS

Attachment 1: Bibliography of All Citations Encountered on Glyphosate.

Attachment 2: Documentation for Worksheets Version 2.02 - Human Health and Ecological Risk Assessments.

Attachment 3: Documentation for the Use of GLEAMS and Auxiliary Programs, SERA AT 2000-01b, dated September 24, 2000.

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ACRONYMS, ABBREVIATIONS, AND SYMBOLS

a.e.	acid equivalents
a.i.	active ingredient
AEL	adverse-effect level
ACGIH	American Conference of Governmental Industrial Hygienists
AChE	acetylcholinesterase
AMPA	aminomethylphosphonate
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
bw	body weight
ChE	cholinesterase
cm	centimeter
2,4-D	dichlorophenoxyacetic acid
EC_{50}	concentration causing 50% inhibition of a process
EC_{100}	concentration causing complete inhibition of a process
EDSTAC	Endocrine Disrupter Screening and Testing Advisory Committee
EIS	environmental impact statement
F	female
F_1	first filial generation
FEL	frank effect level
FH	Forest Health
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FS	Forest Service
FQPA	Food Quality Protection Act
g	gram
GC	gas chromatography
GRAS	generally recognized as safe
HQ	hazard quotient
IARC	International Agency for Research on Cancer
IPA	isopropylamine
IRIS	Integrated Risk Information System
kg	kilogram
$K_{o/c}$	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
K_p	skin permeability coefficient
L	liter
lb	pound
LC_{50}	lethal concentration, 50% mortality
LD_{50}	lethal dose, 50% mortality
LD_{95}	lethal dose, 95% mortality
LOAEL	lowest-observed-adverse-effect level

m	meter
M	male
MATC	maximum allowable toxicant concentration
mg	milligram
mg/kg/day	milligrams of agent per kilogram of body weight per day
mL	milliliter
MRID	master record identification number
MS	mass spectrometry
MSDS	material safety data sheet
MW	molecular weight
MOS	margin of safety
MSDS	material safety data sheet
NCI	National Cancer Institute
NNG	N-nitrosoglyphosate
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOEL	no-observed-effect level
NPE	nonylphenol polyethoxylate
NRC	National Research Council
OPP	Office of Pesticide Programs
pKa	dissociation constant
POEA	polyoxyethyleneamine
ppm	parts per million
RBC	red blood cells
RED	reregistration eligibility decision
RfD	reference dose
RTU	ready to use
UF	uncertainty factor
U.S.	United States
U.S. EPA	U.S. Environmental Protection Agency
USDA	United States Department of Agriculture
USGS	United States Geological Survey
>	greater than
≥	greater than or equal to
<	less than
≤	less than or equal to
=	equal to
≃	approximately equal to

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

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

CONVERSION OF SCIENTIFIC NOTATION

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

EXECUTIVE SUMMARY

INTRODUCTION

This document provides risk assessments for human health effects and ecological effects to support an assessment of the environmental consequences of using glyphosate in Forest Service vegetation management programs. 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 glyphosate, an assessment of potential exposure to this compound, an assessment of the dose-response relationships, and a characterization of the risks associated with plausible levels of exposure.

In the preparation of this risk assessment, literature searches of glyphosate were conducted in the open literature using PubMed, TOXLINE as well as the U.S. EPA CBI files. Several reviews and risk assessments on glyphosate conducted by the U.S. EPA and others were also consulted. The search of U.S. EPA's FIFRA/CBI files indicated that there are 5829 submissions on glyphosate and glyphosate formulations. While many of these studies were conducted to support the initial registration and reregistration of glyphosate, a substantial number of studies were conducted and submitted to U.S. EPA after 1993, the date of the U.S. EPA Reregistration Eligibility Decision document on glyphosate. Because of the extensive published literature on glyphosate, the reregistration document for glyphosate was used where possible to summarize information for the earlier CBI studies. Although full copies of some key studies were obtained from the earlier CBI submissions, the acquisition of the CBI studies focused on the post-1993 period.

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 and these risk assessment do not cite all of the available literature. To review each of these studies would far exceed the resources available to the Forest Service and, more importantly, would make the document very difficult to read and review. In some respects, an all inclusive and detailed review of each study would tend to obscure rather than inform. As an alternative, this document focuses on information that is likely to impact the risk assessments.

PROGRAM DESCRIPTION

Glyphosate is a herbicide that is used in Forest Service programs primarily in conifer release, noxious weed control, and site preparation. There are currently 35 commercial formulations of glyphosate that are registered for forestry applications. All commercial formulations of glyphosate that are used in forestry applications contain the isopropylamine salt of glyphosate. Some formulations contain only this salt of glyphosate as an aqueous solution. Other formulations contain surfactants and some of these surfactants are toxic, particularly to aquatic organisms. Technical grade glyphosate contains an impurity, N-nitrosoglyphosate, but the amount of this impurity in glyphosate has been classified as toxicologically insignificant by the U.S. EPA. A surfactant used in at least one major commercial formulation contains 1,4-dioxane, and the toxicity of this impurity is specifically considered in this risk assessment. The most

common method of application for glyphosate in Forest Service programs involves is backpack-applied directed foliar sprays. Other application methods that are use occasionally are broadcast foliar ground applications, cut stem applications, and direct application to the emergent aquatic vegetation. Based on recent Forest Service use reports, the typical application rate is about 2 lb a.e./acre, with most application rates occurring over a range of 0.5 lbs a.e./acre to 7 lbs a.e./acre. The total annual use of glyphosate by the Forest Service is only about 0.275 percent of the agricultural use. Thus, there is no basis for asserting that Forest Service programs will substantially contribute to general concentrations of glyphosate nationally. The potential for local contamination of environmental media by the use of glyphosate in Forest Service programs is discussed in the human health risk assessment and the ecological risk assessment.

HUMAN HEALTH RISK ASSESSMENT

Hazard Identification – The herbicidal activity of glyphosate is due primarily to the inhibition of the shikimate pathway which is involved in the synthesis of aromatic amino acids in plants and microorganisms. This metabolic pathway does not occur in humans or other animals and thus this mechanism of action is not directly relevant to the human health risk assessment. Two specific biochemical mechanisms of action have been identified or proposed for glyphosate: uncoupling of oxidative phosphorylation and inhibition of hepatic mixed function oxidases. Both glyphosate and the polyethoxylated tallow amine (POEA) surfactant used in Roundup will damage mucosal tissue, although the mechanism of this damage is likely to differ for these two agents. Many of the effects of acute oral exposure to high doses of glyphosate or Roundup are consistent with corrosive effects on the mucosa.

The available experimental studies indicate that glyphosate is not completely absorbed after oral administration and is poorly absorbed after dermal applications. Two dermal absorption studies have been published on glyphosate and both of these studies indicate that glyphosate is very poorly absorbed across the skin.

Like all chemicals, glyphosate as well as commercial formulations of glyphosate may be toxic at sufficiently high exposure levels. In rats and mice, acute oral LD_{50} values of glyphosate range from approximately 2,000 to 6,000 mg/kg. Formulations of glyphosate with a POEA surfactant have been used in many suicides and attempted suicides. Gastrointestinal effects (vomiting, abdominal pain, diarrhea), irritation, congestion, or other forms of damage to the respiratory tract, pulmonary edema, decreased urinary output sometimes accompanied by acute renal tubular necrosis, hypotension, metabolic acidosis, and electrolyte imbalances, probably secondary to the gastrointestinal and renal effects, are seen in human cases of glyphosate/surfactant exposure.

One of the more consistent signs of subchronic or chronic exposure to glyphosate is loss of body weight. This effect has been noted in mice, rats, dogs, and rabbits. This observation is consistent with experimental data indicating that glyphosate may be an uncoupler of oxidative phosphorylation. Other signs of toxicity seem general and non-specific. A few studies report changes in liver weight, blood chemistry that would suggest mild liver toxicity, or liver pathology. Changes in pituitary weight have also been observed. Signs of kidney toxicity, which might be

expected based on the acute toxicity of glyphosate, have not been reported consistently and are not severe. Various hematological changes have been observed that may be secondary to mild dehydration.

Glyphosate has been specifically tested for neurotoxicity in rats after both acute and subchronic exposures and has been tested for delayed neurotoxicity in hens. In both the animal data as well as the clinical literature involving suicide attempts, there is no clear pattern suggestive of a specific neurotoxic action for glyphosate or its commercial formulations. The weight of evidence suggests that any neurologic symptoms associated with glyphosate exposures are secondary to other toxic effects. No studies are reported that indicate morphologic abnormalities in lymphoid tissues which could be suggestive of an effect on the immune system. As discussed in the ecological risk assessment, one study has asserted that glyphosate causes immune suppression in a species of fish. This study, however, is deficient in several respects and does not provide a basis for impacting the hazard identification for effects on the immune system.

Only three specific tests on the potential effects of glyphosate on the endocrine system have been conducted and all of these tests reported no effects. All of these assays are *in vitro* – i.e., not conducted in whole animals. Thus, such studies are used qualitatively in the hazard identification to assess whether there is a plausible biologic mechanism for asserting that endocrine disruption is plausible. Because they are *in vitro* assays, measures of *dose* and quantitative use of the information in dose/response assessment is not appropriate. For glyphosate, these studies to not indicate a basis for suggesting that glyphosate is an endocrine disruptor. Nonetheless, glyphosate has not undergone an extensive evaluation for its potential to interact or interfere with the estrogen, androgen, or thyroid hormone systems. Thus, the assessment of the potential endocrine effects of glyphosate cannot be overly interpreted.

Glyphosate has been subject to multi-generation reproduction studies which measure overall effects on reproductive capacity as well as teratology studies which assay for a compounds ability to cause birth defects. Signs of teratogenic activity have not been observed in standard assays in both rats and rabbits. In a multi-generation reproduction study in rats, effects on the kidney were observed in male offspring. This effect is consistent with the acute systemic toxicity of glyphosate, rather than a specific reproductive effect. Several other subchronic and chronic studies of glyphosate have been conducted with no mention of treatment-related effects on endocrine glands or reproductive organs. A single study has reported substantial decreases in libido, ejaculate volume, sperm concentrations, semen initial fructose and semen osmolality as well as increases in abnormal and dead sperm in rabbits after acute oral exposures to glyphosate. This study is inconsistent with other studies reported on glyphosate and is poorly documented – i.e., specific doses administered to the animals are not specified. In addition, the use of gelatin capsules, as in this study results, in a high spike in body burden that is not typical or particularly relevant to potential human exposures – other than attempted suicides. Numerous epidemiological studies have examined relationships between pesticide exposures or assumed pesticide exposures in agricultural workers and reproductive outcomes. Of those studies that have specifically addressed potential risks from glyphosate exposures, adverse reproductive

effects have not been noted.

Based on standard animal bioassays for carcinogenic activity *in vivo*, there is no basis for asserting that glyphosate is likely to pose a substantial risk. The Re-registration Eligibility Decision document on glyphosate prepared by the U.S. EPA indicates that glyphosate is classified as Group E: Evidence of non-carcinogenicity for humans. This classification is also indicated in U.S. EPA's most recent publication of tolerances for glyphosate and is consistent with an assessment by the World Health Organization. This assessment has been challenged based on some studies that indicate marginal carcinogenic activity. As with any compound that has been studied for a long period of time and tested in a large number of different systems, some equivocal evidence of carcinogenic potential is apparent and may remain a cause of concern, at least in terms of risk perception. While these concerns are understandable, there is no compelling basis for challenging the position taken by the U.S. EPA and no quantitative risk assessment for cancer is conducted as part of the current analysis.

Glyphosate formulations used by the Forest Service are classified as either non-irritating or only slightly irritating to the skin and eyes in standard assays required for product registration. Based on a total of 1513 calls to a poison control center reporting ocular effects associated with the use of Roundup, 21% were associated with no injury, 70% with transient minor injury, 2% with some temporary injury. The most frequently noted symptoms included blurred vision, a stinging or burning sensation, lacrimation. No cases of permanent damage were reported.

Various glyphosate formulations contain a POEA surfactant at a level of up to about 20%. Other formulations of glyphosate recommend the use of a surfactant to improve the efficacy of glyphosate. While surfactants are typically classified as “inert” ingredients in herbicides, these compounds are not toxicologically inert and some surfactants may be more toxic than the herbicides with which they are used. Although surfactants may play a substantial role in the interpretation of a large number of suicides and attempted suicides involving the ingestion of glyphosate formulations, primarily Roundup, the acute mammalian toxicity of different glyphosate formulations do not appear to differ substantially. This is in contrast to the available data on the toxicity of various formulations to aquatic species, as detailed in the ecological risk assessment.

Exposure Assessment – Exposure assessments are developed for both workers and members of the general public. Two types of work exposure assessments are considered: general and accidental/incidental. The term *general* exposure assessment is used to designate those exposures that involve estimates of absorbed dose based on the handling of a specified amount of a chemical during specific types of applications. The accidental/incidental exposure scenarios involve specific types of events that could occur during any type of application. For general exposures in workers, exposure rates are expressed in units of mg of absorbed dose per kilogram of body weight per pound of chemical handled. For glyphosate, there are several worker exposure studies involving backpack applications that can be used to assess the quality general estimates used in many Forest Service risk assessments. These studies indicate that these general methods may be extremely conservative. Nonetheless, for this risk assessment, the standard worker exposure rates

are used, recognizing that the upper range of exposures may overestimate risk. This conservative approach has little impact on the interpretation of risk because none of the worker exposures exceed a hazard quotient of unity. Central estimates of worker exposures span a very narrow range from 0.026 mg/kg/day to about 0.045 mg/kg/day. The upper range of exposures for the different application methods are about a factor of 10 higher, spanning a range from about 0.1 mg/kg/day to 0.3 mg/kg/day.

Under normal circumstances, members of the general public should not be exposed to substantial levels of glyphosate as a result of Forest Service activities. 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 highly conservative scenarios are developed for this risk assessment. 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. Most acute accidental exposure scenarios for members of the general public are less than or similar to the general exposure scenarios in workers. The major exception is the scenario for an accidental spill of 200 gallons of a field solution into a small pond. This leads to modeled estimates of exposure in the range of 0.3 to about 4 mg/kg/day. This is an extraordinarily extreme and conservative scenario that is used in all Forest Service risk assessments. Most longer term estimates of exposure for members of the general public are much lower than exposure estimates for workers. The one exception involves the longer term consumption of contaminated fruit, which leads to time-weighted average estimated doses of 0.003 to 0.08 mg/kg/day.

Dose-response Assessment – Generally, the dose-response assessments used in Forest Service risk assessments adopt RfDs proposed by the U.S. EPA as indices of 'acceptable' exposure. An RfD is basically defined as a level of exposure that will not result in any adverse effects in any individual. The U.S. EPA RfDs are used because they generally provide a level of analysis, review, and resources that far exceed those that are or can be conducted in the support of most Forest Service risk assessments. In addition, it is desirable for different agencies and organizations within the federal government to use concordant risk assessment values.

The most recent RfD on glyphosate is that proposed by the U.S. EPA Office of Pesticide Programs. This RfD of 2 mg/kg/day was proposed originally in the RED for glyphosate and was also used in the recent glyphosate pesticide tolerances. This RfD is based on teratogenicity study in rabbits (Rodwell et al. 1980b) in which no effects observed in offspring at any dose levels and maternal toxicity was observed at 350 mg/kg/day with a NOAEL of 175 mg/kg/day . Using an uncertainty factor of 100 – 10 for sensitive individuals and 10 for species-to-species extrapolation

– U.S. EPA/OPP derived the RfD of 2 mg/kg/day, rounding the value of 1.75 mg/kg/day to one significant digit.

For the current risk assessment, the RfD 2 mg/kg/day derived by U.S. EPA/OPP is used as the basis for characterizing risk from longer-term exposures in this risk assessment. For short-term exposures, the value of 2 mg/kg/day recommended by U.S. EPA's Office of Drinking Water is used. Since this is identical to the chronic RfD, this approach is equivalent to applying the same RfD to be short-term and long-term exposures. Given the lack of a significant dose-duration relationship for glyphosate, this approach seems appropriate.

Risk Characterization – The risk characterization for both workers and members of the general public are reasonably consistent in unambiguous. For both groups, there is very little indication of any potential risk at the typical application rate of 2 lbs a.e./acre. Even at the upper range of plausible exposures in workers, most hazard quotients are below the level of concern.

For workers, the highest hazard quotient – i.e., 0.2, the upper range for workers involved in broadcast ground spray – is below the level of concern by a factor of about 5. The highest hazard quotient for any accidental exposure scenario for workers - i.e., 0.006 for the upper range of the hazard quotient for spill over the lower legs for one hour - is lower than the level of concern by a factor of over 150. Confidence in these assessments is reasonably high because of the availability of dermal absorption data in human as well as worker exposure studies. The Forest Service may apply glyphosate at a maximum rate of 7 lbs a.e./acre, a factor of 3.5 higher than the typical application rate of 2 lbs a.e./acre. This has essentially no impact of the risk characterization for workers. The highest hazard quotient for the typical application rate is 0.2. For an application rate of 7 lbs a.e./acre, the corresponding hazard quotient would be higher by a factor of 3.5 or 0.7, which is still below the level of concern.

From a practical perspective, the most likely accidental exposure for workers that might require medical attention involves accidental contamination of the eyes. Glyphosate and glyphosate formulations are skin and eye irritants. Quantitative risk assessments for irritation are not normally derived, and, for glyphosate specifically, there is no indication that such a derivation is warranted. Glyphosate with the POEA surfactant is about as irritating as standard dish washing detergents, all purpose cleaners, and baby shampoos. As with the handling of any chemical, including a variety of common household products, reasonable care should be taken to avoid contact of skin and eyes.

The only area of remarkable uncertainty involving worker exposures concerns the potential health effects during brown-and-burn operations. The combustion of wood and wood by-products may produce a number of toxic compounds. This is a concern with brown-and-burn operations but does not pertain to the use of glyphosate or any other herbicide. The potential effects of combustion products is common to all risk assessments of materials that might be subject to burning. With the exception of some plastics, the combustion products of which are known to pose a risk to fire fighters, the combustion products of most chemicals have not been examined in

detail. The necessity of addressing this data gap must be weighed against the need to address other data gaps on glyphosate and other chemicals. The combustion products of burning wood and vegetation are respiratory irritants as well as carcinogens, and exposure to these combustion products should be avoided. There is no basis for believing that the presence of low or even high levels of glyphosate residues will have a significant impact on this hazard.

For members of the general public, none of the longer-term exposure scenarios exceed or even approach a level of concern. Although there are several uncertainties in the longer-term exposure assessments for the general public, the upper limits for hazard indices are below a level of concern by factors of about 25 (longer term consumption of contaminated fruit) to over two million (2,500,000 for longer-term consumption of fish by the general population). The risk characterization is thus relatively unambiguous: based on the available information and under the foreseeable conditions of application and exposure, there is no route of exposure or exposure scenario suggesting that the general public will be at risk from longer-term exposure to glyphosate. As with the hazard characterization for workers, an application rate of 7.5 lbs a.e./acre makes no difference in the assessment of potential risks. At this application rate, the highest hazard quotient would be about 0.14 [0.04 × 3.5], which is still below a level of concern by a factor of about 7.

One acute exposure scenario does exceed the level of concern at the upper range at the typical application rate of 2 lbs a.e./acre. The exposure scenario for the consumption of contaminated water after an accidental spill into a small pond results in an excursion above the RfD at the upper limit of exposure – i.e, a hazard quotient of 2. This exposure scenario is extreme to the point of limited plausibility. This sort of scenario is routinely used in Forest Service risk assessments as an index of the measures that should be taken to limit exposure in the event of a relatively large spill into a relatively small body of water. For glyphosate, as well as for most other chemicals, this exposure assessment indicates that such an event would require measures to ensure that members of the general public do not consume contaminated water.

At the highest application rate that might be used in Forest Service programs, the accidental spill scenario is the only other scenario that results in a hazard quotient above unity. At this application rate, the associated dose is about 14 mg/kg, which is still below the dose of 184 mg/kg associated with no apparent overt effects in humans by a factor of over 10.

ECOLOGICAL RISK ASSESSMENT

Hazard Identification – There are several standard toxicity studies in experimental mammals that were conducted as part of the registration process and there is a large body of published information on the toxicity of glyphosate to mammals. Just as these studies are used in the human health risk assessment to identify the potential toxic hazards associated with exposures to glyphosate, they can also be used to identify potential toxic effects in wildlife mammalian species. Loss of body weight is the most commonly seen effect of glyphosate in mammals. Inhibition of oxidative phosphorylation has been implicated as a possible mechanism by which glyphosate causes weight loss in experimental mammals; however, there is not adequate information about

terrestrial wildlife from which to make a further assessment about the importance of this mechanism. As in the human health risk assessment, the potential significance of non-specific toxic effects can be assessed from the available toxicity studies in mammals. Because toxicity data in mammals are available in few species of experimental mammals, the use of these data to assess the potential hazards to large number of diverse mammalian wildlife species is an uncertain process. Nonetheless, there do not appear to be any systematic differences among mammalian species, including humans, when comparable toxicity values are expressed in units of mg/kg/day. While the available data are limited, this apparent consistency among species diminishes concern with the use of data based on a limited subset of species to characterize risk for terrestrial mammals in general.

In assessing potential effects in birds, the most relevant data for this risk assessment are the standard dietary and bird reproduction studies required for registration as well as the acute oral LD_{50} studies. The available toxicity studies do not suggest any specific or unique toxicity in birds compared to mammals. As in mammals, there is suggestive evidence that glyphosate may inhibit oxidative phosphorylation and consequently reduce food conversion efficiency. Also consistent with the data in experimental mammals is the apparent lack of teratogenic activity in birds.

The honey bee is the standard test organism for assessing the potential effects of pesticides on terrestrial invertebrates and there is a standard set of studies available on this species. In addition, studies are available on a relatively wide range of other terrestrial invertebrates including earthworms, isopods, snails, spiders, butterflies, and other terrestrial arthropods.

Glyphosate is readily metabolized by soil bacteria and many species of soil microorganisms can use glyphosate as sole carbon source. Nonetheless, microorganisms, like higher plants, do have the shikimate pathway for the production of aromatic amino acids. At the molecular level, glyphosate occupies the binding site of phosphoenol pyruvate, the second substrate of 5-enolpyruvylshikimate 3-phosphate synthase, mimicking an intermediate state of the ternary enzyme-substrate complex. This inhibits the shikimic acid pathway in plants, effectively blocking the synthesis of certain phenolic compounds and the synthesis of aromatic amino acids. This, in turn, leads to a variety of toxic effects in plants, including the inhibition of photosynthesis in plants as well as inhibition of respiration and nucleic acid synthesis in plants and microorganisms.

Since glyphosate inhibits this pathway, toxicity to microorganisms may be expected and glyphosate has been considered as an antimicrobial agent for human pathogens. Nonetheless, there is very little information suggesting that glyphosate will be harmful to soil microorganisms under field conditions and a substantial body of information indicating that glyphosate is likely to enhance or have no effect on soil microorganisms. Most field studies involving microbial activity in soil after glyphosate exposures note an increase in soil microorganisms or microbial activity and the application of glyphosate may cause transient increases in soil fungi that may be detrimental to some plants. While the mechanism of this apparent enhancement is unclear, it is plausible that glyphosate treatment resulted in an increase in the population of pathogenic fungi in soil because glyphosate was used as a carbon source by the fungi and/or treatment with glyphosate resulted in

increased nutrients for fungi in the soil. There is no indication that the transient enhancement in populations of soil fungi or bacteria will result in any substantial or lasting damage to soil ecology.

In higher plants, inhibition of the shikimic acid pathway leads to an inhibition or cessation of growth, cellular disruption, and, at sufficiently high levels of exposure, plant death. The time course for these effects can be relatively slow, depending on the plant species, growth rate, climate, and application rate. Gross signs of toxicity include wilting and yellowing of the vegetation, followed by browning, breakdown of plant tissue, and, ultimately, root decomposition. Standard toxicity studies are available on seedling emergence and vegetative vigor in a number of different plant species. The drift studies are also highly relevant to the assessment of risk in that unintended drift is one of the more plausible exposure scenarios for nontarget terrestrial plant species. The lowest reported effect level in drift studies is 1/33 of an application rate of 1.121 kg/ha that was associated with transient damage in soybeans. This treatment corresponds to 0.034 kg/ha [1.121 kg/ha ÷ 33] or about 0.03 lb/acre. At much higher concentrations – in the range of 0.7 lbs/acre – there is a plausible basis for concern that exposure to substantial glyphosate drift may have long term impacts on bryophyte and lichen communities.

In addition to the laboratory bioassays or field observations on single species, there are a number field studies that have assessed the effects of glyphosate on groups of terrestrial organisms, both animals and plants. These studies indicate that effects on terrestrial animals are likely to be secondary to effects on vegetation when glyphosate is applied at application rates comparable to or greater than those contemplated by the Forest Service. In some cases, the effects noted in filed studies appeared to be beneficial to some species under study. In most cases, the effects noted were changes in population density that reflected changes in food availability or suitable habitat.

In aquatic species, the acute lethal potency of glyphosate and glyphosate formulations has been relatively well-defined. These values are typically expressed as time-specific LC_x values where *x* is the estimate of the proportion of fish that die – e.g., 96 hour LC_{50}. A large number of acute LC_{50} values have been determined in various species of fish. As in the human health risk assessment, the formulation of glyphosate with surfactants, especially the POEA surfactant commonly used in glyphosate formulations, has a pronounced effect on the acute lethal potency of glyphosate.

The U.S. EPA typically uses LC_{50} values or fractions of LC_{50} values as the basis for characterizing risk, as in the U.S. EPA RED on glyphosate. A common concern with this approach is that more subtle non-lethal effects that may impact of the stability of fish populations in the field may not be properly assessed. The available information on the sub-lethal effects associated with glyphosate is summarized in this risk assessment and NOEC (no observable effect concentration) values form the basis of the risk characterization.

Lastly, field studies are available on the effects of glyphosate applications on fish populations. As with the risk characterization for terrestrial species, these studies have limitations in terms of their quantitative use in a risk assessment but are nonetheless highly relevant to the risk assessment and

may be used to further assess the quality of the risk characterization based on laboratory bioassay.

The toxicity of glyphosate to aquatic plants has been evaluated by U.S. EPA based on studies submitted for the registration of glyphosate. In addition, several studies are available from the open literature as well as more recent studies submitted to U.S. EPA. These studies are available for both algae and aquatic macrophytes. As would be expected from a herbicide, glyphosate is much more toxic to aquatic plants than animals.

Exposure Assessment – Terrestrial animals might be exposed to any applied herbicide from direct spray, the ingestion of contaminated media (vegetation, prey species, or water), grooming activities, or indirect contact with contaminated vegetation. The highest exposures for terrestrial vertebrates will occur after the consumption of contaminated vegetation or contaminated insects. In acute exposure scenarios, doses as high as 225 mg/kg are estimated. Other routes of exposure, like the consumption of contaminated water or direct spray, lead to lower levels of exposure. In chronic exposure scenarios, the estimated daily doses at the upper limits of exposure are in the range of about 50 to 80 mg/kg/day and are associated with highly conservative assumptions regarding the consumption of contaminated vegetation.

The primary hazards to non-target terrestrial plants are associated with unintended direct deposition or spray drift. Unintended direct spray will result in an exposure level equivalent to the application rate. At least some plants that are sprayed directly with glyphosate at or near the recommended range of application rates will be damaged. Based on the AgDRIFT model, no more than 0.0058 of the application rate would be expected to drift 100 m offsite after low boom ground applications. In order to encompass a wide range of field conditions, GLEAMS simulations were conducted for clay, loam, and sand at annual rainfall rates from 5 to 250 inches. Under arid conditions (i.e., annual rainfall of about 10 inches or less), there is no or very little runoff. Under these conditions, degradation, not dispersion, accounts for the decrease of glyphosate concentrations in soil. At higher rainfall rates, plausible offsite movement of glyphosate results in runoff losses that range from about negligible up to about 45% of the application rate, depending primarily on the amount of rainfall rather than differences in soil type.

The potential for effects on aquatic species are based on estimated concentrations of glyphosate in water that are identical to those used in the human health risk assessment without further elaboration. For an accidental spill, the central estimate for the concentration of glyphosate in a small pond is estimated at about 18.2 mg/L with a range from 1.8 to 127 mg/L. For longer term exposure scenarios, the expected concentrations of glyphosate in ambient water range from 0.0001 to 0.008 mg/L with a central value of 0.001 mg/L.

Dose-response Assessment – For mammals, the toxicity data used to characterize risk are identical to those used in the human health risk assessment – i.e., a NOAEL of 175 mg/kg with an associated LOAEL of 350 mg/kg. The 175 mg/kg NOAEL and 350 mg/kg LOAEL values are used for both the acute and chronic risk assessments. This approach is taken because of the lack of a substantial dose-duration or dose-severity relationship for glyphosate. For birds, a dose of

100 mg/kg is used as a NOAEL for characterizing chronic risks. It should be noted that this dose is very close to the NOAEL of 175 mg/kg used for mammals and is consistent with the apparent lack of variability in the toxicity of glyphosate among species. As in the assessment for mammals, this NOAEL is based on a repeated dose study for reproductive effects. The acute NOAEL is taken as 562 mg/kg from a five-day dietary studies in bobwhite quail and mallard ducks. Toxicity to terrestrial invertebrates is characterized using a standard set of studies in honey bees. The NOEC used in this risk assessment is taken as 50 µg/bee.

The assessment of potential effects in plants is based on standard toxicity studies required for pesticide registration involving pre-emergence and post-emergence exposures. In seedling emergence assays, very high concentrations – i.e., 10 lb a.i./acre or about 7.5 lbs a.e./acre – will modestly inhibit seed germination in both monocots and dicots. The NOEC for seed germination is 4.5 lb a.e./acre in both monocots and dicots. This value is used to assess the consequences of off-site movement of glyphosate in runoff. Glyphosate appears to be more toxic in vegetative vigor assays – i.e., direct application to the foliage of growing plants. The lowest reported NOEC for growth in standard bioassays required for registration is 0.035 lb a.e./acre. The highest reported NOEC for growth is 0.56 lb a.e./acre. This range of values for sensitive and relatively insensitive species is used to assess the consequences of off-site drift of glyphosate.

The dose-response assessment for fish is substantially complicated by information indicating that some fish species such as salmonids are more sensitive to glyphosate than other species of fish and by information indicating that some surfactants are very toxic to fish and may substantially increase to the toxicity of glyphosate to fish. These factors are further complicated by gaps in the available data. Given the apparently high sensitivity of some salmonids to glyphosate, it would be desirable to have a life cycle toxicity study or at least an egg-and-fry study available on salmonids. In addition, given the apparently high toxicity of surfactant formulations compared to technical grade glyphosate, a life cycle toxicity study on at least one formulation containing a toxic surfactant would be desirable. Such studies, however, are not available. Consequently, an approximation method commonly used is mixtures risk assessment (the relative potency method) is employed to estimate a chronic NOEC of 2.57 mg/L for technical grade glyphosate in sensitive species of fish based on an observed NOEC value of 25.7 mg/L in tolerant species of fish. Similarly, NOEC values for glyphosate formulations containing toxic surfactants are estimated at 0.36 mg/L for sensitive species and 0.64 mg/L for tolerant species. A similar approach is used estimate the potential for acute effects based on 96-hour LC_{50} values. LC_{50} values rather than data on sublethal effects are used to characterize risks from acute exposures because most of the data on sublethal effects are based on very short-term exposures to concentrations in the range of 96-hour LC_{50} values. Most of the available toxicity data suggest that amphibians are no more sensitive to glyphosate than fish. Consequently, a separate dose-response assessment for amphibians is not conducted in this risk assessment.

The issues in the dose-response assessment for aquatic invertebrates are very similar to those encountered in the dose-response assessment for fish. There is sufficient data to assert that some glyphosate formulations that contain toxic surfactants may be much more toxic to aquatic

invertebrates than technical grade glyphosate. There is only one chronic study on technical grade glyphosate and no chronic studies on glyphosate formulations. Similar to the approach used in the dose-response assessment for fish, a chronic NOEC of 50 mg/L for technical grade glyphosate is used to estimate a chronic NOEC of 0.7 mg/L for glyphosate formulations containing toxic surfactants. The potential for acute effects in aquatic invertebrates are based on LC_{50} values of 780 mg/L for technical grade glyphosate and 11mg/L for glyphosate formulations containing toxic surfactants.

Glyphosate appears to be about equally toxic to both algae and aquatic macrophytes. In terms of growth inhibition, the NOEC of 3 mg/L in duckweed is used to characterize risk due to inhibition. At lower concentrations – i.e., in the range of 0.002 mg/L to 0.3 mg/L or higher – stimulation of algal growth may be a more common response and has been noted in several studies.

Risk Characterization – The current risk assessment for glyphosate generally supports the conclusions reached by U.S. EPA: *Based on the current data, it has been determined that effects to birds, mammals, fish and invertebrates are minimal.* At the typical application rate of 2 lbs a.e./acre, none of the hazard quotients for acute or chronic scenarios reach a level of concern even at the upper ranges of exposure for terrestrial organisms. For the application rate of 7 lbs a.e./acre, central estimates of the hazard quotients somewhat exceed the level of concern for the direct spray of a honey bee. That the upper range of the hazard quotients, the level of concern is exceeded modestly in acute scenarios for a large mammal consuming contaminated vegetation and a small bird consuming insects. In the chronic exposure scenarios, the hazard quotient for a large bird consuming contaminated vegetation on site exceeds the level of concern by a factor of about 3. As with all longer term exposure scenarios involving the consumption of contaminated vegetation, the plausibility of this exposure scenario is limited because damage to the treated vegetation – i.e., vegetation directly sprayed at the highest application rate – would reduce and perhaps eliminate the possibility of any animal actually consuming this vegetation over a prolonged period.

For relatively tolerant nontarget species of plants, there is no indication that glyphosate is likely to result in damage at distances as close as 25 feet from the application site. For sensitive species at the upper range of application rates, there is a modest excursion about the NOEC at offsite distances of 100 feet or less. It should be noted, however, that all of these drift estimates are based on low-boom ground sprays. Many applications of glyphosate are conducted by directed foliar applications using backpacks. In such cases, little if any damage due to drift would be anticipated. Nontarget terrestrial plants are not likely to be affected by runoff of glyphosate under any conditions.

The primary hazards to fish appear to be from acute exposures to the more toxic formulations. At the typical application rate of 2 lbs a.e./acre, the hazard quotients for the more toxic formulations at the upper ranges of plausible exposure indicate that the LC_{50} values for these species will be not reached or exceeded under worst-case conditions. At an application rate of 7 lbs a.e./acre, the acute exposures are estimated to slightly exceed the LC_{50} value for typical species and exceed the

LC_{50} value for sensitive species by a factor of about 2. In these worst-case scenarios, the exposure estimates are based on a severe rainfall (about 7 inches over a 24 hour period) in an area where runoff is favored – a slope toward a stream immediately adjacent to the application site. This is a standard worst-case scenario used in Forest Service risk assessments to guide the Forest Service in the use of herbicides. This risk characterization strongly suggests that the use of the more toxic formulations near surface water is not prudent.

The use of less toxic formulations result in acute hazard quotients that do not approach a level of concern for any species. Nonetheless, the hazard quotient of 0.08 for sensitive species at an application rate of 2 lbs/acre is based on an LC_{50} value rather than a NOEC. Thus, the use of glyphosate near bodies of water where sensitive species of fish may be found (i.e., salmonids) should be conducted with substantial care to avoid contamination of surface water. Concern for potential effects on salmonids is augmented by the potential effects of low concentrations of glyphosate on algal populations.

The likelihood of direct acute toxic effects on aquatic invertebrates or longer term direct effects on any fish species seems extremely remote based on central estimates of the hazard quotient and unlikely base on upper ranges of the hazard quotient. The hazard quotient of 0.044 for longer term effects of the more toxic formulations on sensitive fish is based on an estimated NOEC and thus is not, in itself, of substantial concern. Aquatic plants appear to be somewhat less sensitive to glyphosate than the most sensitive aquatic animals. There is no indication that adverse effects on aquatic plants are plausible.

1. INTRODUCTION

This document provides risk assessments for human health effects and ecological effects to support an assessment of the environmental consequences of using glyphosate in Forest Service vegetation management programs. This risk assessment is an update to the previous USDA Forest Service risk assessment of glyphosate (SERA 1996). A large number of commercial formulations of glyphosate are available and all formulations that are currently registered for forestry applications are covered in this risk assessment.

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 glyphosate, an assessment of potential exposure to this compound, an assessment of the dose-response relationships, and a characterization of the risks associated with plausible levels of exposure. These are the basic steps recommended by the National Research Council of the National Academy of Sciences (NRC 1983) for conducting and organizing risk assessments.

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

In the preparation of this risk assessment, literature searches of glyphosate were conducted in the open literature using PubMed, TOXLINE as well as the U.S. EPA CBI files. Several reviews and risk assessments on glyphosate conducted by the U.S. EPA were also consulted. These include the science chapters for human health (U.S. EPA/OPP 1993a) and ecological effects (U.S. EPA/OPP 1993b), the U.S. EPA Reregistration Eligibility Decision (RED) document on glyphosate (U.S. EPA/OPP 1993), pesticide tolerances for glyphosate (U.S. EPA/OPP 2002), the U.S. EPA Drinking Water Criteria Document on glyphosate (U.S. EPA/ODW 1992) and the IRIS entry for this compound (U.S. EPA/IRIS 1993). Additional reviews consulted in the preparation of this document include the EXTOXNET review of this compound (Extoxnet 1996), summaries prepared by the registrant of glyphosate (Monsanto The Agricultural Group 1995a,b,c,d), risk assessments conducted by the World Health Organization on glyphosate (WHO 1994) and AMPA, a metabolite of glyphosate (WHO 1998), public health goals for concentrations of glyphosate in drinking water prepared by CalEPA (CalEPA 1997; Howd et al. 2000), a reduced risk rationale for Roundup ULTRA (Wratten 1998), a human health risk assessment on glyphosate and glyphosate formulations published by Williams et al. (2000) as well as a review of environmental concerns with the use of glyphosate (Cox 1998a; Cox 1998b).

The search of U.S. EPA's FIFRA/CBI files indicated that there are 5829 submissions on glyphosate and glyphosate formulations. While many of these studies were conducted to support the initial registration and reregistration of glyphosate, a substantial number of studies (n=1288) were conducted and submitted to U.S. EPA after 1993, the date of the U.S. EPA Reregistration Eligibility Decision document on glyphosate (U.S. EPA/OPP 1993). Because of the extensive published literature on glyphosate, the reregistration document for glyphosate (U.S. EPA/OPP 1993) was used where possible to summarize information for the earlier CBI studies. Although full copies of some key studies (n=47) were obtained from the earlier CBI submissions, the acquisition of the CBI studies focused on the post-1993 period (n=138). Full text copies of the CBI studies [n=185] were kindly provided by the U.S. EPA Office of Pesticide Programs. The CBI studies were reviewed, and synopses of the information that can be disclosed from most relevant studies are included in the appendices to this document.

The human health and ecological risk assessments presented in this document are not, and are not intended to be, comprehensive summaries of all of the available information and these risk assessment do not cite all of the available literature. The level of detail presented in the appendices and the discussions in chapters 2, 3, and 4 of the risk assessment are intended to be sufficient to support a review of the risk analyses. As noted above, glyphosate has been extensively tested and nearly 6000 studies on glyphosate have been identified. To review each of these studies would far exceed the resources available to the Forest Service and, more importantly, would make the document very difficult to read and review. In some respects, an all inclusive and detailed review of each study would tend to obscure rather than inform.

As an alternative, this document focuses on information that is likely to impact the risk assessments. This information was identified from a screening of each of the identified citations using available abstracts, key words, and other available details. In addition, the relevance of studies was also assessed by consulting the available reviews, detailed above. Nonetheless, the selection of studies for inclusion into this risk assessment is an admittedly judgmental process. In order to maintain transparency, this risk assessment is accompanied by a complete bibliography of all studies encountered in the literature search. This bibliography is included as Attachment 1 and indicates which documents were retrieved.

For glyphosate specifically, there is a body of literature on the development, use, and safety of genetically-modified glyphosate tolerant crops such as soybeans (Shirai et al. 1998) and tobacco (Ye et al. 2001). This document, which concerns the non-agricultural use of glyphosate by the Forest Service, does not address any issues concerning crops that are genetically-modified for glyphosate tolerance.

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 in the body of these risk assessments 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 (2001a).

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

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

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

In considering different forms of variability, almost no risk estimate presented in this document is given as a single number. Usually, risk is expressed as a central estimate and a range, which is sometimes very large. Because of the need to encompass many different types of exposure as

well as the need to express the uncertainties in the assessment, this risk assessment involves numerous calculations.

Most of the calculations are relatively simple, and the very simple calculations are included in the body of the document. Some of the calculations, however, are cumbersome. For those calculations, a set of worksheets is included as an attachment to the risk assessment. The worksheets provide the detail for the estimates cited in the body of the document. The worksheets are divided into the following sections: general data and assumptions, chemical specific data and assumptions, exposure assessments for workers, exposure assessments for the general public, and exposure assessments for effects on nontarget organisms. The worksheets are included at the end of this risk assessment and further documentation for these worksheets are included as Attachment 2 (SERA 2001b). As detailed in Attachment 2, two versions of the worksheets are available: one in a word processing format and one in a spreadsheet format. 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.

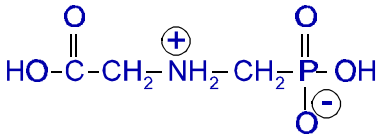
2. PROGRAM DESCRIPTION

2.1. OVERVIEW

Glyphosate is a herbicide that is used in Forest Service programs primarily in conifer release, noxious weed control, and site preparation. There are currently 35 commercial formulations of glyphosate that are registered for forestry applications. All commercial formulations of glyphosate that are used in forestry applications contain the isopropylamine salt of glyphosate. Some formulations contain only this salt of glyphosate as an aqueous solution. Other formulations contain surfactants and some of these surfactants are toxic, particularly to aquatic organisms. Technical grade glyphosate contains an impurity, N-nitrosoglyphosate, but the amount of this impurity in glyphosate has been classified as toxicologically insignificant by the U.S. EPA. A surfactant used in at least one major commercial formulation contains 1,4-dioxane, and the toxicity of this impurity is specifically considered in this risk assessment. The most common method of application for glyphosate in Forest Service programs involves is backpack-applied directed foliar sprays. Other application methods that are use occasionally are broadcast foliar ground applications, cut stem applications, and direct application to the emergent aquatic vegetation. Based on recent Forest Service use reports, the typical application rate is about 2 lb a.e./acre, with most application rates occurring over a range of 0.5 lbs a.e./acre to 7 lbs a.e./acre. The total annual use of glyphosate by the Forest Service is only about 0.275 percent of the agricultural use. Thus, there is no basis for asserting that Forest Service programs will substantially contribute to general concentrations of glyphosate nationally. The potential for local contamination of environmental media by the use of glyphosate in Forest Service programs is discussed in the human health risk assessment and the ecological risk assessment.

2.2. CHEMICAL DESCRIPTION AND COMMERCIAL FORMULATIONS

Glyphosate is the common name for N-(phosphonomethyl)glycine:



Selected chemical and physical properties of glyphosate are summarized in Table 2-1. Additional information is presented in worksheet B03. At ambient temperatures, glyphosate is a white crystalline substance. In the crystalline form, glyphosate has both positive and negative regions of charge, indicated by the circled plus (**+**) and minus (**-**) signs in the schematic above. Such dipolar ion species are sometimes referred to as a *zwitterions*. In aqueous solutions, the hydrogen atoms of the carboxylic acid (**COOH**) and phosphate ($\mathbf{PO_2H_2}$) groups may be associated (e.g., **-COOH**) or dissociated (e.g., $\mathbf{-COO^-} + \mathbf{H^+}$) depending on the pH of the solution. The dissociation constants, or pK_a values, for these reactions are illustrated in Figure 2-1. The pH of most

biological fluids range from approximately 5 to 9. Thus, within this range of pH, glyphosate has a net negative charge and is predominantly in form of H_2G^{-1} or HG^{-2}, as illustrated in Figure 2-1.

Technical grade glyphosate contains an impurity, N-nitrosoglyphosate, which is sometimes abbreviated as NNG. Specific information on nitrosamine concentrations in glyphosate formulations have been submitted to U.S. EPA (e.g., Hirsch and Augustin 1987). This information has been reviewed in the preparation of the current risk assessment but specific details may not be disclosed in this risk assessment except for information that has been made publically available by U.S. EPA. The U.S. EPA has determined that 92% of technical grade glyphosate contains NNG at less than one part per million (<1 mg/L) and that this amount is toxicologically insignificant.

Similarly, a surfactant used in Roundup contains 1,4-dioxane as an impurity. The upper limit of this compound in Roundup is about 0.03% (Monsanto 1990). The toxicologic significance of these compounds are discussed in Section 3.1.9.

The previous USDA Forest Service risk assessment of glyphosate (SERA 1996) had covered only four formulations: Roundup, Roundup Pro, Accord, and Rodeo. Since the preparation of the 1996 risk assessment, glyphosate has come off patent protection, resulting in a rapid increase in registrants and formulations. Thus, there are currently 35 commercial formulations of glyphosate that are registered for forestry applications. Each of the formulations are detailed in Appendix 1. All commercial formulations of glyphosate that are used in forestry applications contain the isopropylamine salt of glyphosate.

Several liquid formulations of glyphosate appear to contain either glyphosate alone in water (e.g., Aquamaster, Glyfos Aquatic, Roundup Custom, Rodeo). Other liquid formulations of glyphosate in a tallow amine surfactant (e.g., Credit, Glyfos, Glyfos Pro, Glyfos X-TRA, Honcho, Mirage, Razor, Roundup ORIGINAL, Roundup PRO). Some formulations of glyphosate do not indicate whether or not surfactants are present in the formulation.

The specific identity of the surfactants, other inerts, contaminants, and impurities has been disclosed to the U.S. EPA as part of the registration process and this information has been reviewed in the preparation of this risk assessment (e.g., Barclay 1987a,b,c; Benard 2002; Brakel 1999; Buchanan 1998; Fickel and Mahlburg 1999; Friis 1995a,b,c; Lystbaek 1994; Mierkowski 1999; Miller 2002a,b,c; Stevens 2000a,b,c; Taylor 1993; Wratten 1999). This information includes information on the manufacturing process, identity and quantity of the inerts/impurities in the formulations as well as additional information on the composition of some inerts that are themselves complex mixtures. This information may not be disclosed in this risk assessment because it is classified as *trade secret* under Sections 10(f) and 12(a)(2)(D) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). While this is a limitation in terms of the ability to communicate specific types of information to the general public and other interested parties, some information is also available in the open literature and is discussed in this risk assessment.

Inerts are classified by the U.S. EPA as ranging from inerts of toxicologic concern (List 1) to inerts of minimal concern (List 4) (U.S. EPA/OPP 1998b). Some inerts - i.e., those listed under SARA Title III, Section 313 - are specified on the product material safety data sheets, as specified in Appendix 1, and can be publicly disclosed. Most formulations of glyphosate that do not contain a surfactant indicate that a nonionic surfactant should be added to the field solution prior to application. The concentration of surfactants in glyphosate formulations tends to range from about 1% to 11% and with the most common class of surfactants being characterized as polyoxyethyleneamines or POEA (Acquavella et al. 1999a). As detailed in both the human health risk assessment (Section 3) and the ecological risk assessment (Section 4), the use of glyphosate with a surfactant may substantially impact risk.

2.3. APPLICATION METHODS

Glyphosate formulations may be applied by directed foliar, broadcast foliar, or aerial methods. The most common method of application for glyphosate in Forest Service programs involves is backpack-applied directed foliar sprays. In directed foliar applications, the herbicide sprayer or container is carried by backpack and the herbicide is applied to selected target vegetation. Application crews may treat up to shoulder high brush, which means that chemical contact with the arms, hands, or face is plausible. To reduce the likelihood of significant exposure, application crews are directed not to walk through treated vegetation. Usually, a worker treats approximately 0.5 acre/hour with a plausible range of 0.25-1.0 acre/hour. Glyphosate may also be applied in hack and squirt applications, in which the bark and cambium of a standing tree is cut with a hatchet and the herbicide is then applied to the cut using a squirt bottle. This treatment is used to eliminate large trees during site preparation, conifer release operations, or rights-of-way maintenance. As with selective foliar applications, a worker usually will treat approximately 0.5 acres/hour with a plausible range of 0.25–1.0 acres/hour.

Broadcast foliar ground applications may occasionally be conducted and involve the use of a two to six nozzle boom mounted on a tractor or other heavy duty vehicle. With this equipment, workers will typically treat 11 to 21 acres per hour, with the low end of this range representative of a four-wheel drive vehicle in tall grass and the upper end of the range representative of a large bulldozer (USDA 1989b p 2-9 to 2-10).

Two additional application methods are also used occasionally in Forest Service programs. The first is a cut stem application. This is used in the treatment of some noxious weeds, notably *Arundo donax*. One of the more common methods for treating that plant is to cut the stem, and then spray or paint on some undiluted Foresters' Non-Selective Herbicide or Glyphos Pro to the cut stump surface. The other method of application is an aquatic application for aquatic noxious weeds. This can involve the application of glyphosate, often with a surfactant, to the emergent vegetation – i.e., above-surface plant parts. Glyphosate is not applied over open water in Forest Service programs.

As indicated in Appendix 1, some glyphosate formulations (e.g., Accord SP and Glypro) are labeled for aerial applications. Liquid formulations of glyphosate are applied 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. Aerial applications may only be made under meteorological conditions that minimize the potential for spray drift. In aerial applications, approximately 40–100 acres may be treated per hour.

In some instances, areas treated with glyphosate may be subject to brown-and-burn operations. As indicated in USDA (1989b), these operations involve burning a treated area 45–180 days after treatment with the herbicide.

2.4. USES AND APPLICATION RATES

The use of glyphosate in Forest Service Programs for fiscal year 2001, the most recent year for which data are available, is detailed in Appendix 2 and summarized in Table 2-2. Glyphosate is used in Forest Service Programs primarily in conifer release (58.2%), noxious weed control (15.1%), and site preparation (16.4%). Other minor uses (totaling 10.3% of use) include other weed control (agricultural, aquatic, and nursery), hardwood release, facilities maintenance, recreation improvement, right-of-way management, seed orchard protection, and wildlife habitat improvement. The application rates are about 3.31 lb/acre (SD 1.77) for conifer release, 1.06 lb/acre (SD 2.14) for noxious weed control, and 3.34 lb/acre (SD 1.76) for site preparation.

For this risk assessment, the average application rate will be taken as 2 lb a.e./acre. This is an essentially arbitrary selection but is reasonably close to the overall average application rate used in all types of program activities (Table 2-2). This application rate is used in the worksheets that accompany this risk assessment. The range of application rates will be taken as 0.5 lbs a.e./acre to 7 lbs a.e./acre to reflect plausible ranges that the Forest Service may use. While the upper range is somewhat below the highest reported application rate of 9.96 lb/acre (i.e., Forest 7 in Region 5), it is likely to be more representative of programs that the Forest Service is likely to conduct in the future. This range of application rates is not used in the worksheets but the consequences of varying application rates within this range is considered in the risk characterization for human health (Section 3.4) and ecological effects (Section 4.4).

For this risk assessment, the extent to which a formulation of glyphosate is diluted prior to application primarily influences dermal and direct spray scenarios, both of which are dependent on ‘field dilution’(i.e., the concentration of glyphosate in the applied spray). In all cases, the higher the concentration of glyphosate - equivalent to the lower dilution of glyphosate - the greater the risk. For this risk assessment, the lowest dilution is taken as 5 gallons/acre. The highest dilution is based on 25 gallons of water per acre. A typical dilution rate is taken as 10 gallons/acre. Details regarding the calculation of field dilution rates are given in worksheet B01, and the calculations following this worksheet are summarized in worksheet B02.

It should be noted that the selection of application rates and dilution volumes in this risk assessment is intended to simply reflect typical or central estimates as well as plausible lower and upper ranges. In the assessment of specific program activities, the Forest Service will use

program specific application rates in the worksheets that are included with this report to assess any potential risks for a proposed application.

2.5. USE STATISTICS

The USDA Forest Service (USDA/FS 2002) tracks and reports use by geographical areas referred to as "*Regions*". As illustrated in Figure 2-2, 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 2-2 and detailed further in Table 2-3, the heaviest used of glyphosate occurs in Region 5 (Pacific Southwest) in terms of the number of acres treated, the number of pounds used, and the application rate. Substantial glyphosate use also occurs in Regions 8 (Southern, 7.6%) and 9 (Eastern 9.3%) with moderate use in Region 6 (Pacific Northwest, 3.8%). Glyphosate use by the Forest Service in other regions is insubstantial – i.e., less than 2% of total.

Many formulations of glyphosate are used extensively in agriculture. A summary of the agricultural use of glyphosate is presented in Figure 2-3 (USGS 1998). These use statistics are for 1992, the most recent year for which data are available. As indicated in this figure, over 16,000,000 lbs of glyphosate are applied to crops annually, primarily to soybeans, corn, and citrus in the mid-west and in California. As noted in Table 2-3, the total annual use of glyphosate by the Forest Service for 2001 is about 45,000 lbs, which is 0.275 percent of the agricultural use. While the use of glyphosate by the Forest Service is not trivial, this use is less than that of agricultural uses by a factor of over 300. Thus, there is no basis for asserting that Forest Service programs will substantially contribute to general concentrations of glyphosate nationally. The potential for local contamination of environmental media by the use of glyphosate in Forest Service programs is discussed in detail in the human health risk assessment (Section 3) and the ecological risk assessment (Section 4).

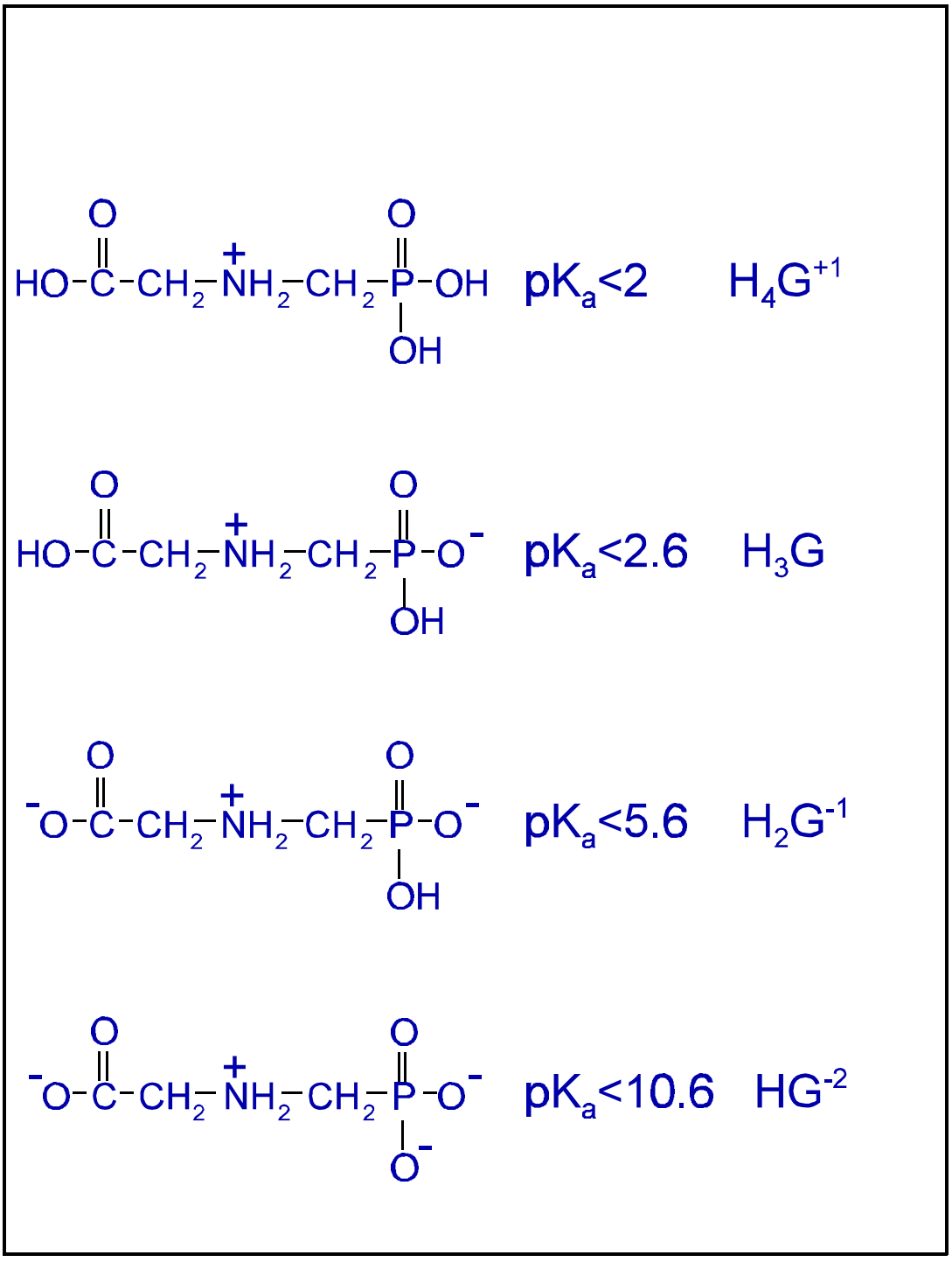


Figure 2-1. Structure and dissociation constants (pK_a) for the various forms of glyphosate.

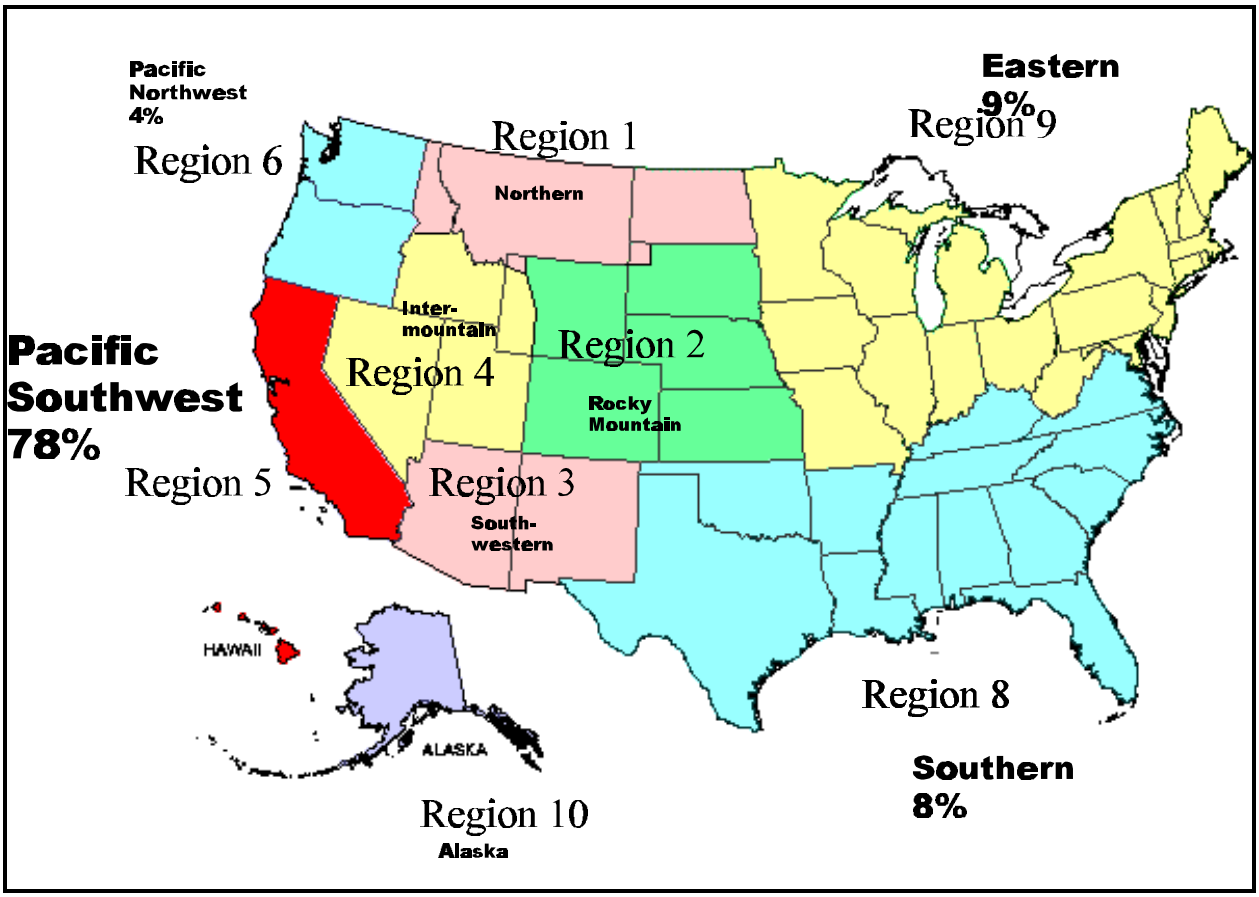


Figure 2-2. Use of glyphosate by the USDA Forest Service in various regions of the United States.

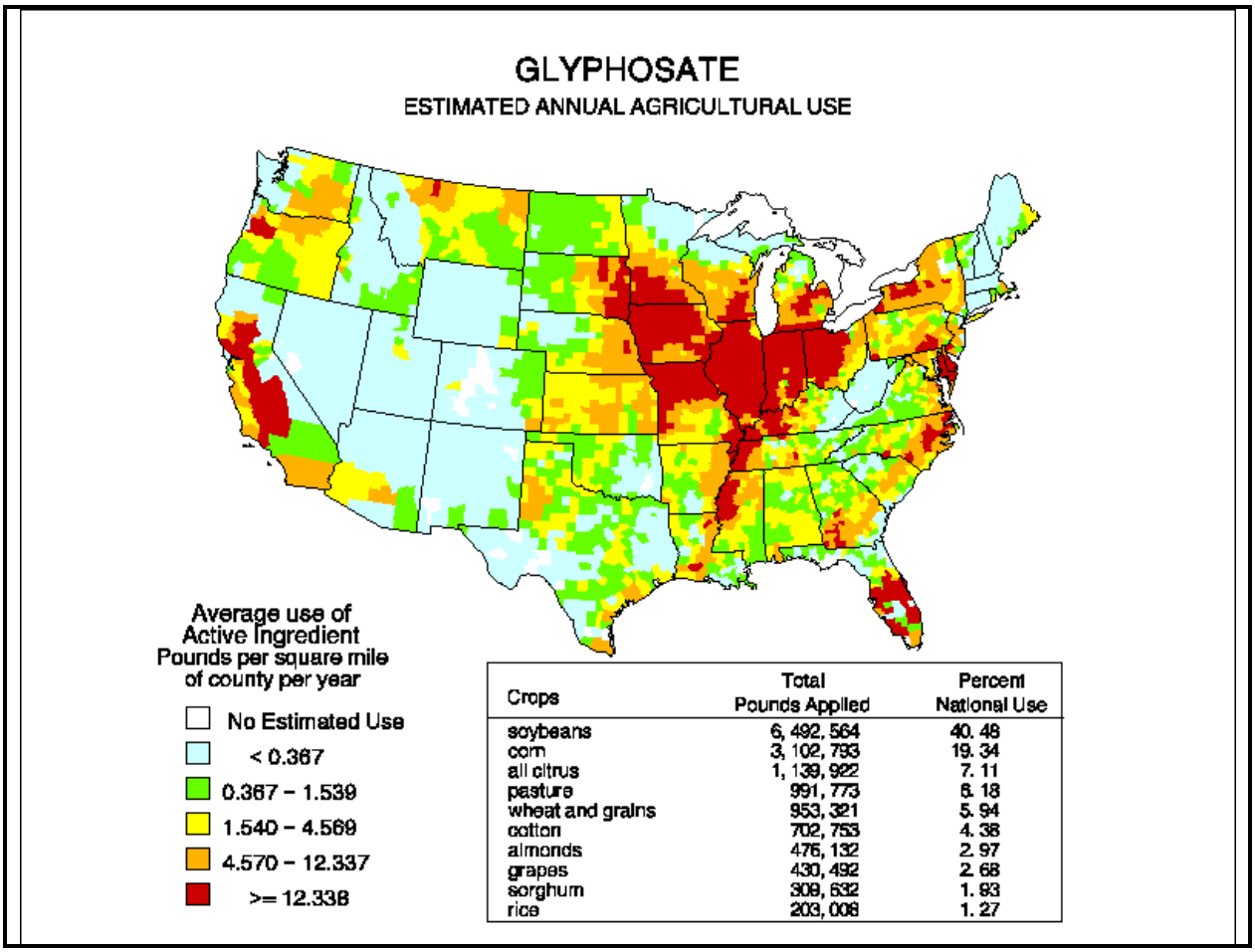


Figure 2-3. Agricultural use of glyphosate in the United States for 1992 (USGS 1998).

Table 2-1. Physical, chemical, and biochemical properties of glyphosate

CAS Number:	1071-83-6
Molecular weight:	169.07 (Budavari 1989)
Melting point (°C):	200 (USDA/ARS 1995)
Vapor pressure (mm Hg):	$< 7 \times 10^{-9}$ mm Hg (25° C) (Weber 1991)
Water solubility:	12 g/L (25°C) (USDA/ARS 1995)
	900 g/L, amine salt (Knisel et al. 1992)
	11.6 g/L (Schuette 1998)
Log K_{ow}:	-3.39 (pH 1.77) (Chamberlain et al. 1996)
	-4.38 (pH 4.61) (Chamberlain et al. 1996)
	-4.85 (pH 6.86) (Chamberlain et al. 1996)
	-4.14 (pH 9.00) (Chamberlain et al. 1996)
	-3.5 (Schuette 1998)
Soil:water part. coef. K_d:	61 g/m^3 (Schuette 1998)
	2100 (500 - 2600) (USDA/ARS 1995)
Soil adsorption K_{oc} (L/kg):	554–34,000 (Piccolo et al; 1994)
	2,600–4,900 (Glass 1987)
	8 to >500,000 (Gerritse et al. 1996)
	54 (Knisel et al. 1992)
Foliar half-life (days):	≃1.6 (Thompson et al. 1994)
	8–10 (Feng and Thompson 1990)
	10.6–26.6 (Newton et al. 1984)
	2.5 (Knisel et al. 1992)
	46 (Siltanen et al. 1981)
Soil half-life (days):	20–40 (Weber 1991)
	<60 (average) (WSSA 1989)
	45–60 (Feng and Thompson 1990)
	29–40 (Newton et al. 1984)
	30-40 (Smith and Aubin 1993)
	47 (Knisel et al. 1992)
	22.1 aerobic, 96.4 anaerobic (Schuette 1998)
	2.8-30 (dissipation, Hatfield 1996)
	37(2-174) for field dissipation (USDA/ARS 1995)
Water half-life (days):	50–70 (U.S. EPA/ODW 1992)
	14 (minimum rate) (Reinert and Rodgers 1987)
	42–70 (Reinert and Rodgers 1987)
	> 35 (Schuette 1998)
	3.5–11.2 days [surface water; some glyphosate in the water column was transferred to sediment and not degraded] (Goldsborough and Brown 1993)
Foliar wash-off fraction	0.6 (Knisel et al. 1992)

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

Use Classification	Acres	Pounds	Proportion of Use by Pounds	lbs/acre
Agricultural Weed Control	4,172.60	628.50	0.014	3.64
Aquatic Weed Control	4.50	4.70	0.000	1.04
Conifer and Hardwood Release	954.10	1,501.20	0.034	1.57
Conifer Release	7,855.00	26,032.50	0.582	3.31
Facilities Maintenance	49.80	48.64	0.001	0.98
Noxious Weed Control	6,368.60	6,768.54	0.151	1.06
Nursery Weed Control	247.30	718.15	0.016	2.90
Recreation Improvement	78.50	39.68	0.001	0.51
Right-of-Way	577.70	895.48	0.020	1.55
Seed Orchard Protection	16.00	10.00	0.000	0.63
Site Preparation	2,189.00	7,319.76	0.164	3.34
Wildlife Habitat Improvement	508.00	753.50	0.017	1.48
Grand Total	19,021.10	44,720.60	1	2.35

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

Forest	Acres	Pounds	lbs/acre	Proportion of Total Acres	Proportion of Total Lbs.
Northern (R1)	133.00	264.00	1.99	0.007	0.006
Rocky Mountain (R2)	264.00	182.00	0.69	0.014	0.004
Southwestern (R3)	3.00	3.00	1.00	0.000	0.000
Intermountain (R4)	405.00	261.00	0.64	0.021	0.006
Pacific Southwest (R5)	8,395.00	34,740.00	4.14	0.441	0.777
Pacific Northwest (R6)	1,003.00	1,706.00	1.70	0.053	0.038
Southern (R8)	3,888.00	3,419.00	0.88	0.204	0.076
Eastern (R9)	4,930.00	4,146.00	0.84	0.259	0.093
Total	**19,021.00**	**44,721.00**	**2.35**		

3. HUMAN HEALTH RISK ASSESSMENT

3.1. HAZARD IDENTIFICATION

3.1.1. Overview. The herbicidal activity of glyphosate is due primarily to the inhibition of the shikimate pathway which is involved in the synthesis of aromatic amino acids in plants and microorganisms. This metabolic pathway does not occur in humans or other animals and thus this mechanism of action is not directly relevant to the human health risk assessment. Two specific biochemical mechanisms of action have been identified or proposed for glyphosate: uncoupling of oxidative phosphorylation and inhibition of hepatic mixed function oxidases. Both glyphosate and the polyethoxylated tallow amine (POEA) surfactant used in Roundup will damage mucosal tissue, although the mechanism of this damage is likely to differ for these two agents. Many of the effects of acute oral exposure to high doses of glyphosate or Roundup are consistent with corrosive effects on the mucosa.

The available experimental studies indicate that glyphosate is not completely absorbed after oral administration and is poorly absorbed after dermal applications. Two dermal absorption studies have been published on glyphosate and both of these studies indicate that glyphosate is very poorly absorbed across the skin.

Like all chemicals, glyphosate as well as commercial formulations of glyphosate may be toxic at sufficiently high exposure levels. In rats and mice, acute oral LD_{50} values of glyphosate range from approximately 2,000 to 6,000 mg/kg. Formulations of glyphosate with a POEA surfactant have been used in many suicides and attempted suicides. Gastrointestinal effects (vomiting, abdominal pain, diarrhea), irritation, congestion, or other forms of damage to the respiratory tract, pulmonary edema, decreased urinary output sometimes accompanied by acute renal tubular necrosis, hypotension, metabolic acidosis, and electrolyte imbalances, probably secondary to the gastrointestinal and renal effects, are seen in human cases of glyphosate/surfactant exposure.

One of the more consistent signs of subchronic or chronic exposure to glyphosate is loss of body weight. This effect has been noted in mice, rats, dogs, and rabbits. This observation is consistent with experimental data indicating that glyphosate may be an uncoupler of oxidative phosphorylation. Other signs of toxicity seem general and non-specific. A few studies report changes in liver weight, blood chemistry that would suggest mild liver toxicity, or liver pathology. Changes in pituitary weight have also been observed. Signs of kidney toxicity, which might be expected based on the acute toxicity of glyphosate, have not been reported consistently and are not severe. Various hematological changes have been observed that may be secondary to mild dehydration.

Glyphosate has been specifically tested for neurotoxicity in rats after both acute and subchronic exposures and has been tested for delayed neurotoxicity in hens. In both the animal data as well as the clinical literature involving suicide attempts, there is no clear pattern suggestive of a specific neurotoxic action for glyphosate or its commercial formulations. The weight of evidence

suggests that any neurologic symptoms associated with glyphosate exposures are secondary to other toxic effects. No studies are reported that indicate morphologic abnormalities in lymphoid tissues which could be suggestive of an effect on the immune system. As discussed in the ecological risk assessment, one study has asserted that glyphosate causes immune suppression in a species of fish. This study, however, is deficient in several respects and does not provide a basis for impacting the hazard identification for effects on the immune system.

Only three specific tests on the potential effects of glyphosate on the endocrine system have been conducted and all of these tests reported no effects. All of these assays are *in vitro* – i.e., not conducted in whole animals. Thus, such studies are used qualitatively in the hazard identification to assess whether there is a plausible biologic mechanism for asserting that endocrine disruption is plausible. Because they are *in vitro* assays, measures of *dose* and quantitative use of the information in dose/response assessment is not appropriate. For glyphosate, these studies to not indicate a basis for suggesting that glyphosate is an endocrine disruptor. Nonetheless, glyphosate has not undergone an extensive evaluation for its potential to interact or interfere with the estrogen, androgen, or thyroid hormone systems. Thus, the assessment of the potential endocrine effects of glyphosate cannot be overly interpreted.

Glyphosate has been subject to multi-generation reproduction studies which measure overall effects on reproductive capacity as well as teratology studies which assay for a compounds ability to cause birth defects. Signs of teratogenic activity have not been observed in standard assays in both rats and rabbits. In a multi-generation reproduction study in rats, effects on the kidney were observed in male offspring. This effect is consistent with the acute systemic toxicity of glyphosate, rather than a specific reproductive effect. Several other subchronic and chronic studies of glyphosate have been conducted with no mention of treatment-related effects on endocrine glands or reproductive organs. A single study has reported substantial decreases in libido, ejaculate volume, sperm concentrations, semen initial fructose and semen osmolality as well as increases in abnormal and dead sperm in rabbits after acute oral exposures to glyphosate. This study is inconsistent with other studies reported on glyphosate and is poorly documented – i.e., specific doses administered to the animals are not specified. In addition, the use of gelatin capsules, as in this study results, in a high spike in body burden that is not typical or particularly relevant to potential human exposures – other than attempted suicides. Numerous epidemiological studies have examined relationships between pesticide exposures or assumed pesticide exposures in agricultural workers and reproductive outcomes. Of those studies that have specifically addressed potential risks from glyphosate exposures, adverse reproductive effects have not been noted.

Based on standard animal bioassays for carcinogenic activity *in vivo*, there is no basis for asserting that glyphosate is likely to pose a substantial risk. The Re-registration Eligibility Decision document on glyphosate prepared by the U.S. EPA indicates that glyphosate is classified as Group E: Evidence of non-carcinogenicity for humans. This classification is also indicated in U.S. EPA's most recent publication of tolerances for glyphosate and is consistent with an assessment by the World Health Organization. This assessment has been challenged based on some studies

that indicate marginal carcinogenic activity. As with any compound that has been studied for a long period of time and tested in a large number of different systems, some equivocal evidence of carcinogenic potential is apparent and may remain a cause of concern, at least in terms of risk perception. While these concerns are understandable, there is no compelling basis for challenging the position taken by the U.S. EPA and no quantitative risk assessment for cancer is conducted as part of the current analysis.

Glyphosate formulations used by the Forest Service are classified as either non-irritating or only slightly irritating to the skin and eyes in standard assays required for product registration. Based on a total of 1513 calls to a poison control center reporting ocular effects associated with the use of Roundup, 21% were associated with no injury, 70% with transient minor injury, 2% with some temporary injury. The most frequently noted symptoms included blurred vision, a stinging or burning sensation, lacrimation. No cases of permanent damage were reported.

Various glyphosate formulations contain a POEA surfactant at a level of up to about 20%. Other formulations of glyphosate recommend the use of a surfactant to improve the efficacy of glyphosate. While surfactants are typically classified as "inert" ingredients in herbicides, these compounds are not toxicologically inert and some surfactants may be more toxic than the herbicides with which they are used. Although surfactants may play a substantial role in the interpretation of a large number of suicides and attempted suicides involving the ingestion of glyphosate formulations, primarily Roundup, the acute mammalian toxicity of different glyphosate formulations do not appear to differ substantially. This is in contrast to the available data on the toxicity of various formulations to aquatic species, as detailed in the ecological risk assessment.

3.1.2. Mechanisms of Action. While the mechanism of action of glyphosate in plants is well-characterized, the mechanism by which glyphosate exerts toxic effects in humans or experimental mammals is not clear. Two specific biochemical mechanisms of action have been identified or proposed: uncoupling of oxidative phosphorylation and inhibition of hepatic mixed function oxidases. In addition, both glyphosate and the POEA surfactant used in Roundup will damage mucosal tissue, although the mechanism of this damage is likely to differ for these two agents.

The herbicidal activity of glyphosate is due primarily to the inhibition of the shikimate pathway which is involved in the synthesis of aromatic amino acids in plants and microorganisms (Section 4.1). This metabolic pathway does not occur in humans or other animals and thus this mechanism of action is not directly relevant to the human health risk assessment. Nonetheless, shikimate pathway inhibitors have been considered as antimicrobial agents for the control of pathogens (Roberts et al. 1998; Roberts et al. 2002; Schonbrunn et al. 2001) and glyphosate has been shown to be effective in prolonging survival in mice infected with a pathogen, *Cryptococcus neoformans* (Nosanchuk et al. 2001).

Oxidative phosphorylation is a fundamental metabolic process in which metabolic energy derived from the oxidation of nutrients is transferred to and stored in high-energy phosphate bonds. The uncoupling of this process results in energy loss in the organism and lead to death. Symptoms of

uncouplers of oxidative phosphorylation include increased heart rate (tachycardia), increased respiratory rate, labored breathing, profuse sweating, fever, metabolic acidosis, and weight loss (ATSDR 2001).

Based on a series of experiments using rat liver mitochondria exposed to the isopropanolamine salt of glyphosate without any surfactant (summarized in detail by U.S. EPA 1992), glyphosate appears to be an uncoupler of oxidative phosphorylation (Bababunmi et al. 1979, Olorunsogo 1982, Olorunsogo and Bababunmi 1980, Olorunsogo et al. 1977, Olorunsogo et al. 1979a,b). This effect has been noted after intraperitoneal doses as low as 15 mg/kg (Olorunsogo et al. 1979a). Many of the observations on whole animals and isolated mitochondria are consistent with an uncoupling of oxidative phosphorylation including decreased body weight, decreased food conversion efficiency and increased body temperature (Section 3.1.3). It is less clear that uncoupling of oxidative phosphorylation is a significant factor in acute exposures. Of the 97 patients covered in the Tominack et al. (1991) report, only seven individuals had mild elevations in body temperature (>99.5°F). In addition, acute gavage doses of 50, 100, or 200 mg glyphosate a.e./kg in rats was associated with hypothermia (a decrease in body temperature) rather than hyperthermia (Horner 1996a).

The other specific mechanism of action that may account for some the effects of glyphosate involves the inhibition of hepatic mixed-function oxidases. This is a class of enzymes comprised of various isozymes of cytochrome P-450 that is involved in the metabolism of a wide variety of endogenous compounds as well as xenobiotics. Decreases in hepatic mixed function oxidase activity in rats has been noted after doses of glyphosate (as Roundup 360 g/L) of 500 mg/kg/day for four days followed by doses of 300 mg/kg/day for 6 days (Hietanen et al. 1983). This decrease in mixed function oxidase activity is only suggestive of cytochrome P-450 inhibition in that a general decrease in mixed function oxidase activity could also be caused by direct liver damage. Nonetheless, it seems reasonable to suggest that this effect may have been caused by P-450 inhibition by glyphosate because glyphosate has been shown to inhibit cytochrome P-450 in plants (Lamb et al. 1998).

Many of the effects of acute oral exposure to high doses of glyphosate or Roundup are consistent with corrosive effects on the mucosa. Glyphosate, the POEA surfactant in Roundup, as well as Roundup itself all cause corrosive effects on the gastric mucosa as well as other tissue (Chang et al. 1999; Hung et al. 1997). While somewhat speculative, it is likely that the mechanisms for this effect differ between glyphosate and the POEA surfactant. As indicated in Section 2, glyphosate is a zwitterion that will have a net negative charge and can be expected to act as an acid at physiological pH. Thus, the effects of glyphosate on mucosal tissue may be due to the acidic action of glyphosate, similar to the effects of high concentrations of hydrochloric acid in dog (Talbot et al. 1991). As detailed in Section 3.1.11, the POEA surfactant behaves essentially like a soap to dissolve cell membranes.

3.1.3. Pharmacokinetics and Metabolism. The available experimental studies indicate that glyphosate is not completely absorbed after oral administration and is poorly absorbed after

dermal applications. Much of the early literature on the pharmacokinetics and metabolism of glyphosate is reviewed by WHO (1994) and Williams et al. (2000). After oral exposure only about 30% of glyphosate is absorbed from the gastrointestinal tract. This has also been noted in more recent studies by Davies (Davies 1996a; Davies 1996b; Davies 1996c; Davies 1996d; Davies 1996e). Although most unabsorbed glyphosate remains in the gastrointestinal tract (Davies 1996e), absorbed glyphosate is widely distributed in the body. Although glyphosate does not substantially concentrate and persist in any tissue, concentrations in the bone tend to be higher than in other tissue (WHO 1994; Davies 1996e). The only known metabolite of glyphosate is AMPA. While this is a common environmental metabolite formed in the degradation of glyphosate (Section 1.3.14.1), only trace amounts of AMPA are formed in mammals (Macpherson 1996; U.S. EPA/ODW 1992; WHO 1994) and most of the administered dose of glyphosate (>97%) is excreted unchanged (Williams et al. 2000).

As discussed further in the dose-response assessment (Section 3.3), dose levels expressed in mg/kg/day cause comparable effects over broad periods of exposure, which is consistent with the rapid elimination of and lack of toxic metabolites from glyphosate (Brewster et al. 1991, Monsanto Co. 1993a,b; NTP 1992).

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 glyphosate is likely to be absorbed from the surface of the skin. Two types of dermal exposure scenarios are considered: immersion and accidental spills. As detailed in SERA (2001a), the calculation of absorbed dose for 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. 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.

Two dermal absorption studies (Wester et al. 1991; Wester et al. 1996) have been published on glyphosate and both of these studies indicate that glyphosate is very poorly absorbed across the skin. Wester et al. (1991) assayed the dermal absorption of ^{14}C-labeled glyphosate in a Roundup formulation in both an *in vitro* system using skin from human cadavers and in the *in vivo* study in monkeys. *In vitro* skin preparations were exposed to undiluted Roundup formulations for up to 8 hours and 1:20 and 1:32 dilutions of Roundup similarly treated for up to 16 hours (Wester et al. 1991, Table 1, p. 728). Based on the 16 hour exposures to the dilute solutions, first-order dermal absorption rates ranged from 1.3×10^{-4} to 1.0×10^{-3} $hour^{-1}$ with an average value of 4.1×10^{-4} $hour^{-1}$. Based on the 8 hour exposures to the concentrated Roundup, first-order dermal absorption rates ranged from 7.5×10^{-5} to 5.0×10^{-4} $hour^{-1}$. Thus, glyphosate in undiluted Roundup – i.e., containing the POEA surfactant – does not appear to be more rapidly absorbed than glyphosate in a more dilute solution of the surfactant. The *in vivo* studies in monkeys indicated that about 1.5% of the

glyphosate was absorbed in 12 hours, corresponding to a first-order dermal absorption rate of 1.3×10^{-3} hour^{-1} [ka = ln(1-proportion absorbed)/duration].

These experimental measurements of dermal absorption are very consistent with the standard methods used to estimate first-order dermal absorption rates (SERA 2001a). The details of the method specified in SERA (2001a) for estimating the first-order dermal absorption coefficient based on the molecular weight and octanol-water partition coefficient are given in worksheet A07a. The application of this method to glyphosate is detailed in worksheet B03 and yields a central estimate of 7.43×10^{-4} hour^{-1} with a range of 1.40×10^{-4} to 3.95×10^{-4} hour^{-1}.

Given the similarities between the estimated values of the first-order dermal absorption rates in worksheet B03 and the experimental values calculated from the study by Wester et al. (1991), the use of either set in this risk assessment makes relatively little difference. Nonetheless, the experimental values for human skin preparations from Wester et al. (1991) are used in all exposure assessments requiring first-order dermal absorption rates as specified in worksheet B05.

Wester et al. (1996) have reported a permeability coefficient, K_p, of $4.59\pm1.56\times10^{-4}$ cm/hour with a lag time of 10.48 hours based on *in vitro* human skin preparation. As detailed in U.S. EPA/ORD (1992) different types of models with or without lag times may be used to estimate dermal permeability coefficients. Using the method recommended by U.S. EPA/ORD (1992), the estimated dermal permeability coefficient for glyphosate (excluding a lag time) is 1.53×10^{-6} cm/hour with a 95% confidence interval of 3.47×10^{-7} to 6.27×10^{-6} cm/hour. The details of the U.S. EPA/ORD (1992) method for estimating K_p based on the molecular weight and octanol-water partition coefficient are given in worksheet A07b. The application of this method to glyphosate is detailed in worksheet B04. Because of the differences in the underlying models – i.e., inclusion or exclusion of a lag time – the estimates based on the method of U.S. EPA/ORD (1992) and the experimental report from Wester et al. (1996) are not directly comparable. For this risk assessment, the simpler model and estimates from U.S. EPA/ORD (1992) are used.

This is a more conservative approach than using the lag-time model because washing with soap and water will effectively remove about 90% of glyphosate applied to the skin (Wester et al. 1994). Thus, under standard spill scenarios used in this risk assessment (Section 3.3), the pesticide is washed off the skin in less than the lag time noted by Wester et al. (1996) and hence exposure would be essentially zero, even though the Kp with lag-time reported by Wester et al. (1996) is substantially higher than the values estimated from the method of U.S. EPA/ORD (1992).

3.1.4. Acute Toxicity. Like all chemicals, glyphosate as well as commercial formulations of glyphosate may be toxic at sufficiently high exposure levels. In rats and mice, acute oral LD_{50} values of glyphosate range from approximately 2,000 to 6,000 mg/kg (Williams et al. 2000) and intraperitoneal LD_{50} values are about 10 times lower, ranging from 134 to 234 mg/kg (Bababunmi et al. 1978). As detailed further in Section 4.3.1. (Dose-Response Assessment for Terrestrial Animals), there appears to be no systematic differences in toxicity among species when doses of

glyphosate are expressed in units of mg/kg body weight. In experimental mammals, signs of acute toxicity after oral or intraperitoneal dosing include increased respiratory rates, elevated rectal temperature, and in some instances asphyxia convulsion. The primary pathological lesion is lung hyperemia (Bababunmi et al. 1978; Olorunsogo et al. 1977; Olorunsogo and Bababunmi 1980).

Formulations of glyphosate with a POEA surfactant have been used in many suicides and attempted suicides (Chang et al. 1999; Garcia-Repetto et al. 1998; Hung et al. 1997; Lee et al 2000; Lin et al. 1999; Temple and Smith 1992; Tominack et al. 1991; Sawada et al. 1988; Yang et al. 1997). Details of these studies are presented in Appendix 4. Gastrointestinal effects (vomiting, abdominal pain, diarrhea), irritation, congestion, or other forms of damage to the respiratory tract, pulmonary edema, decreased urinary output sometimes accompanied by acute renal tubular necrosis, hypotension, metabolic acidosis, and electrolyte imbalances, probably secondary to the gastrointestinal and renal effects, are seen in human cases of glyphosate/surfactant exposure.

In a recent analysis of poisoning incidents associated with suicides or attempted suicides in Taiwan (Lee et al. 2000), fatalities were associated with doses of glyphosate/surfactant formulations in the range of 330±42 mL and that survivors of poisonings were associated with doses of 122±12 mL. This is very similar to previous estimates of fatal and non-fatal doses (Talbot et al. 1991; Tominack et al. 1991). Assuming a body weight of about 60 kg, the lethal dose is about 5500 mg Roundup/kg bw [330 mL × ca. 1000 mg/mL ÷ 60 kg], very similar to the acute LD_{50} of Roundup in rats.

As detailed in Section 3.1.11, the POEA surfactant use in glyphosate formulations (e.g., various formulations of Roundup) is a factor, and probably the dominant factor, in some of the effects seen in humans in cases of the suicidal ingestion of glyphosate formulations.

Glyphosate is commonly used as a model compound in the development of various in vitro screening methods (e.g., Bertheussen et al. 1997; El-Demerdash et al. 2001; Figenschau et al. 1997). Except as noted specifically in the following subsections, most of these studies do not contribute substantially to the risk assessment. Based on a clinical investigation of a poisoning incident, Sorensen and Gregersen (1999) have suggested that glyphosate IPA formulations may present a lower acute risk than glyphosate trimesium formulations such as Touchdown. While this may worth noting in terms of comparative risks across glyphosate formulations, only the IPA formulations used in Forest Service programs (Appendix 1) are specifically considered in this risk assessment.

3.1.5. General Subchronic or Chronic Systemic Toxicity. 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 below for 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.

One of the more consistent signs of subchronic or chronic exposure to glyphosate is loss of body weight. This effect has been noted in mice (U.S. EPA 1986a, NTP 1992), rats (Horner 1996b; Milburn 1996; NTP 1992, Stout and Ruecker 1990), dogs (Brammer 1996), and rabbits (Yousef et al. 1995). This observation is consistent with the work of Olorunsogo and coworkers, summarized in section 3.1.2, indicating that glyphosate may be an uncoupler of oxidative phosphorylation (U.S. EPA/ODW 1992, NTP 1992). Loss of body weight, particularly in studies using dietary exposure, can be secondary to decreased food consumption. In the NTP bioassay using mice, however, weight loss was noted at the two higher dose levels but there were no significant differences in food consumption between any of the treated groups and the control group. Similarly, in rabbits, the weight loss was not associated with a decrease in food consumption (Yousef 1995). In the NTP study using rats (NTP 1992), a slight decrease in food consumption was observed in the high dose group (50,000 ppm in the diet), which amounted to 91% of control values for females and 88% of control values for males. This behavior may account for the weight decrease in females, 95% of controls, and possibly for the weight decrease in males, 82% of controls. In the study by Horner (1996b), a dietary concentration of 20,000 ppm for 13 weeks resulted in a 12% decrease in body weight that could not be attributed to decreased food consumption. At a dietary concentration of 30,000 ppm, this effect has also been noted in dogs (Brammer 1996).

Other signs of toxicity seem general and non-specific. A few studies report changes in liver weight, blood chemistry that would suggest mild liver toxicity, or liver pathology (U.S. EPA 1986, NTP 1992, Stout and Ruecker 1990). Changes in pituitary weight have also been observed (Monsanto Co. 1985). Signs of kidney toxicity, which might be expected based on the acute toxicity of glyphosate, have not been reported consistently and are not severe (Monsanto Co. 1987, NTP 1992, U.S. EPA 1986). As summarized by NTP (1992), various hematological changes have been observed but are not considered severe and are attributed to mild dehydration.

3.1.6. Effects on Nervous System. Glyphosate has been specifically tested for neurotoxicity in rats after both acute (Horner, 1996a) and subchronic exposures (Horner, 1996b) and has been tested for delayed neurotoxicity in hens (Johnson 1997). It should be noted that the hen assay, while not involving a mammal, is the assay of choice for the hazard identification on agents causing delayed neurotoxicity (U.S. EPA/PPTS, 1998). In all three assays, glyphosate was negative for signs of neurotoxicity.

In the acute study by Horner (1996a), 10 male and 10 female rats were given doses of 50, 100, or 200 mg glyphosate a.e./kg and observed for two weeks. Initially – i.e., 6 hours after dosing – the animals exhibited decreased activity, subdued behavior, and hypothermia. However, there were no effects on landing foot splay, sensory perception, muscle strength, or locomotor activity and no abnormal histologic changes in the central or peripheral nervous system tissue. In the subchronic study (Horner, 1996b), groups of 12 male and 12 female rats were exposed to glyphosate in the diet at concentrations of 2000, 8000, or 20000 ppm for 13 weeks. Although effects were noted on growth and food utilization, there were no neurologic effects based on locomotor activity, no changes in brain weight or dimensions, and no evidence of damage to

nerve tissue (peripheral or central). In hens (n=20) given a single dose (gavage) of glyphosate at 2000 mg/kg, a slight decrease in brain AChE activity was observed but there were no signs of delayed locomotor ataxia and no signs of neuropathology (Johnson 1997).

Williams et al. (2000) also describe a study in which neurological examinations were conducted on dogs that received a single oral dose of 59 or 366 mg/kg of Roundup and the information is attributed to an unpublished study by Monsanto which is cited as Naylor (1988). This study was not identified in a search of the U.S. EPA/CBI files and has not been reviewed in preparation of this risk assessment. According to Williams et al. (2000):

> *"A detailed examination consisting of 12 different measurements of spinal, postural, supporting, and consensual reflexes was performed before treatment, during the postadministration observation period, and again on the following day. Reflexes appeared normal, and there were no clinical signs indicative of neuromuscular abnormalities."*

In subchronic studies in mice and rats (NTP, 1992), morphological examinations were conducted of brain (including basal ganglia, a site of injury in Parkinsonism); however, it is unclear from the report whether or not spinal cord and sciatic nerve were examined. In any event, the NTP (1992) study did not report abnormal findings in these tissues, nor did it report clinical signs of neurotoxicity. The NTP (1992) study observed histological changes in salivary glands in both rats and mice. These changes were less severe in animals that received glyphosate in combination with a dosage of propranolol, an antagonist of β-adrenergic neurotransmitters. Propranolol also completely prevented similar changes produced by isoproterenol, a β-adrenergic agonist. NTP (1992) concluded from these results that glyphosate may have produced the salivary gland changes by acting through an adrenergic mechanism. This conclusion has been challenged as being difficult to reconcile with the absence of β-adrenergic effects (e.g., on heart rate and blood pressure) when glyphosate was administered intravenously to dogs or rabbits (Williams et al., 2000). However, it is possible that, rather than acting by a direct adrenergic mechanism, glyphosate could have produced an adrenergic-mediated stimulation of the salivary glands through some indirect mechanism exerted during prolonged repeated dosing. In a one-year feeding study of rats, Milburn (1996) also reports increased incidence of mild focal basophilia of the acinar cells of parotid salivary gland in both sexes at 20000 ppm but not at 2000 ppm. No signs of neurotoxicity, however, were noted and the mechanism of this effect is unclear.

Schiffman et al. (1995) conducted a study of the effects of glyphosate on taste response in gerbils. This study appears to be the only reported investigation of the effects of glyphosate on sensory mechanisms. Glyphosate (1 or 10 mM) applied to the tongue of anesthetized gerbils decreased taste receptor response to table salt, sugars, and acids. These tests on glyphosate involved exposure periods of one minute and were conducted along with tests on 10 other pesticides, with one minute rinses between each agent. The mechanism of this effect on the taste response has not been investigated and the implications in terms of dietary preferences in the field cannot be assessed. The effect could have been produced by a general biochemical alteration in the

epithelial cells of the tongue, including the specialized cells that detect taste (glyphosate has been shown to produce injury to the oral cavity), by chemical injury to the tongue, or by a direct neurotoxic effect on the sensory nerve endings. Thus, effects reported in Schiffman et al. (1995) cannot be classified clearly as a glyphosate-induced neurologic effect.

As with the animal data, no clear pattern suggestive of neurotoxicity is apparent in an extensive and detailed literature on health outcomes of accidental and intentional (e.g., suicide attempts) gross over-exposures to glyphosate or its commercial formulations (Chang et al., 1999; Dickson et al., 1988; Hung et al., 1997; Lee et al., 2000; Menkes et al., 1991; Pushnoy et al., 1998; Talbot et al., 1991; Temple and Smith, 1992; Tominack et al., 1991; Sawada et al., 1988; Sorensen and Gregersen, 1999). In the hundreds of reported cases, neurological symptoms that are unrelated to respiratory tract distress and shock (confusion, drowsiness, collapse, coma) associated with severe acute glyphosate toxicity cannot be identified. In a review of 92 cases, only 11 individuals were reported as having an abnormal mental state prior to the onset of severe respiratory and/or cardiovascular complications; most of these cases received atropine or pralidoxime, neurotoxicants used as antidotes for certain organophosphate insecticides that inhibit acetylcholinesterase (in these cases, organophosphate intoxication and cholinesterase inhibition was suspected, although glyphosate is not a potent cholinesterase inhibitor) (Tominack et al., 1991). In a review of 93 cases, 12 were reported as having neurological symptoms (confusion, coma) two of which occurred after cardiovascular resuscitation. The cause of symptoms in 10 other cases were not distinguished from secondary respiratory tract and/or cardiovascular distress (Talbot et al., 1991). Thus, the weight of evidence suggests that any neurologic symptoms associated with glyphosate exposures were secondary to other toxic effects.

Garry et al. (2002) has conducted a self-reporting survey of individuals exposed to herbicides and other pesticides, including glyphosate. This study reports that 6 or 14 children of parents who had used phosphonamino herbicides had parent-reported attention deficit disorder. While Garry et al. (2002) indicated that the odds ratio for this is statistically significant (OR=3.6; CI 1.35 to 9.65), it should be appreciated that the use of lay diagnosed disease and self-reported exposure histories diminishes the utility of this study for hazard identification.

Barbosa et al. (2001) reported a case of Parkinsonism in an adult male who was exposed to glyphosate. This study is essentially anecdotal and does not provide a clear or even credible causal relationship between glyphosate and neurotoxic effects. Nonetheless, the report by Barbosa et al. (2001) must be examined aggressively.

Parkinsonism is a degenerative disease of the central nervous system that impairs movement. The subject of the Barbosa et al. (2001) report was a 54-year old male who experienced an extensive dermal exposure to the herbicide while spraying a garden. The acute and transient symptoms included eye irritation (*conjenctival hyperemia*) and skin rash which progressed to blisters. One month after the exposure, the individual developed hand tremors. He was subsequently diagnosed with Parkinsonism, based on the results of a neurological examination and brain imaging.

Parkinsonism is a chronic degenerative disorder that could have been present in the patient prior to the exposure.

While the case reported by Barbosa et al. (2001) may have involved gross over-exposure to glyphosate, this over-exposure, in itself, is not dismissive of a possible neurologic risk. As noted above, extreme and sometimes fatal over-exposures to glyphosate are not generally associated with neurologic effects. In addition, there is an at least tenuous biological basis for suggesting a potential association. Glyphosate is a structural analog of glycine, a physiological agent that serves as an inhibitory neurotransmitter in the CNS. Glycine, which is also a naturally occurring amino acid and is essential for normal growth and development, has been implicated as an excitotoxin when present at high concentrations in brain tissue (Johnson and Ascher, 1987; Newell et al., 1997). Excitotoxicity has been hypothesized as a possible mechanism of Parkinsonism induced by the neurotoxicants MPTA (1-methyl-4-phenyl–2-3-6-tetrahydropyridine) and N-methylamino-L-alanine (Kanthasamy et al., 1997; Karcz et al., 1999; Spencer et al., 1987).

At this point, there is no evidence to conclude that glyphosate can produce or exacerbate Parkinsonism; indeed, the Barbosa et al. (2001) observation stands in contrast to the abundant case literature that suggests glyphosate is not a neurotoxicant in humans. However, the risk assessment community should be alert to any follow-up studies of glyphosate interactions with the pathophysiological mechanisms that underlie excitotoxicity and Parkinsonism, such as the NMDA (N-methyl-D-aspartate) receptor/ion channel complex. Nonetheless, the possible connection between the onset of Parkinsonism and the exposure to glyphosate cannot be established from the single case reported by Barbosa et al. (2001), as the apparent concurrence of the two effects could be coincidental. A coincidental association is suggested by the fact that no other cases of glyphosate-related Parkinsonism have been reported.

3.1.7. Effects on Immune System. Glyphosate has been tested specifically for effects on the immune system in both humans and experimental mammals. In experimental mammals, the only reported *in vivo* study (Blakley 1997) assayed for the effects of glyphosate on immune response to antigens. In this study, mice were exposed for 26 days to Roundup in drinking water (0, 0.35, 0.70, or 1.05 %) and humoral (antibody) immune response was assessed using sheep red blood cell challenge. The response in exposed mice was not different than that of control (unexposed) mice. This is consistent with *in vitro* assays using human immunocompetent cells — natural killer cells and cytotoxic T cells — which indicated that exposure to glyphosate or Roundup at concentrations ranging from 0.01 to 10 µmoles had no effect on immune system function (Flaherty et al. 1991). Further, there is no evidence that glyphosate or glyphosate formulations produce sensitization in acute dermal sensitization tests performed in guinea pigs (Stebbins and Brooks 1999e; Stebbins and Brooks 1999j; U.S. EPA/OPP 1993a,b,c; Williams et al. 2000). As noted in the previous discussions of subchronic (Section 3.1.5) and neurologic effects (Section 3.1.6) and detailed further in Appendices 5 and 6, no studies are reported that indicate morphologic abnormalities in lymphoid tissues which could be suggestive of an effect on the immune system.

In humans, experimental, clinical, and field studies have evaluated the ability of glyphosate formulations to induce allergic responses. Maibach (1986) exposed volunteers to Roundup and found that direct dermal application did not produce allergic or photoallergic responses. Williams et al. (2000) describes a study in which dermal exposure to Roundup (approximately 9 or 4.1% glyphosate as the isopropylamine salt) did not produce allergy or sensitization (Shelanski et al., 1973). A study of five forest workers who participated in mixing and spraying operations did not observe changes in blood leukocyte counts or symptoms of allergy (e.g., skin rash, respiratory symptoms) (Jauhiainen et al., 1991). Although cases of skin rashes following dermal exposures to glyphosate formulations have been reported (Barbosa et al., 2001), these effects are thought to derive primarily from irritation rather than allergy, based on observations of Maibach (1986). Hindson and Diffey (1984a) reported that a formulation of glyphosate used in the United Kingdom, Tumbleweed, could cause photosensitization. The effect, however, was subsequently attributed to an adjuvant, benzisothiazolone (Hindson and Diffey 1984b). Benzisothiazolone is not used in the glyphosate formulations covered by this risk assessment. Based on the study by Maibach (1986) using volunteers, there is no evidence that glyphosate itself causes photoirritation or photosensitization.

As noted in Section 4.1.3, El-Gendy et al. (1998) has reported that glyphosate caused immune suppression in a species of fish. As detailed in Section 4.1.31, this study was deficient in several respects and does not provide a basis for impacting the hazard identification for effects on the immune system.

3.1.8. Effects on Endocrine Function. In terms of functional effects that have important public health implications, effects on endocrine function would be expressed as diminished or abnormal reproductive performance. This issue is addressed specifically in the following section (Section 3.1.9). This section is limited to direct and largely mechanistic assays that can be used to assess potential direct action on the endocrine system.

Only three specific tests on the potential effects of glyphosate on the endocrine system have been conducted and all of these tests reported no effects. Glyphosate was inactive as an estrogen receptor agonist (*estrogenic activity*) in MCF-7 human breast cancer cells (Lin and Garry, 2000) as well as in yeast and trout hepatocyte assays (Petit et al., 1997). In a third assay, glyphosate did not inhibit steroid synthesis in MA-10 mouse Leydig tumor cells by disrupting expression of the steroidogenic acute regulatory (StAR) protein (Walsh et al., 2000). This protein mediates the rate-limiting step in the mitochondrial synthesis of steroid hormones (the transfer of cholesterol to the inner mitochondrial membrane). In the Walsh et al. (2000) study, however, Roundup did inhibit steroid synthesis, probably due to the effects of the surfactant on membrane function. All of these assays are *in vitro* – i.e., not conducted in whole animals. Thus, such studies are used qualitatively in the hazard identification to assess whether there is a plausible biologic mechanism for asserting that endocrine disruption is plausible. Because they are *in vitro* assays, measures of *dose* and quantitative use of the information in dose/response assessment is not appropriate. For glyphosate, these studies to not indicate a basis for suggesting that glyphosate is an endocrine disruptor.

Notwithstanding the negative results on endocrine function, the current RfD for glyphosate is based on reproductive effects, as discussed further in Sections 3.1.8 and 3.3. In addition, glyphosate has not undergone an extensive evaluation for its potential to interact or interfere with the estrogen, androgen, or thyroid hormone systems (i.e., assessments on hormone availability, hormone receptor binding or postreceptor processing as recommended by EDSTAC (1998). Thus, the assessment of the potential endocrine effects of glyphosate cannot be overly interpreted.

3.1.9. Reproductive and Teratogenic Effects. Glyphosate has been subject to multi-generation reproduction studies which measure overall effects on reproductive capacity as well as teratology studies which assay for a compounds ability to cause birth defects (Appendix 6).

Signs of teratogenic activity have not been observed in standard assays in both rats (Moxon 1996a; Farmer et al. 2000b; Rodwell et al. 1980a) and rabbits (Moxon 1996b; Rodwell et al. 1980b). Summaries of these studies are given in Appendix 6. No teratogenic effects in soft-tissue were observed in any study at doses of up to 3500 mg/kg/day. The only abnormal developement was delayed bone development (ossification). This was seen in rats at 3500 mg/kg/day (Rodwell et al. 1980a; Farmer et al. 2000b) and rabbits at 300 mg/kg/day (Moxon 1996b). Severe signs of maternal toxicity, including mortality, were observed in rats at 3500 mg/kg/day (Farmer et al. 2000b). Less severe signs of maternal toxicity (diarrhea, reduced fecal output, reduced food intake and body weight) were observed in rabbits at doses of 175 mg/kg/day and higher (Moxon 1996b).

In a multi-generation reproduction study in rats (Schroeder and Hogan 1981), unilateral focal tubular dilation of the kidney was observed in male F_{3b} pups at 30 mg/kg/day but not at 10 mg/kg/day. As discussed in section 3.3, the U.S. EPA has classified 30 mg/kg/day as the LOAEL and has based the RfD for glyphosate on the 10 mg/kg/day NOAEL for this effect. This effect is consistent with the acute systemic toxicity of glyphosate, rather than a specific reproductive effect.

Daruich et al. (2001) assayed effects of glyphosate on enzymatic activity in pregnant rats with a commercial formulation of glyphosate (specified as Herbicygon) that is used in Argentina. Changes in several biochemical parameters were noted but these were accompanied by significant decreases in food and water consumption. Since this study did not use a food and water restricted control, the observed effects cannot be attributed directly to glyphosate.

A 2-year dietary study, in which rats were exposed to 0, 2,000, 8,000 or 20,000 ppm glyphosate in diet, examined morphology of the reproductive organs, mammary glands, and all major endocrine glands, including the testis, ovary, pituitary, and thyroid (Stout and Ruecker, 1990). No treatment-related effects on reproductive organs or endocrine glands were observed at or below the maximally tolerated dose (20,000 ppm in diet) which resulted in decreased weight gain and histopathologic changes in liver, stomach, and eye lens. U.S. EPA (2001) summarized a study in which dogs were exposed to 0, 20, 100, and 500 mg/kg/day *"glyphosate in gelatin*

capsules" for 1 year (Reyna 1985). The summary notes that a decrease in absolute and relative pituitary weight was observed at the 100 and 500 mg/kg/day dose levels.

Subchronic studies, in which mice and rats were exposed to 3,125, 6,250, 12,500, 25,000, or 50,000 ppm glyphosate in the diet, examined morphology of all reproductive organs; mammary glands; and major endocrine glands, including adrenal, ovary, pancreas, parathyroid, pituitary, thymus and thyroid; the study also evaluated sperm counts and morphology and estrous cycle length (NTP, 1992). No treatment-related effects were observed on the morphology of reproductive organs or endocrine glands at or below the maximally tolerated dose (50,000 ppm in diet) which resulted in decreased weight gain in both rats and mice. A statistically significant decrease (20%) in sperm count was observed in male rats exposed to 25,000 or 50,000 ppm. NTP (1992) concluded that there was no evidence of adverse effects on the reproductive system of rats or mice, and summarized the findings as follows:

> *"Measures of sperm density, or the number of sperm/g caudal epididymal tissue, were reduced somewhat in male rats in the 2 highest dose groups (25,000, 50,000 ppm); other spermatozoal measurements were not different from controls in rats or mice. There was a slight lengthening of the estrous cycle in high dose female rats (50,000 ppm), but the biologic significance of these findings, if any, is not known."*

Several other subchronic and chronic studies of glyphosate are noted in Williams et al. (2000), with no mention of treatment-related effects on endocrine glands or reproductive organs; however, the specific tissues that were evaluated are not reported.

Yousef et al. (1995) has reported substantial decreases in libido, ejaculate volume, sperm concentrations, semen initial fructose and semen osmolality as well as increases in abnormal and dead sperm in rabbits after acute exposures to glyphosate. The authors report that all of the effects were statistically significant at $p<0.05$. A serious limitation of this study is that the authors report the doses as proportions of 0.01 and 0.1 of the LD_{50} but do not specify the actual doses. Using a reported rabbit LD_{50} of 3,800 mg/kg (SERA 1996), the doses would correspond to 38 and 380 mg/kg. As discussed by Hastings (1995), the Yousef et al. (1995) study also does not specify the formulation that was used.

The toxicological significance of the observed effects described by Yousef et al. (1995) is clear. As noted above, however, a 3-generation study in rats found no treatment-related effects of glyphosate on mating, fertility, or reproductive parameters at doses of 3, 10, or 30 mg/kg body weight, although changes in kidney morphology were noted at the 30 mg/kg/day dose level (Schroeder and Hogan 1981). In addition and as also summarized above, very high dietary concentrations of glyphosate have not be associated with impaired reproductive performance or signs of damage in testicular tissue.

The basis for the inconsistency between the Yousef et al. (1995) study and all other studies that have assessed the reproductive effects of glyphosate cannot be identified unequivocally. As discussed by Williams et al. (2000), the Yousef et al. (1995) study can be criticized for a number of reporting and experimental design limitations or deficiencies. In addition, it should be noted that the rabbits in the Yousef et al. (1995) study were dosed by gelatin capsules whereas the Schroeder and Hogan (1981) multigeneration study involved dietary exposures. The use of gelatin capsules is a reasonable mode of administration but, like gavage exposures, it results in a high spike in body burden that is not typical or particularly relevant to potential human exposures – other than attempted suicides. On the other hand, dietary exposures, as used in the Schroeder and Hogan (1981) study, result in more gradual and steady exposures over the course of the day that are more comparable and relevant to potential human exposures.

In a subsequent study, Yousef et al. (1996) have demonstrated that glyphosate may reduce sperm motility in the range of 116 µM to about 300 µM in protein free media and 500 µM to about 740 µM in a media with protein. The mechanism of the this effect is not clear but it may be related to the ability of glyphosate to inhibit oxidative phosphorylation. While this *in vitro* study cannot be applied directly to the risk assessment, it is worth noting that the lowest reported effect concentration, 116 µM, corresponds to a concentration of about 19.6 mg/L [116 µMoles/L × 169.07 µg/µMole = 19,612 µg/L], which is in turn about a factor of 10 above the NOAEL used in the dose-response assessment.

Numerous epidemiological studies have examined relationships between pesticide exposures or assumed pesticide exposures in agricultural workers and reproductive outcomes. Very few studies, however, have attempted to characterize exposures, either qualitatively or quantitatively, to specific pesticides (Arbuckle and Sever, 1998). Of those studies that have specifically addressed potential risks from glyphosate exposures, adverse reproductive effects have not been associated with glyphosate exposure.

The Ontario Farm Health Study collected information on pregnancy outcomes and pesticide use among Ontario farm couples. Three retrospective cohort studies of this group (Arbuckle et al. 2001; Curtis et al. 1999; Savitz et al. 1997) have examined relationships between exposures to glyphosate formulations (defined as self-reported participation in mixing and/or spraying operations) and reproductive outcomes. One study analyzed self-reported spontaneous miscarriages of 3,984 pregnancies among 1,898 couples who self-reported exposures to glyphosate formulations within a period beginning two months before pregnancy and ending the month of conception (Savitz et al., 1997). Risk of miscarriage was unrelated to self-reported exposure to glyphosate formulations. A second study of spontaneous abortions among 2,110 women and 3,936 pregnancies disaggregated the herbicide exposures into pre- and post-conception and spontaneous abortions into early- (< 12 wk) and late-term (12-19 wk) abortions (Arbuckle et al., 2001). Spontaneous abortions were not associated with post-conception glyphosate formulation exposure; however, the odds ratio for abortions and post-conception exposure was 1.4 (1.0-2.1), and for late-term abortions was 1.7 (1.0-2.9). The latter odds ratios were not adjusted for maternal age which is a risk factor for spontaneous abortion. When

maternal age was considered in a regression tree analysis, spontaneous abortions were found to be unrelated to glyphosate formulation use. Curtis et al. (1999) examined fecundity among 1,048 farm couples who self-reported exposures to glyphosate formulations within a period beginning 2 months prior to trying conception (to account for time of spermatogenesis) and ending at pregnancy. Fecundity was unrelated to glyphosate exposure.

Larsen et al. (1998a) examined relationships between use of pesticides and semen quality among farmers in Denmark. Participants in the study included 161 farmers who self-reported crop spraying with a variety of pesticides, that included Roundup (7% prevalence of use) and 87 farmers who did not use pesticides. Semen samples were collected at the start of the spraying season and 12-18 weeks after the first spraying. Evaluations included sperm count, morphology, chromatin structure and motility; and serum concentrations of reproductive hormones (testosterone, LH, FSH). Semen quality and reproductive hormone levels were unrelated to pesticide use. In a related study, fecundity was compared among farmers who did or did not participate in pesticide spraying operations (Larsen et al., 1998b). Fecundity was determined from the number of self-reported menstrual cycles or months between discontinuation of birth control and pregnancy. Participants included 450 traditional farmers who reported that they sprayed pesticides, 72 traditional farmers who did not participate in spraying operations, and 94 organic farmers who reported not using pesticides on their crops. Fecundity was unrelated to pesticide use or participation in pesticide spraying operations.

3.1.10. Carcinogenicity and Mutagenicity. Information regarding the mutagenicity and carcinogenicity of glyphosate has been reviewed in detail by U.S. EPA (U.S. EPA/ODW 1992; U.S. EPA/OPP 1993a,b,c), the World Health Organization (WHO 1994) as well as in the open literature (Cox 2002; Williams et al. 2000).

Based on standard animal bioassays for carcinogenic activity *in vivo* (Appendix 5), there is no basis for asserting that glyphosate is likely to pose a substantial risk. The Re-registration Eligibility Decision document on glyphosate (U.S. EPA/OPP 1993a) indicates that glyphosate is classified as Group E: Evidence of non-carcinogenicity for humans. This classification is also indicated in U.S. EPA's most recent publication of tolerances for glyphosate (U.S. EPA/OPP 2002). This is also consistent with the assessment by WHO (1994) and review by (Williams et al. 2000). Cox (2002) has challenged the interpretation of the cancer data but does not provide any reanalyses of the data. Tumors have been observed in some of the chronic toxicity studies (Appendix 3). As discussed in U.S. EPA/ODW (1992), the studies conducted before 1990 were judged by U.S. EPA as insufficient for evaluating the potential carcinogenicity of glyphosate because the observed responses were equivocal or the dose levels were inappropriate (i.e., the highest dose used was not the maximum tolerated dose). U.S. EPA requested the study by Stout and Ruecker (1990) and judged it to be adequate. Although the study indicated increases in some tumor types (pancreatic islet cell adenomas in low dose male rats, hepatocellular adenomas in male rats, and C-cell adenomas of the thyroid males and females), the effects were not dose related. Gold et al. (1997) reports cancer potency estimates of 5.9×10^{-5} to 4.8×10^{-4} $(mg/kg/day)^{-1}$for glyphosate. The potency parameters provided by Gold et al. (1997), however,

are based on experimental data in which there were no statistically significant increases in tumor rates at any dose level.

Roundup has been shown to cause an increase in chromosomal aberrations in a plant (*Allium sp*.) associated with cell abnormalities in spindle fiber (Rank et al. 1993), DNA adduct formation in mice (Reluso et al. 1998) and single strand breaks in mice (Bolognesi et al. 1997). None of the *in vivo* studies using mammalian species or mammalian cell lines have reported mutagenic activity (i.e., NTP 1992, Rank et al. 1993). Two studies (Vyse and Vigfusson 1979, Vigfusson and Vyse 1980) report a significant increase in sister chromatid exchanges in human lymphocytes *in vitro*. The authors of these studies conclude from their results that glyphosate is, at most, slightly mutagenic. In addition, some positive assays in the fruit fly have been reported (Kale et al. 1995; Kaya et al., 2000) as well as positive results in lymphocyte cultures (Lioi et al. 1998a; Lioi et al. 1998b). Nonetheless, most of the other screening studies for mutagenicity are negative (Appendix 7). Based on the weight of evidence of all available studies, U.S. EPA (U.S. EPA/ODW 1992; U.S. EPA/OPP 1993a; U.S. EPA/OPP 2002) concluded that glyphosate is not mutagenic.

The human data on the potential carcinogenic activity of glyphosate is sparse. Hardell and Erikson (1999a) reported an increased cancer risk of non-Hodgkin lymphoma (NHL) in individuals in Sweden who have a history of exposure to glyphosate. The increased risk was not statistically significant. Acquavella et al. (1999) have criticized the methodology used by Hardell and Erikson (1999a). As part of the response to this criticism, Hardell and Erikson (1999b) reported that an additional analysis of their data pooled with data from another study demonstrated a statistically significant increase in NHL associated with exposures to glyphosate. Details of the pooled analysis are not provided by Hardell and Erikson (1999b).

These results are of concern to the Forest Service and the Forest Service requested that the U.S. EPA review these studies (Rubin 2000). The U.S. EPA (Tompkins 2000) replied that:

> *The Office of Pesticides Programs Health Effects Division has reviewed the journal article entitled "A Case-Control Study of Non-Hodgkin Lymphoma and Exposure to Pesticides" and concluded that the study does not change EPA's risk assessment for the currently registered uses of glyphosate.*

This issue is also addressed in the most recent U.S. EPA/OPP (2002) assessment:

> *This type of epidemiologic evaluation does not establish a definitive link to cancer. Furthermore, this information has limitations because it is based solely on unverified recollection of exposure to glyphosate-based herbicides.*

Given the marginal mutagenic activity of glyphosate and the failure of several chronic feeding studies to demonstrate a dose-response relationship for carcinogenicity and the limitations in the available epidemiology study, the Group E classification given by the U.S. EPA/OPP (1993a,

2002) appears to be reasonable. As with any compound that has been studied for a long period of time and tested in a large number of different systems, some equivocal evidence of carcinogenic potential is apparent and may remain a cause of concern, at least in terms of risk perception (e.g., Cox 2002). While these concerns are understandable, there is no compelling basis for challenging the position taken by the U.S. EPA and no quantitative risk assessment for cancer is conducted as part of the current analysis.

3.1.11. Irritation and Sensitization. Glyphosate formulations used by the Forest Service are classified as either non-irritating or only slightly irritating to the skin and eyes in standard assays required for product registration. Based on several eye and skin irritation studies submitted to the U.S. EPA as part of the registration process, the U.S. EPA/OPP (1993c) classifies glyphosate as mildly irritating to the eyes (Category III) and slightly irritating to the skin (Category IV). Literature on the irritant effects of unformulated glyphosate is summarized by Williams et al. (2000). The free acid of glyphosate is severely irritating to the eyes but the IPA salt of glyphosate, the form that is in all formulations used by the Forest Service, is nonirritating to the skin and eyes. As discussed in Section 3.1.14, POEA and other surfactants used in glyphosate formulations may be severely irritating to the eyes, skin, and other mucosal surfaces such as the gastrointestinal tract and lungs.

Based on a total of 1513 calls to a poison control center reporting ocular effects associated with the use of Roundup, 21% were associated with no injury, 70% with transient minor injury, 2% with some temporary injury. One case was classified as a major effect which took more than 2 weeks to resolve. This case, however, involved an individual exposed to a dilute solution of Roundup while wearing extended wear contact lenses. In addition, symptoms were apparent in both the exposed and unexposed eye. Thus, it is unclear if the ocular signs observed in this individual were attributable to the Roundup exposure. For all patients, the most frequently noted symptoms included blurred vision, a stinging or burning sensation, lacrimation. No cases of permanent damage were reported. (Acquavella et al. 1999).

3.1.12. Systemic Toxic Effects from Dermal Exposures. As discussed in section 3.1.3, glyphosate is poorly absorbed from the skin and thus systemic toxic effects from dermal exposure are likely to be less than those from oral exposure. In terms of acute exposures, however, there is relatively little apparent difference in the oral and dermal toxicity of glyphosate because glyphosate is relatively non-toxic by either route. For example, the acute oral toxicity of glyphosate expressed at the LD_{50} in rats is listed by U.S. EPA/OPP (1993c) as >4320 mg/kg. Based on this LD_{50}, glyphosate is classified as Category III for oral toxicity. Similarly, the acute dermal toxicity of glyphosate expressed at the LD_{50} in rabbits is listed by U.S. EPA/OPP (1993c) as >2000 mg/kg and is also classified as Category III. In both of these LD_{50} values, the "greater than" designation (>) indicates that less than 50% of the animals died at the maximum dose tested, in this example 4320 mg/kg for oral exposure and 2000 mg/kg for dermal exposure. The difference in these doses is an artifact of the highest doses used in the toxicity studies and does not suggest that glyphosate is more toxic by the dermal route than by the oral route of exposure.

As indicated in Appendix 3, all glyphosate formulations have dermal LD_{50} values in rats or rabbits that are >2000 mg/kg and most are >5000 mg/kg.

A more meaningful assessment of the dermal toxicity of glyphosate can be made from repeated dose 21-day studies. The U.S. EPA RED for glyphosate (U.S. EPA/OPP 1993c) cites a 1982 study (MRID 00098460) in which glyphosate was applied to the intact or abraded skin of rabbits at doses of 10, 1000 or 5000 mg/kg/day, five days per week, for three weeks. The only treatment related effects included slight irritation of the abraded skin (a local and not a systemic effect), decreased food consumption, and decreased serum lactic dehydrogenase activity at 5000 mg/kg/day. In a more recent but similarly designed study in rats (Pinto 1996), dermal doses of 250, 500, 1000 mg/kg/day caused no effects on body weight, food consumption, hematology, clinical chemistry, or organ weights and there were no signs of dermal irritation or pathologic changes in any tissue.

3.1.13. Inhalation Exposures [including Brown-and-Burn Operations]. Some volatile pesticides may present practical risks in normal applications but inhalation is not an important route of exposure for most low volatile herbicides (Dowling and Seiber 2002). Because of the low volatility rate for technical grade glyphosate (Tria 1994) and the available inhalation toxicity studies on a number of glyphosate formulations (Appendix 3), the U.S. EPA waived the requirement of an acute inhalation study for technical grade glyphosate (U.S. EPA 1993b, p. 10). The acute inhalation LC_{50} value of the isopropylamine salt glyphosate is >6.37 mg/L – i.e., no mortality in any of five rats of each sex exposed to this concentration for four hours (Mcguirk 1999a). As indicated in Appendix 3, the short-term (typically 4 hours) inhalation LC_{50} values for various glyphosate formulations range from >1.3 mg/L to >7.3 mg/L. The lowest LC_{50} value that is not designated with a greater than (>) symbol is 2.6 mg/L, the reported LC_{50} value for Credit, Honcho, Mirage, Roundup Original, and Roundup ProDry. This appears to reference the acute inhalation study by Dudek and Cortner (1998) in which 20% mortality (1/5 rats of each sex) was observed after 4-hour inhalation exposures to MON 77063 at a concentration of 2.6 mg/L.

A case of *"Roundup Pneumonitis"* has recently been reported by Pushnoy et al. (1998). This involved an individual with shortness of breath, respiratory irritation, and dizziness. Exposure to Roundup had involved disassembling sprayer equipment that had been used in the application of Roundup. As discussed by Goldstein et al. (1999), the plausibility of association between Roundup exposure and the development of these symptoms is tenuous given that this individual may have been exposed to diesel fuel aerosols, chlorinated solvents, smoking, or welding fumes. Jamison et al. (1986) has suggested a potential effect associated with glyphosate after inhalation exposures to flax dust. In this study, human volunteers were exposed to two different types of flax dust: one derived from glyphosate treated flax and the other derived from flax not treated with glyphosate. The glyphosate treated flax consistently caused a greater depression in respiratory function than the dust from flax not treated with glyphosate. As noted by the authors, the glyphosate was applied to the flax six weeks prior to testing and it is likely that there was very little glyphosate residue on the flax. The authors also note that particles size distribution of the two dusts used in the study was not significantly different. Based on particle size distribution data

presented in this publication (Jamison et al. 1986, Table 1, p. 810), however, the glyphosate treated flax dust contained about 25% more particles in the 0-1μ range. Particles in this range typically penetrate to the alveolar sacs (Razman and Klassen 1996). Thus, even though the distributions in the particle sizes for the two forms of flax may not be statistically significantly different, the higher concentration of respirable particles in the glyphosate treated flax may be contributed to the apparent difference in biological activity.

Although inhalation of glyphosate is not a typical route of exposure, it may occur during brown-and-burn operations. Brown-and-burn operations are conducted 30 to 180 days after treatment with the herbicide. As discussed by Bush et al. (1987), the combustion of several herbicides does not result in exposure to toxic air concentrations of herbicides. These investigators, however, did not look specifically at glyphosate and did not take toxic combustion products into consideration.

The thermal degradation of glyphosate has been studied by Flora and Simon (1981). During combustion at temperatures ranging from 200°C to 240°C, glyphosate forms a polycondensate. This range of temperatures is typical of slow combustion but is far less than the 800–1,000°C temperatures of an actively burning wood stove or fireplace (Bush et al. 1987). No information is available regarding the toxicological properties of the combustion product identified by Flora and Simon (1981) or other combustion products of glyphosate.

3.1.14. Role of Surfactant. As summarized in Appendix 1, various glyphosate formulations contain a polyethoxylated tallow amine (POEA) surfactant at a level of up to about 20% (200 g/L) and Roundup Pro contains a phosphate ester neutralized polyethoxylated tallow amine surfactant at a level of 14.5% (145 g/L). Tallow contains a variety of fatty acids including oleic (37–43%), palmitic (24–32%), stearic (20–25%), myristic (3–6%), and linoleic (2–3%) acids as well as small amounts of cholesterol, arachidonic, elaidic, and vaccenic acids (Budavari 1989). The other formulations of glyphosate recommend the use of a surfactant to improve the efficacy of glyphosate. There is an extensive amount of literature on glyphosate indicating that the addition of surfactants can greatly enhance phytotoxicity of herbicides (De Ruiter and Meinen 1996, De Ruiter and Meinen 1998; Denis and Delrot 1997; Laerke 1995; Miller et al. 1998; O'Sullivan et al. 1981; Riechers et al. 1995; Sundaram 1990; Sundaram et al. 1996).

While surfactants are typically classified as "inert" ingredients in herbicides, these compounds are not toxicologically inert. It is beyond the scope of this risk assessment to specifically review all of the information available on surfactants. Much of the available information on the toxicity of surfactants used with glyphosate have been summarized in SERA (1997) and more recent studies (Chang et al. 1999; Garry et al. 1999; Lin and Garry 2000; Reluso et al. 1998) reenforce the conclusion reached in SERA (1997) that some surfactants may be more toxic than the herbicides with which they are used. Although surfactants may play a substantial role in the interpretation of a large number of suicides and attempted suicides involving the ingestion of glyphosate formulations, primarily Roundup, the acute mammalian toxicity of different glyphosate formulations do not appear to differ substantially (Appendix 3a and 3b). This is in contrast to the

available data on the toxicity of various formulations to aquatic species, as detailed in Section 4.1.3 and summarized in Appendix 3c.

While a number of surfactants may be used in conjunction with glyphosate, the most important to this risk assessment is the POEA or phosphate ester neutralized POEA. The POEA surfactant was originally used with glyphosate in Roundup formulations. The phosphate ester neutralized POEA is the surfactant currently used in Roundup Pro (Appendix 1). By far the most relevant study on the toxicity of the POEA surfactant used in Roundup involves a series of teratology studies in rats using glyphosate (98.7% purity), the POEA surfactant used in many glyphosate formulations, and a phosphate ester neutralized POEA (Farmer et al. 2000b). In this study, groups of pregnant female rats were dosed on days 6 through 19 of gestation with glyphosate at 300, 1000, or 3500 mg/kg/day, POEA at 15, 100, and 300 mg/kg/day, or the neutralized POEA at 15, 50, or 150 mg/kg/day. For glyphosate, severe maternal poisoning was observed at 3500 mg/kg/day and this was associated with reduced fetal body weights and sternal ossification, as well as fetal death. The NOAEL for both maternal and fetal toxicity was 1000 mg glyphosate/kg/day. The surfactants also caused mortality in dams at the highest doses tested: 300 mg/kg/day for POEA and 150 mg/kg/day for neutralized POEA. In addition, a dose of 100 mg POEA/kg/day caused mild clinical signs of toxicity and decreased food consumption in dams. No fetotoxic effects were reported at any dose level. Thus, in repeated dosing, the NOAEL for glyphosate of 1000 mg/kg/day was substantially higher than the NOAEL for either POEA (15 mg/kg/day) or neutralized POEA (50 mg/kg/day).

The potential role of the surfactant in the toxicity of Roundup was first emphasized by the Sawada et al. (1988) in their analysis of poisoning cases in humans. They indicate that the acute LD_{50} of POEA is *"less than one-third that of roundup and its active ingredient"* and reference this statement to a chapter by Atkinson (1985) in *The Herbicide Glyphosate* (Grossbard and Atkinson 1985). The Sawada reference has been quoted in turn by Martinez and Brown (1991) as indicating that *"... POEA by itself has a LD_{50} of 1-2 g/kg"*. Atkinson (1985) does cite an LD_{50} of 4.3 g/kg for glyphosate [a rounding of the rat oral LD_{50} of 4,320 mg/kg reported in U.S. EPA (1986a) and earlier U.S. EPA reports] and indicates that this is about the same as the acute oral LD_{50} for isopropylamine salt in rats, 4.9 g/kg. Atkinson (1985), however, does not give an acute oral LD_{50} for POEA or any other surfactant. Although there is evidence that POEA is more toxic than glyphosate to aquatic species (Section 4), the acute oral toxicity of Roundup (glyphosate and surfactant, LD_{50} in rats of 5400 mg/kg) is almost the same as that of glyphosate (LD_{50} in rats of 5,600 mg/kg).

Based on these LD_{50} values, the LD_{50} of the surfactant can be estimated under the assumption of dose addition (Finney 1971). This assumption requires that the components in the mixture have the same mode of action. This assumption is not certain, but it is consistent with the observation by Talbot et al. (1991) that both glyphosate and POEA may exert some of their acute toxicity via irritation of biological membranes. The assumption of dose addition is also not interactive—that is, it assumes that the components in the mixture do not influence the toxicity of one another.

This assumption is conservative, compared with other non-interactive models of joint action (Mumtaz et al. 1994).

For some uniform measure of toxicity (ζ) (e.g., LD_{50}), the toxicity of any mixture (ζ_M) is predicted, under the assumption of dose addition, by:

$$\zeta_M = \frac{\zeta_1}{(\pi_1 + \rho\pi_2)} \quad \textbf{(3-1)}$$

where ζ_1 is the effective exposure (e.g., LD_{50} or LD_{95} values) for one compound, π_1 and π_2 are the proportions of each compound in the mixture, and ρ is the potency defined as $\zeta_1 \div \zeta_2$. Furthermore, given the toxicity of a defined mixture (ζ_M) and one of the components (ζ_1), the potency of the second component can be calculated as:

$$\rho = \frac{(\zeta_1/\zeta_M) - \pi_1}{\pi_2} \quad \textbf{(3-2)}$$

Here, the term *defined mixture* indicates that π_1 and π_2 are known. From this relationship, the effective exposure (i.e., toxic potency) of the second component (ζ_2) can be estimated as:

$$\zeta_2 = \frac{\zeta_1}{\rho} \quad \textbf{(3-3)}$$

Using the nominal LD_{50} for Roundup of 5,400 mg/kg, a π_1 of 0.356 for glyphosate (356 g/L), and π_2 of 0.15 for POEA (150 g/L), the estimated LD_{50} for POEA would be almost exactly 1,200 mg/kg, consistent with dose additivity. This approach, as detailed below, would be a misapplication of the above equations.

To estimate the toxicity of POEA from the Roundup (glyphosate+POEA) LD_{50}, this LD_{50} must be converted from units of glyphosate to total mixture mass (glyphosate+POEA). In other words, an LD_{50} of 5,400 mg glyphosate/kg bw is equivalent to a combined mass (glyphosate and POEA) of about 7,560 mg [1.4·5,400 mg], since the ratio of POEA to glyphosate is approximately 0.4 [150 g/L ÷ 356 g/L]. Similarly, the correct π_1 for glyphosate is about 0.7 [356 ÷ (150+356)] and the correct π_2 for POEA is about 0.3 [150 ÷ (150+356)]. Using this approach, the potency of POEA relative to glyphosate is about 0.14 and the estimated oral LD_{50} in rats is for POEA is about 40,000 mg/kg [5,600 mg/kg ÷ 0.14]. This estimate is consistent with the published results of Martinez, summarized in the following paragraph, in which no mortality was noted in rats after oral doses of up to 14,286 mg/kg POEA.

Martinez and coworkers (Martinez and Brown 1991; Martinez et al. 1990) conducted a series of experiments specifically designed to assess the role of the surfactant in the acute toxicity of Roundup. In these studies, compounds were administered to groups of five rats either by gavage [direct instillation into the stomach] or direct installation into the trachea. Oral exposures to

Roundup at doses of 1, 3, and 5 mL/animal caused 0%, 40%, and 100% mortality, respectively, over a 24-hour observation period. Taking an average body weight of 350 g/rat reported by Martinez and Brown (1991), the mid-dose level corresponds to approximately 3,050 mg/kg [3 mL · 356 mg a.e./mL ÷ 0.350 kg], only somewhat less than and consistent with the reported LD_{50} for Roundup of 5,400 mg/kg (Monsanto Co. 1982a,b). POEA, administered by gavage, caused no deaths at doses of 1, 3, and 5 mL/animal. Since ethoxylated surfactants generally have a density of about 1g/mL (Kosswig 1994, p. 789), the doses of POEA correspond to approximately 2,857, 8,571, and 14,286 mg/kg. The low acute oral toxicity of POEA is consistent with the similarity between the acute oral toxicity of glyphosate and Roundup, discussed above.

In the earlier study by Martinez et al. (1990), an oral dose with Roundup RTU or Roundup concentrate caused delayed (6 hours) pulmonary edema, consistent with clinical observations in humans, as summarized above. The authors concluded that *"... delayed pulmonary edema combined with blood stained weeping from the nose, diarrhea, distended GI tract, and ascites is in excellent agreement with ... The clinical picture of ... hypovolemic shock"*, as described by Sawada et al. (1988). In the individuals involved in the Taiwan studies of glyphosate poisoning, however, hematocrit, blood urea nitrogen, and central venous pressure determinations were not consistent with hypovolemia.

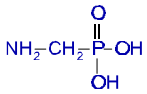
Intratracheal instillations in rats resulted in much more toxic effects at much lower dose levels. Roundup at doses of 0.1, 0.2, and 0.4 mg/animal caused 80% mortality at the low dose and 100% mortality at the two higher doses as well as an increase in lung weights. POEA, at the same dose levels, caused 20%, 70%, and 100% mortality as well as increases in lung weights, although the increases were less than those observed with Roundup (Martinez and Brown 1991, Table 1, p. 44). Pathological examinations indicated that both Roundup, and to a lesser extent POEA, cause hemorrhaging and congestion of the lungs after intratracheal instillations. Martinez and Brown (1991) conclude that POEA potentiates the pulmonary toxicity of glyphosate. Since, however, these investigators did not test glyphosate alone, the basis for their conclusion is not clear.

Adam et al. (1997) have studied the effects of glyphosate, POEA, mixtures of glyphosate and POAE, as well as a commercial formulation of Roundup (41% glyphosate IPA and 18% POEA) in rats after gavage (oral) and intratracheal installations (i.e., directly to the lungs). Respiratory effects and pulmonary damage were more severe in the rats dosed with any of the POEA containing treatments than with glyphosate alone. Similarly, the gastrointestinal effects of the POEA containing treatments were uniformly more severe than seen in rats treated with glyphosate alone. Tai et al. (1990) reported that injections of Roundup in rats led to cardiac depression caused solely by POEA and partially antagonized by glyphosate.

Based on drinking water studies of both glyphosate and Roundup (glyphosate with POEA), the surfactant does not affect the rapid elimination rate of glyphosate in mammals (NTP 1992).

3.1.15. Impurities and Metabolites.

3.1.15.1. Aminomethylphosphonate (AMPA) **--** The primary metabolite of glyphosate in mammals and other organisms is aminomethylphosphonate (AMPA):



AMPA

which is formed together with glyoxylate (HCO-COOH).

In mammals, only very small amounts of AMPA, less than 1% of the absorbed dose, are formed (U.S. EPA/ODW 1992, Brewster et al. 1991). In addition, AMPA is an environmental metabolite of glyphosate. This is to say that AMPA is formed in environmental media such as soil and water as a breakdown product of glyphosate. For example, Mao (1996) found that AMPA reached approximately 21.2% of applied dose of glyphosate by day 181 under anaerobic conditions in pond water. In addition, glyphosate is readily metabolized by soil bacteria with AMPA as a major metabolite (Dick and Quinn 1995a; Dick and Quinn 1995b). It should be noted that AMPA is also formed in the degradation of amino(trimethylenephosphonic) acid, a compound used as a scale inhibitor and additive in washing agents (Schweinsberg et al. 1999)

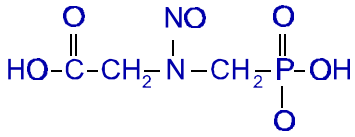
These two differing sources of exposure – i.e., as an endogenous metabolite in mammals and as an environmental metabolite – must be handled differently in this risk assessment. The approach of examining the potential importance of the metabolism of a chemical agent by a mammal is common in the risk assessment of xenobiotics, which generally involve the formation of one or more mammalian metabolites, some of which may be more toxic than the parent compound. Usually, the parent compound is selected as the agent of concern because the toxicology studies and monitoring studies provide information about the agent. Thus, the dose metameter for the risk assessment is most clearly expressed in terms of the parent compound. In cases where a toxic metabolite is known to be handled differently by humans, this simple approach may be modified. There is no indication that such a modification is necessary for glyphosate. Thus, in terms of assessing direct exposures to technical grade glyphosate, the inherent exposures to AMPA as a metabolite are encompassed by the existing toxicity data on glyphosate.

This approach does not, however, encompass concern for exposures to AMPA as an environmental metabolite. As noted above, about 20% of applied dose of glyphosate may be found in water as AMPA after about six months. The toxicity and environmental fate of AMPA has been reviewed recently by WHO (1997), Cox (2002), and Williams et al. (2000). In addition, the U.S. EPA/OPP (2002) has reviewed this information and assessed the potential consequences of exposures to AMPA as an environmental degradate. Based on this review, the U.S. EPA/OPP (2002) concluded:

> *The nature of the residue in plants and animals is adequately understood and consists of the parent, glyphosate. The Agency has decided that only glyphosate parent is to be regulated in plant and animal commodities and that the major metabolite, AMPA (aminomethylphosphonic acid) is not of toxicological concern regardless of its levels in food.* – U.S. EPA/OPP (2002, p. 17725)

While Cox (2002) has cited concerns for AMPA based on a limited subset of the literature on this compound, no formal dose-response and exposure assessment is presented that would argue against the position of U.S. EPA/OPP (2002). Further, the position taken in U.S. EPA/OPP (2002) is supported by the conclusions of the more extensive reviews by both WHO (1997) and Williams et al. (2002). Although data are sufficient to conduct a separate risk assessment on AMPA (e.g., Holson 1991a,b; Kier and Stegeman 1993; Stout 1991; Tompkins 1991), this would not be a judicious expenditure of limited resources on the part of the Forest Service. The position taken by U.S. EPA/OPP (2002) appears to be reasonable and is well-supported. Consequently, in this risk assessment, AMPA is not quantitatively considered in the dose-response and exposure assessments.

3.1.15.2. N-nitrosoglyphosate (NNG) -- Glyphosate also contains N-nitrosoglyphosate (NNG) as an impurity:



NNG

Nitroso compounds are characterized by the *N=O* group, a double bond between a nitrogen and oxygen. Nitrosamines are nitroso compounds in which the nitroso group is attached to a nitrogen atom, *N-N=O*. NNG contains the nitrosoamine group. Certain groups of nitrosoamines have served as model compounds in some of the classical studies on chemical carcinogenicity. While there is a general concern for the carcinogenic potential of nitroso compounds, the contribution of specific nitroso compounds to carcinogenic risk is difficult to quantify (Mirvish 1995).

The EPA re-registration document (RED) for glyphosate states:

> *Technical grade glyphosate contains N-nitrosoglyphosate (NNG) as a contaminant. Carcinogenicity testing of nitroso contaminants is normally required only in those cases in which the level of nitroso compounds exceeds 1.0 ppm. Analyses showed that greater than 92% of the individual technical glyphosate samples contained less than 1.0 ppm NNG. The Agency concluded that the NNG content of glyphosate was not toxicologically significant.*

As part of the conduct of this risk assessment, data available to U.S. EPA for RED as well as the more recent data on the levels of *N-nitrosoglyphosate* and related compounds has been reviewed (Bernard 2002; Hirsch and Augustin 1987). This information is classified as trade secret under FIFRA and cannot be detailed in this risk assessment. Nonetheless, no information has been encountered in the CBI files or in the open literature that contradicts the above assessment in the RED. In addition, none of the recent reviews on the toxicity of glyphosate cite contamination with *N-nitrosoglyphosate (NNG)* as a concern (Cox 2002; WHO 1994; Williams 2000). Consequently, as with AMPA, a detailed dose-response and exposure assessment for NNG does not appear to be justified with in this risk assessment or as a separate assessment.

3.1.15.3. 1,4-Dioxane – 1,4-Dioxane, is a contaminant in POEA. U.S. EPA (U.S. EPA/IRIS 1992) considers dioxane to be a carcinogen, Class B2: Probable human carcinogen and has derived a cancer potency factor (referred to by U.S. EPA as a slope factor) of 0.011 $(mg/kg/day)^{-1}$. This assessment has been reviewed by and is in concordance with the analysis by the Agency for Toxic Substances and Disease Registry (DeRosa et al. 1996). Dioxane is present in Roundup at a level of approximately 0.03% (Monsanto Co. 1990) or 300 mg/L (300 ppm). This is about a factor of 0.00084 less than the level of glyphosate in Roundup [300 mg dioxane/L in Roundup ÷ 356,000 mg glyphosate/L in Roundup].

In a previous Forest Service risk assessment on glyphosate (USDA 1989a,b,c), it was demonstrated that the upper limit of risk associated with contamination was extremely low – e.g., $<1 \cdot 10^{-7}$ (Borrecco and Neisess 1991). The cancer potency factor used in this risk assessment was 0.0076 $(mg/kg/day)^{-1}$, almost the same as the value currently recommended by U.S. EPA (i.e., both round to 0.01). Borrecco and Neisess (1991) derived toxicity based criteria for 1,4-dioxane and use the information to calculate margins of safety for exposure to 1,4-dioxane. According to the available toxicity data, dioxane does not present unique toxic effects; therefore, its toxicity, except for cancer) is likely to be encompassed by the available toxicity data on Roundup.

3.2. EXPOSURE ASSESSMENT

3.2.1. Overview. Exposure assessments are developed for both workers and members of the general public. Two types of work exposure assessments are considered: general and accidental/incidental. The term *general* exposure assessment is used to designate those exposures that involve estimates of absorbed dose based on the handling of a specified amount of a chemical during specific types of applications. The accidental/incidental exposure scenarios involve specific types of events that could occur during any type of application. For general exposures in workers, exposure rates are expressed in units of mg of absorbed dose per kilogram of body weight per pound of chemical handled. For glyphosate, there are several worker exposure studies involving backpack applications that can be used to assess the quality general estimates used in many Forest Service risk assessments. These studies indicate that these general methods may be extremely conservative. Nonetheless, for this risk assessment, the standard worker exposure rates are used, recognizing that the upper range of exposures may overestimate risk. This conservative approach has little impact on the interpretation of risk because none of the worker exposures exceed a hazard quotient of unity. Central estimates of worker exposures span a very narrow range from 0.026 mg/kg/day to about 0.045 mg/kg/day. The upper range of exposures for the different application methods are about a factor of 10 higher, spanning a range from about 0.1 mg/kg/day to 0.3 mg/kg/day.

Under normal circumstances, members of the general public should not be exposed to substantial levels of glyphosate as a result of Forest Service activities. 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 highly conservative scenarios are developed for this risk assessment. 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. Most acute accidental exposure scenarios for members of the general public are less than or similar to the general exposure scenarios in workers. The major exception is the scenario for an accidental spill of 200 gallons of a field solution into a small pond. This leads to modeled estimates of exposure in the range of 0.3 to about 4 mg/kg/day. This is an extraordinarily extreme and conservative scenario that is used in all Forest Service risk assessments. Most longer term estimates of exposure for members of the general public are much lower than exposure estimates for workers. The one exception involves the longer term consumption of contaminated fruit, which leads to time-weighted average estimated doses of 0.003 to 0.08 mg/kg/day.

3.2.2. Workers. A summary of the exposure assessments for workers is presented in Table 3-1. Two types of exposure assessments are considered: general and accidental/incidental. The term *general* exposure assessment is used to designate those exposures that involve estimates of absorbed dose based on the handling of a specified amount of a chemical during specific types of applications. The accidental/incidental exposure scenarios involve specific types of events that could occur during any type of application. Details regarding all of these exposure assessments are presented in the worksheets that accompany this risk assessment, as indicated in Table 3-1. These exposure assessments as well as other similar assessments for the general public (see Section 3.2.3) are based on the typical application rate of 2 lbs a.e./acre (see Section 2). The consequences of using different application rates in the range considered by the Forest Service are discussed further in the risk characterization (see Section 3.4).

3.2.2.1. General Exposures – As described in SERA (2001a), 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 rates generally used for each of these application methods is summarized in Table 3-2. As described in SERA (2001a), 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).

As detailed in Section 2, the most common method of application for glyphosate in Forest Service programs is backpack-applied directed foliar sprays. As indicated in Table 3-2, the default rates derived in SERA (2001a) for this method of application is 0.003 mg/kg bw per lb applied with a range of 0.0003 to 0.01 mg/kg bw per lb applied. For glyphosate, there are several worker exposure studies involving backpack applications that can be used to assess the quality of these values (Edmiston et al. 1995; Jauhianen et al. 1991; Lavy et al. 1992; Machado-Neto et al. 2000; Middendorf 1993; and Schneider et al. 1999). Three of these studies (Edmiston et al. 1995; Machado-Neto et al. 2000; Schneider et al. 1999) provide only deposition data and cannot be used directly to assess the use of the standard exposure rates summarized in Table 3-2. The other three studies (Jauhianen et al. 1991;Lavy et al. 1992; Middendorf 1993) involved backpack applications with both biomonitoring – i.e., urinary analysis – as well as deposition data as measures of exposure and are thus most relevant to the assessment of the general exposure values summarized in Table 3-2.

In the study by Jauhiainen et al. (1991), biological monitoring was conducted on five workers applying Roundup. Each worker handled an average of 9.8 L of an 8% solution of Roundup (360 g a.i./L or 270 g a.e/L). Thus, the amount of glyphosate acid handled each day was approximately 0.211 kg [9.8 L × 0.08 × 0.270 kg/L] (Jauhiainen et al. 1991, p. 62, column one, top of page) or about 0.5 lbs. Urine samples [not total daily urine] were collected at the end of each work day for 1 week during the application period, and one sample was taken 3 weeks after the applications. The urine samples were assayed for glyphosate using gas

chromatography/electron capture with a limit of detection of 0.1 ng/µL or 0.1 mg/mL. No glyphosate was detected in any of the urine samples using this method.

One urine sample was assayed for glyphosate by gas chromatography/mass spectroscopy (GC/MS) and glyphosate was detected at a level of 0.085 ng/µL, equivalent to 0.085 µg/mL. Assuming that this urine sample was representative and using the default body weight of 70 kg and urinary output of 2000 mL/day (Worksheet A-02), the absorbed dose would be 0.17 mg or 170 µg [0.085 µg/mL × 2,000 mL] or 0.0024 mg/kg bw [0.17 mg ÷ 70 kg]. The corresponding exposure rate would be 0.0048 mg/kg bw per lb a.e. applied [0.0024 mg/kg bw ÷ 0.5 lb a.e.]. This value is very similar to the central estimate of 0.003 mg/kg bw per lb applied that is generally used for directed foliar applications (Table 3-2).

As with the study by Jauhianen et al. (1991), the Lavy et al. (1992) study involved applications of Roundup. Nursery workers applied Roundup to small weeds in a nursery bed by placing a 290 mL (2.5x3.5 cm) cylindrical metal shield surrounding the spray nozzle over the weed—to protect adjacent conifer seedlings—and then spraying the weeds with Roundup. Biological monitoring consisted of 5-day complete urine collections. In a total of 355 urine samples, no glyphosate was detected (limit of detection = 0.01 µg/mL). Assuming that the concentration of glyphosate in the urine was just below the limit of detection and assuming a urinary output of 2,000 mL (Worksheet A-02), the total absorbed dose would be 20 µg or 0.02 mg. The most exposed individual in this study weighed 63.5 kg and handled, on average, 0.54 kg [1.18 lbs] of glyphosate per day. Thus, the maximum absorbed dose of 0.02 mg corresponds to 0.0003 mg/kg bw [0.02 mg ÷ 63.5 kg] and 0.00025 mg/kg bw per lb applied [0.0003 mg/kg ÷ 1.18 lbs]. This is modestly below the lower range of the value of 0.0003 mg/kg bw per lb applied is generally used for directed foliar applications (Table 3-2). Based on passive monitoring, estimated exposure rates were about 1.3×10^{-3} (2.6×10^{-4} to 1.27×10^{-2}) mg/kg bw per lb applied. This central estimate and range is virtually identical to the values for directed foliar applications given in Table 3-2.

The study by Middendorf (1993) also involved backpack (directed foliar) applications of Roundup, albeit in a more dilute mixture (2.3%). Middendorf (1993) provides data (urinary excretion, lbs applied, body weight, and deposition) on 15 workers at three different application sites. The average exposure rate for all workers was approximately 0.00032 mg/kg bw per lb applied with a range of 0.00013 to 0.001 mg/kg bw per lb applied. The central estimate from the Middendorf (1993) study is virtually identical to the lower range of 0.0003 mg/kg bw per lb typically used for directed foliar applications and the upper range noted in the Middendorf (1993) study is somewhat below the central estimate of 0.003 mg/kg bw given in Table 3-2.

The three worker studies (Jauhianen et al. 1991; Lavy et al. 1992; Middendorf 1993) that provide biomonitoring data sufficient to estimate absorbed doses in workers support the use of the exposure rates summarized in Table 3-2. If anything, the upper range of exposure – i.e., 0.01 mg/kg bw per lb applied – is likely to overestimate exposure. None of the estimates based on biomonitoring approach this rate. Nonetheless, for this risk assessment, the standard worker exposure rates are used, recognizing that the upper range of exposures may be extremely

conservative. As discussed further in Section 3.4 (Risk Characterization), this conservative approach has little impact on the interpretation of risk because none of the worker exposures exceed a hazard quotient of unity.

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 can be regarded as conservative. In the absence of any published or otherwise documented work practice statistics to support the use of a lower limit, this conservative approach is used.

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.

As detailed in worksheets C01a (directed foliar), C01b (broadcast foliar), and C01c (aerial), 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 ranges for the amounts handled per day are calculated as the product of the range of acres treated per day and the application rate. Similarly, the central estimate of the daily absorbed dose is calculated as the product of the central estimate of the exposure rate and the central estimate of the amount handled per day. The ranges of the daily absorbed dose are calculated as the range of exposure rates and the ranges for the amounts handled per day. The lower and upper limits are similarly calculated using the lower and upper ranges of the amount handled, acres treated per day, and worker exposure rate.

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.

Some glyphosate formulations can cause irritant effects in 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 2001a). 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. As specified in Table 3-2, the details of these exposure estimates are presented in the worksheets appended to this risk assessment.

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 wearing 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, the experimental dermal permeability coefficient (Kp) for glyphosate is not used in this risk assessment because of the differences in the underlying models used for the exposure assessment

(no lag period) and the model used to estimate the experimental Kp that included a lag period. As further discussed in Section 3.1.3, this is the more conservative approach.

Exposure scenarios involving chemical spills on to 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. As summarized in Section 3.1.3, the first-order dermal absorption rates are taken from the study by Wester et al. (1991): an average value of 4.1×10^{-4} $hour^{-1}$ with a range of 1.3×10^{-4} to 1.0×10^{-3} $hour^{-1}$. These values are included in Worksheet B05 rather than the values calculated in Worksheet B03, which are based on molecular weight and the $K_{o/w}$ for glyphosate.

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 taken from SERA (2000).

3.2.3. General Public.

3.2.3.1. General Considerations – Under normal circumstances, members of the general public should not be exposed to substantial levels of glyphosate as a result of Forest Service activities. 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 highly conservative scenarios are developed for this risk assessment.

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 Table 3-3, and the details regarding the assumptions and calculations involved in these exposure assessments are provided in worksheets D01-D09. The remainder of this section focuses on a qualitative description 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 (see 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. As with the similar worker exposure scenarios, the first-order absorption dermal absorption rates are taken from the study by Wester et al. (1991).

For direct spray scenarios, it is assumed that during a ground application, a naked child is sprayed directly with glyphosate. The scenario also assumes that the child is completely covered (that is, 100% of the surface area of the body is exposed), which makes this an extremely conservative exposure scenario that is likely to represent the 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. These assumptions are detailed and referenced 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 directly available for glyphosate, and the estimation methods of Durkin et al. (1995) are used as defined in worksheet D03. Other estimates used in this exposure scenario involve estimates of body weight, skin surface area, and first-order dermal absorption rates. The estimates of body weight and surface area are detailed in Worksheet A03. As with the direct spray scenarios, the first-order absorption dermal absorption rates are taken from the study by Wester et al. (1991).

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 glyphosate in ambient water are acute/accidental exposure from an accidental spill and longer-term exposure to glyphosate 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.

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 glyphosate is considered. This is an extremely conservative scenario dominated by arbitrary variability. 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 glyphosate in a small pond is estimated to range from 1 mg/L to 126 mg/L with a central estimate of about 18 mg/L (Worksheet D05).

The other acute exposure scenario for the consumption of contaminated water involves runoff into a small stream. There are several relevant monitoring studies that are useful for estimating exposure to glyphosate in streams. After an aerial application of Roundup at a rate of 2 kg a.i./ha [about 1.8 lb a.i./acre] over a 10 km^2 area in Vancouver Island, British Columbia, maximum concentrations in streams that were intentionally oversprayed reached about 0.16 mg/L and rapidly dissipated to less than 0.04 mg/L after 10 minutes. After a storm event, peak concentrations in stream water were less than 0.15 mg/L, rapidly dissipating to less than 0.02 mg/L before the end of the storm event (Feng et al. 1990, Kreutzweiger et al. 1989). At the same application rate, another Canadian study noted maximum stream concentrations of 0.109–0.144 mg/L, occurring 7–28 hours after aerial application. Similar results were noted in a study conducted in Oregon (Newton et al. 1984). Maximum water levels in streams reached 0.27 mg/L. This concentration was associated with repeated helicopter applications – i.e., direct spray) across a small stream at an application rate of 3.3 kg/ha (equivalent to 2.9 lbs/acre). In a more recent series of studies conducted in Oregon, Michigan, and Georgia, peak concentrations in streams shortly after application of glyphosate at 4.1 kg/ha (about 3.6 lbs/acre) ranged from less than 0.1 mg/L to about 1 mg/L (Newton et al. 1994, Figure 4, p. 1799). The upper range of 1 mg/L corresponds to 0.28 mg/L per lb applied. As reviewed by Neary and Michael (1996), some applications have resulted in much lower concentrations in streams, in the range of 0.003 to 0.007 mg/L per lb applied (Neary and Michael 1996, Table 11, p. 253).

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. Consequently, for this component of the exposure assessment, the monitored levels in ambient water are compared to modeled estimates based on GLEAMS (Groundwater Loading Effects of Agricultural Management Systems). GLEAMS is a root zone model that can be used to examine the fate of chemicals in various types of soils under different meteorological and hydrogeological conditions (Knisel et al. 1992). 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 to estimating concentrations in ambient water are given in Attachment 2.

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 pond dimensions (1000 m^3 or about 0.25 acres with an average depth of 1 meter) are the same as those used in the acute spill scenario.

The chemical specific values used in the GLEAMS modeling are summarized in Table 3-4. As discussed in Section 3.1.15, glyphosate degrades in the environment to metabolites whose toxicity appears to be of the same order or less than the toxicity of glyphosate. For the risk assessment, only glyphosate is modeled and the half-time in water is set to 1000 days – i.e., a gross overestimate that is intended to functionally ignore microbial degradation. This is a conservative approach in that the concentration of glyphosate (as opposed to less toxic degradation products) is maximized.

The GLEAMS modeling yielded estimates glyphosate runoff and percolation that were used to estimate concentrations in the stream adjacent to a treated plot, as detailed in Section 5.5 of Attachment 2. The results of the GLEAMS modeling for the small stream are summarized in Table 3-5 and the corresponding values for the small pond are summarized in Table 3-6. These estimates are expressed as the 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.

Overall, the monitoring data are in relatively good agreement with the estimates from GLEAMS. The upper range of the estimates based on monitoring data – i.e., 0.28 mg/L per lb applied from Newton et al. 1994 – is very close to peak rates of about 0.2 to 0.4 mg/L per lb applied from the GLEAMS stream modeling (Table 3-6). The lower range of values from the monitoring data of 0.003 to 0.007 mg/L per lb applied (Neary and Michael 1996) is reasonably close to maximum values of 0.001 to 0.007 mg/L per lb applied from GLEAMS with rainfall rates of 15 inches per year or about 0.4 inches per storm event (Table 3-6).

Given the close correspondence between the monitoring data and modeling estimates of peak concentrations in stream water, the selection of monitoring data or modeling estimates makes very little difference to the exposure assessment. For this risk assessment, the range of WCR will be taken as 0.001 to 0.4 mg/L per lb applied per acre. The lower range is somewhat arbitrarily set: in very arid environments, no contamination is likely. The upper range of 0.4 mg/L per lb applied is based on the upper range of the modeled stream concentrations from GLEAMS based on sandy soil. The typical WCR is taken as 0.02 mg/L per lb applied per acre. This is the geometric mean of the range and the approximate value of maximum concentrations in stream water modeled for clay and loam soils at an annual rainfall rate of 50 inches per year.

3.2.3.4.2. LONGER-TERM EXPOSURE -- The scenario for chronic exposure to glyphosate from contaminated water is detailed in worksheet D07. This scenario assumes that an adult (70 kg male) consumes contaminated ambient water (2 liters/day) for a lifetime.

As with the above stream scenario, the estimated concentrations in pond water are based on modeled estimates from GLEAMS which are supported by monitoring data. The specific methods used to calculate the concentration of glyphosate in a small pond based on the GLEAMS output are detailed in Section 5.4 of Attachment 2.

The results of the GLEAMS modeling for the pond is summarized in Table 3-5 and the specific estimates of concentrations of glyphosate in ambient water that are used in this risk assessment are summarized in Worksheet B06. 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 applied per acre.

The typical WCR is taken as 1 µg/L or 0.001 mg/L. This is about the average concentration that could be expected over a wide range of rainfall rates in clay or loam soil. The upper limit is taken as 0.008 mg/L, approximately the longer-term average concentration from sandy soil at rainfall rates of 25 inches per year. The lower limit of the WCR is taken as 0.0001 mg/L, about the average concentration from clay soil at an annual rainfall rate of 15 inches per year or from loam at an annual rainfall rate of 10 inches per year.

Monitoring data on glyphosate in pond water are reasonably consistent with these estimates. Over a period of 70 days after aerial application of 2.1 kg/ha (about 1.8 lbs/acre), Goldsborough and Brown (1993) reported concentrations of about 0.001–0.002 mg/L in the water of ponds that were less than 1 hectare (2.47 acres) in surface area and about 0.9 to 1.5 meters deep. Similarly, by 30 days after aerial applications of 3.7 lb/acre adjacent to small ponds (<1 m deep and 50 m^2 or 0.012 acres in surface area), monitored concentrations were in the range of 0.001 to 0.002 mg/L (Newton et al. 1994). Even in ponds that were directly sprayed with glyphosate at a rate of 0.89 kg a.i./ha (0.8 lbs a.i./acre), initial concentrations of between about 0.02 to 0.15 mg/L dissipated to about 0.001 mg/L by day 12 after application (Goldsborough and Beck 1989, Figure 1, p. 540).

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).

Glyphosate has a relatively low potential for bioconcentration. In a bioconcentration study using ^{14}C-glyphosate, bioconcentration in carp exposed to levels in water of 5–50 µg/L ranged from about 10 after 1 day of exposure to about 40 after 14 days of exposure (Wang et al. 1994a). These estimates of bioconcentration, however, are based on total radioactivity rather than the identification of glyphosate residues. Consequently, the apparent bioconcentration appears to reflect the binding of glyphosate metabolites, including mineralized carbon, to fish tissue. Based on the study by Forbis (1989), the U.S. EPA/OPP (1993c, p. 36) used maximum bioconcentration factors of 0.38 for edible tissues and 0.52 for whole fish. Calabrese and Baldwin (1993) have reviewed a number of different methods for estimating BCF values in fish based on chemical and

physical properties. Using a log $K_{o/w}$ of -4.85 at pH 6.86 (from Chamberlain et al. 1996 as summarized in Table 2-2), the estimated BCF values in fish would be well below unity, consistent with the study by Forbis (1989) and the BCF values used by U.S. EPA/OPP (1993c). For the current risk assessment, the values reported by Forbis (1989) and used by EPA/OPP (1993c) will be used to estimate dietary exposure to fish. These values are included in Worksheet B02 and used in all exposure assessments involving the consumption of contaminated fish. In the exposure assessment for humans, the assumption is made that the individual consumes only the edible portion of the fish. In the ecological risk assessment, the assumption is made that the predator completely consumes the fish and the whole body BCF is used.

For both the acute and longer-term exposure scenarios involving the consumption of contaminated fish, the water concentrations of glyphosate used are identical to the concentrations used in the contaminated water scenarios (see Section 3.2.3.4). The acute exposure scenario is based on the assumption that an adult angler consumes fish taken from contaminated water shortly after an accidental spill of 200 gallons of a field solution into a pond that has an average depth of 1 m and a surface area of 1000 m^2 or about one-quarter acre. No dissipation or degradation is considered. Because of the available and well-documented information and substantial differences in the amount of caught fish consumed by the general public and native American subsistence populations (U.S. EPA 1996), 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 glyphosate 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 -- Under normal circumstances and in most types of applications, it is extremely unlikely that humans will consume vegetation contaminated with glyphosate. Any number of accidental scenarios could be developed involving either spraying of crops, gardens, or edible wild vegetation. Again, in most instances and particularly for longer-term scenarios, treated vegetation would probably show signs of damage from exposure to glyphosate (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 that is accidentally sprayed. One of the more plausible scenarios involves the consumption of contaminated berries after the accidental spray of an area in which wild berries grow. The most relevant publication for assessing exposure from such a scenario is that of Siltanen et al. (1981). These investigators monitored levels of glyphosate on cowberries and bilberries after backpack sprays of Roundup at an application rate of 0.25 and 0.75 kg a.i./ha [0.22 and 0.67 lb a.i./acre]. At 6 days after treatment with 0.67 lb/acre, residues on cowberries were 1.6 mg/kg. At 7 days after treatment, residues on bilberries were 2.1 mg/kg. The residue data plotted over a 70-day post-application observation period are illustrated in Figure 3-2.

These data fit a first order model ($p=0.004$) with a dissipation rate of 0.015 day^{-1}, which corresponds to a half-time of about 46 days. This model is indicated by the thick solid line in

Figure 3-1. Although the data fit a simple one-compartment first order model, visual inspection of the data suggests that a two-compartment first order model could also be applied.

The central estimate of residues immediately after application are approximately 1.6 ppm (mg/kg) with a 95% upper limit of 4 ppm. This corresponds to a residue rate of about 2.4 ppm per lb per acre [1.6 ppm ÷ 0.67 lb a.i./acre] with an upper limit of 5.9 ppm per lb per acre [4 ppm ÷ 0.67 lb a.i./acre]. As summarized in Worksheet A04, this is close to the estimate 1.5 ppm per lb per acre with an upper range of 7 ppm per lb per acre from the empirical relationships between application rate and concentration on fruit developed by Hoerger and Kenaga (1972) and somewhat lower than the estimate 7 ppm per lb per acre with an upper range of 15 ppm per lb per acre developed by Fletcher et al. (1994) which is in turn based on a re-analysis of data from Hoerger and Kenaga (1972). Because the study by Siltanen et al. (1981) uses glyphosate on two different types of fruit and because the results are reasonably consistent between the two types, there is no reason to use either the general relationships developed by Hoerger and Kenaga (1972) or Fletcher et al. (1994) for scenarios involving contaminated fruit. For other scenarios involving other types of vegetation, the estimates from Fletcher et al. (1994) are used since they are somewhat more conservative than the earlier estimates by Hoerger and Kenaga (1972).

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 glyphosate 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 and the dissipation on the vegetation is estimated using the halftime of 46 days from Siltanen et al. (1981). As summarized in Table 2-2, this is the most conservative value – i.e., the longest halftime which leads to the highest time-weighted average residues. 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 result in a less conservative exposure assessment).

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, $\mathbf{C_t}$, can be calculated based on the initial concentration, $\boldsymbol{C_0}$, as:

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

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

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

For the acute exposure scenario, it is assumed that a woman consumes 1 lb (0.4536 kg) of contaminated fruit. Based on statistics summarized in U.S. EPA/ORD (1996) and presented in worksheet D04, this consumption rate is approximately the mid-range between the mean and upper 95% confidence interval for the total vegetable intake for a 64 kg woman. The range of exposures presented in Table 3-3 is based on the range of concentrations on fruit and the typical application rate for glyphosate. The longer-term exposure scenario is constructed in a similar way, except that the estimated exposures include the range of fruit consumption (Worksheet A03) as well as the range of concentrations on fruit.

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 for glyphosate 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. Generally, the dose-response assessments used in Forest Service risk assessments adopt RfDs proposed by the U.S. EPA as indices of 'acceptable' exposure. An RfD is basically defined as a level of exposure that will not result in any adverse effects in any individual. The U.S. EPA RfDs are used because they generally provide a level of analysis, review, and resources that far exceed those that are or can be conducted in the support of most Forest Service risk assessments. In addition, it is desirable for different agencies and organizations within the federal government to use concordant risk assessment values.

The most recent RfD on glyphosate is that proposed by the U.S. EPA Office of Pesticide Programs. This RfD of 2 mg/kg/day was proposed originally in the RED for glyphosate and was also used in the recent glyphosate pesticide tolerances. This RfD is based on teratogenicity study in rabbits (Rodwell et al. 1980b) in which no effects observed in offspring at any dose levels and maternal toxicity was observed at 350 mg/kg/day with a NOAEL of 175 mg/kg/day . Using an uncertainty factor of 100 – 10 for sensitive individuals and 10 for species-to-species extrapolation – U.S. EPA/OPP derived the RfD of 2 mg/kg/day, rounding the value of 1.75 mg/kg/day to one significant digit.

For the current risk assessment, the RfD 2 mg/kg/day derived by U.S. EPA/OPP is used as the basis for characterizing risk from longer-term exposures in this risk assessment. For short-term exposures, the value of 2 mg/kg/day recommended by U.S. EPA's Office of Drinking Water is used. Since this is identical to the chronic RfD, this approach is equivalent to applying the same RfD to be short-term and long-term exposures. Given the lack of a significant dose-duration relationship for glyphosate, this approach seems appropriate.

3.3.2. Existing Guidelines. Generally, the dose-response assessments used in Forest Service risk assessments adopt RfDs proposed by the U.S. EPA as indices of 'acceptable' exposure. An RfD is basically defined as a level of exposure that will not result in any adverse effects in any individual. The U.S. EPA RfDs are used because they generally provide a level of analysis, review, and resources that far exceed those that are or can be conducted in the support of most Forest Service risk assessments. In addition, it is desirable for different agencies and organizations within the federal government to use concordant risk assessment values. The current risk assessment is somewhat complicated by the fact that the U.S. EPA has proposed two chronic RfDs for glyphosate and World Health Organization has proposed another comparable value, referred to as an ADI (acceptable daily intake).

The most recent RfD on glyphosate is that proposed by the U.S. EPA Office of Pesticide Programs. This RfD of 2 mg/kg/day was proposed originally in the RED for glyphosate (U.S. EPA/OPP 1993c) and was also used in the recent glyphosate pesticide tolerances (U.S. EPA/OPP 2002). This RfD is based on teratogenicity study in rabbits (Rodwell et al. 1980b) in which doses of 75, 175, or 350 mg/kg/day were administered by gavage on days 6-27 of gestation. As detailed in Appendix 6, no effects observed in offspring at any dose levels. Maternal toxicity – i.e., nasal discharge, diarrhea, altered physical appearance and death among dams – was observed

at 350 mg/kg/day. Using an uncertainty factor of 100 – 10 for sensitive individuals and 10 for species-to-species extrapolation – U.S. EPA/OPP (1993c) derived the RfD of 2 mg/kg/day, rounding the value of 1.75 mg/kg/day to one significant digit.

The U.S. EPA has also derived an RfD on glyphosate of 0.1 mg/kg/day (U.S. EPA/IRIS 1990). This RfD was originally derived in 1990 by the U.S. EPA Integrated Risk Information System (IRIS) workgroup and is the current (Nov. 2002) RfD posted on IRIS. This RfD is based on a dietary 3-generation reproduction study (Schroeder and Hogan 1981), which is also detailed in Appendix 6. In this study, rats were exposed to glyphosate in the diet with resulting dose rates of 0, 3, 10 and 30 mg/kg/day. No signs of maternal toxicity were observed. The only effect in offspring was an increase in the incidence of unilateral renal tubular dilation in male pups from the F3b mating. Thus, the NOAEL was identified as 10 mg/kg/day and an uncertainty factor of 100 was applied to derive an RfD of 0.1 mg/kg/day.

Unlike the two RfD values proposed by the U.S. EPA, the ADI proposed by WHO (1994) is not based on a reproductive toxicity study. Instead, WHO (1994) selected a life-time feeding study in rats (Lankas and Hogan 1981). The Lankas and Hogan (1981) study is detailed in Appendix 5 and involved dietary concentrations of 0, 30, 100, or 300 ppm for 26 months which corresponded to approximate daily doses (expressed as mg/kg body weight) of 0, 3.1, 10.3, or 31.5 mg/kg/day for males and 0, 3.4, 11.3, or 34.0 mg/kg/day for females. No effects were seen at any dose levels and thus WHO (1994) used a NOAEL of 31.5 mg/kg/day and uncertainty factor of 100. Rounding to one significant digit, the recommended ADI was set at 0.3 mg/kg/day.

The U.S. EPA/OPP will sometimes derive acute RfD values that can be used to assess risks associated with very short-term exposures – i.e., accidental spills. No acute RfD has been proposed, however, for glyphosate.

The Office of Drinking Water (U.S. EPA/ODW 1992) has proposed a 10-day health advisory for glyphosate of 17.5 mg/L and a longer-term health advisory of 1 mg/L. The longer-term health advisory is based on the U.S. EPA RfD of 0.1 mg/kg/day reference dose, as summarized above. The 10-day health advisory is based on the NOAEL of 175 mg/kg/day from Rodwell et al. 1980b, which is also summarized above. An uncertainty factor of 100 was applied to this NOAEL and the 10-day exposure limit was set at 1.75 mg/kg/day. This value was multiplied by 10 kg, the default weight for a child used by U.S. EPA/ODW (1992) and divided by 1 L, the default amount of water consumed by a child. Rounding the value of 1.75 mg/kg/day to one significant digit, this is equivalent to a short-term RfD of 2 mg/kg/day, identical to the chronic RfD currently recommended by U.S. EPA/OPP (1993c; 2002).

3.3.3. Dose-Response and Dose-Severity Relationships. There is a striking concordance between the available human and animal data on the acute toxicity of glyphosate. The dose-mortality data in humans is consistent with estimates of oral LD_{50} values in experimental mammals. Several different dose-response models can be use to quantitatively compare the lethality data on humans with those available on experimental mammals. In general, different

dose-response models yield similar results in the region of observed responses but may differ substantially in the low dose region. To estimate the LD_{50} in humans, variants of the multistage model were used, one non-threshold and one with a threshold. Both models yielded virtually identical estimates of the LD_{50}, approximately 3000 mg/kg, very similar to the range of 2000 to 6000 mg/kg reported in experimental mammals (Section 3.1.4).

For systemic toxic effects, it is generally assumed that population thresholds exist. In other words, below a certain dose, no individual in the population will respond. This assumption is fundamental to risk assessment methods for systemic toxic effects. For cancer, population thresholds are not generally assumed and non-threshold models are considered appropriate. The threshold version of the multi-stage model used in this analysis yielded an estimate of the threshold at about 445 mg/kg.

The dose-severity relationships for experimental mammals and humans are also similar, as illustrated in Figure 3-2. In this figure, the animal data are taken from Appendices 4 and 5. In cases where dietary exposure levels were not converted to units of dose in mg/kg/day, such conversions were made using the methods presented in U.S. EPA (1986b, Reference Values for Risk Assessment). The animal data are categorized using four standard severity levels: NOEL (no observed effect level), NOAEL (no observed adverse effect level), AEL (adverse effect level), and FEL (frank effect level), as discussed in SERA (2001a). Three different groups of end-points are presented: general systemic toxic effects (***T***), reproductive or developmental effects (***R***), and acute LD_{50} values (***A***). The estimated human oral LD_{50}, as estimated above, is plotted as a FEL with the LD_{50} values from experimental mammals.

These studies span exposure periods ranging from 1 day to more than 2 years. The exposure axis is not presented in this figure. As discussed below, the duration of exposure is not an important variable in the toxicity of glyphosate, probably because of the rapid rate of glyphosate excretion. The data from study on which the RfD is based as well as the RfD itself are plotted and labeled with arrows.

Figure 3-2 also includes human data from the study by Tominack et al. (1991). These investigators report mean dose levels associated with four levels of severity. Patients in the least severe category were asymptomatic. The average amount of Roundup consumed by these patients was 31 mL. Assuming an average body weight of 60 kg for the individuals from Taiwan and using the concentration of 356 g of glyphosate a.e./L, this corresponds to an average dose of 184 mg/kg. This is plotted as a box just below the NOEL line in Figure 3-2 and labeled as *"No apparent effects"*. Patients with transient signs or symptoms localized to the oral mucosa or gastrointestinal tract had, on average, consumed 72 mL ($\simeq$427 mg/kg). This point is labeled as *"Mild poisoning"* in Figure 3-2. Patient with *"Moderate poisoning"* had consumed on average 176 mL ($\simeq$1,044 mg/kg). These patients evidenced gastrointestinal tract irritation lasting less than 24 hours, transient decreases in blood pressure or decreased urinary output, transient hepatic or renal damage, acid-base disturbances, or pulmonary dysfunction which did not require intubation. *"Severe poisoning"*, which included fatal cases, occurred in patients who had on

average consumed 216 mL (≃1,282 mg/kg). The publication by Tominack et al. (1991) also reports the variability of the doses associated with each of these severity levels.

For experimental mammals, the dose-severity relationships can be assessed using categorical regression analyses (Durkin et al. 1992; Hertzberg 1989; McCullagh 1980). This approach correlates categorical responses—such as NOELs, NOAELs, AELs, and FELs—with factors that may influence the response such as dose and duration of exposure. The method results in estimates of the probability of a group of animals subjected to a given exposure being classified into a given category. For the statistical analyses, data on NOELs and NOAELs were combined. This was done for two related reasons. First, the primary concern for this risk assessment is the delineation between regions of adverse and non-adverse effects. Thus, the distinction between a NOEL and NOAEL is not critical. Second, many reported NOELs could be artifacts of the level of detail at which the animals are examined. For example, simply because there are no adverse effects based on gross examination of organs does not mean that effects might not be seen if all organs were examined microscopically. Consequently, analyses were conducted using both four categories (NOELs, NOAELs, AELs, and FELs) as well as two categories (NOELs and NOAELs combined as well as AELs and FELs combined).

Initially, the categorical regression was conducted on both dose and duration of exposure. The effect of duration was not statistically significant ($p=0.7267$). This seems reasonable given the data on the influence of duration of exposure on toxicity. For example, all of the LD_{50} values shown in Figure 3-2 involved single doses. Many of the AELs, some of which are doses at or above reported LD_{50} values, involved exposure periods of up 2 years. This apparently anomalous result can be explained by two factors. First, all of the LD_{50} studies involved intubations: the animal was given the total dose by stomach tube at one time. Most of the subchronic and chronic studies involved dietary exposures, in which the daily dose was spread out over the course of the day depending on the animals eating habits. Thus, the animals who were intubated in LD_{50} studies received essentially more severe exposures for a given dose. Secondly, for chemicals that are eliminated rapidly and do not cause cumulative damage, there is often very little relationship between the duration of exposure and the severity of response for a fixed dose level.

Because of the lack of significance of duration, the analysis was re-run using only dose as the independent variable. The results of this analysis indicate that the probability of an adverse effect at the RfD of 0.1 mg/kg/day is 0.0005. At doses of 1 mg/kg/day the probability of observing an adverse effect is 0.003. At a dose that is 100 fold above the RfD (i.e., 10 mg/kg/day) the probability of an adverse effect is 0.12. This analysis suggest that the current RfD is highly protective and that the proposed alternative RfD of 2 mg/kg/day is also protective. At this higher level, the probability of an adverse effect is 0.006.

All of the above estimates are based on the two category analysis - the segregation of any adverse effect from non-adverse effects. They indicate the probability of a group of animals exposed at the specified dose level evidencing responses sufficiently, albeit perhaps minimally, severe to classify the dose level as *adverse* based on the responses observed in the group of animals.

The four category analysis can be used to estimate the probability of observing effects that would be classified as *frank signs of toxicity*. These effects are sufficiently severe that they can be observed in the whole organism without the use of invasive methods. The probability of a frank toxic effect at the RfD of 0.1 mg/kg/day is 0.00005. At the proposed alternative RfD of 2 mg/kg/day, the probability increases to only 0.0006.

The consistency between the categorical analysis using data on groups of experimental animals and dose-response analyses of the human lethality data using the multi-stage model is relatively good. At the estimated threshold for lethality, 445 mg/kg, the probability of observing a frank toxic effect is about 0.04. At this dose, the non-threshold version of the multi-stage model estimates the probability of mortality at about 0.02. At the estimated human LD_{50} of about 3000 mg/kg, the categorical regression using two categories (NOELs and NOAELs combined as well as AELs and FELs combined) indicates the probability of observing an adverse or frank effect at 0.7. The four category model, however, substantially underestimates the probability of observing a FEL, 0.13. Visual inspection of Figure 3-2 suggests that this is attributable to the relatively small number of FELs in experimental mammals and the overlap of FELs with AELs. As discussed above, this overlap may be related to the rapid elimination and lack of cumulative damage in longer-term studies.

A somewhat more detailed analysis could be conducted on data collected by Tominack et al. (1991) that would provide information on the probabilities of individuals rather than groups being classified as adverse responders to given doses of glyphosate. The necessary data for such an analysis [amount consumed, body weight or sex/age, and severity classification] is not presented in the Tominack publication.

The significance of the categorical regression on animals and the available human data relates to the use of the uncertainty factor. As summarized in the previous section, the current RfD as well as the proposed U.S. EPA Office of Pesticides alternative use an uncertainty factor of 10 for species to species extrapolation (i.e., extrapolating from experimental animals to humans). This is a common default procedure. For glyphosate, however, the available data suggest that humans are no more sensitive to glyphosate than experimental mammals. This in turn suggests that the current and proposed RfD may be overly protective by a factor of 10 or greater. In other words, the RfDs suggest that no adverse effects are anticipated at doses of 0.1-2 mg/kg/day. The human data suggest that no frank adverse effects are likely at doses substantially above 10 mg/kg/day.

3.3.4. RfD Values Used in Risk Assessment. As with any chemical that has been extensively studied, the data base on glyphosate is large, complex, and open to differing interpretations. Based on the categorical regression analysis summarized in the previous section, all of the RfD values currently recommended would appear to be protective for both short- and long-term exposures. Notwithstanding this, however, the availability of three different chronic values must be reconciled explicitly.

The ADI of 0.3 mg/kg/day that is proposed by WHO (1994) is discussed by U.S. EPA/OPP (1993c, p. 19). The Schroeder and Hogan (1981) study used by WHO (1994) failed to identify an effect level. Thus, the NOAEL of 31.5 mg/kg/day identified in the Schroeder and Hogan (1981) study is essentially "free-standing". In other words, the true threshold for toxicity could be much higher. In such cases, it is generally appropriate to utilize a different study that identifies both a NOAEL and a LOAEL and base the RfD on the NOAEL. This is the approach taken in U.S. EPA/OPP (1993c), using a NOAEL of 175 mg/kg/day and a LOAEL of 350 mg/kg/day from the gavage teratogenicity study in rabbits (Rodwell et al. 1980b)

The Schroeder and Hogan (1981) study is cited but not discussed in U.S. EPA/OPP (1993c). In addition, U.S. EPA/OPP (1993c) does not discuss the RfD derived by U.S. EPA/IRIS (1990). Thus, the LOAEL of 30 mg/kg/day based on increase in renal tubular dilation in male F3b pups (Schroeder and Hogan 1981) is not specifically addressed by or compared to the NOAEL of 175 mg/kg/day used by U.S. EPA/OPP (1993c).

Nonetheless, the U.S. EPA/OPP (1993a) Science Chapter, which is a support document prepared for the RED, does explicitly discuss the renal tubular dilation reported by Schroeder and Hogan (1981) at 30 mg/kg/day and notes that this effect was not seen in a later two-generation reproductive study conducted by Reyna (1990) that involved doses of up to 1500 mg/kg/day. Thus, U.S. EPA/OPP (1993a) classified the effects reported by Schroeder and Hogan (1981) as "spurious". Given that the Reyna (1990) study involved three dose levels above 30 mg/kg/day – i.e., 100, 500, and 1500 mg/kg/day – and given that similar lesions have not been noted in other studies, this decision by U.S. EPA/OPP (1993a) appears to be reasonable.

An additional factor to consider in assessing the protectiveness of the U.S. EPA/OPP (1993c) RfD of 2 mg/kg/day and the corresponding NOAEL of 175 mg/kg/day is the report by Yousef et al. (1995) of increases in abnormal and dead sperm in rabbits after acute exposures to glyphosate. As discussed in some detail in Section 3.1.9, the Yousef et al. (1995) study is not well documented and does not specify the absolute doses used but only cites the doses relative to the LD_{50} for glyphosate, which is also not specified in the Yousef et al. (1995) study. Assuming the doses of 38 and 380 mg/kg estimated for this study (see Section 3.1.9) are reasonable approximations, the presumptive LOAEL of 38 mg/kg is not consistent with the better documented reproductive NOAEL of 30 mg/kg/day from Schroeder and Hogan (1981). [Note that the unilateral renal tubular dilation in male F3b pups reported at 30 mg/kg/day by Schroeder and Hogan (1981) is a LOAEL for systemic toxicity but, since no effects were observed on reproduction, this dose is a NOAEL for reproductive toxicity.] Thus, while the report by Yousef et al. (1995) must be considered, it is not supported by other well-conducted and well-documented studies and does not impact the selection of the RfD for this current risk assessment.

Thus, for the current risk assessment, the RfD 2 mg/kg/day derived by U.S. EPA/OPP (1993c) and used by U.S. EPA/OPP (2002) will be used as the basis for characterizing risk from longer-term exposures in this risk assessment (Section 3.4). For short-term exposures, the value of 2 mg/kg/day recommended by U.S. EPA/ODW (1992) will be used. Since this is identical to the

chronic RfD, this approach is equivalent to applying the same RfD to be short-term and long-term exposures. Given the lack of a significant dose-duration relationship for glyphosate (Section 3.3.3.), this approach seems appropriate.

3.4. RISK CHARACTERIZATION

3.4.1. Overview. The risk characterization for both workers and members of the general public are reasonably consistent in unambiguous. For both groups, there is very little indication of any potential risk at the typical application rate of 2 lbs a.e./acre. Even at the upper range of plausible exposures in workers, most hazard quotients are below the level of concern.

For workers, the highest hazard quotient – i.e., 0.2, the upper range for workers involved in broadcast ground spray – is below the level of concern by a factor of about 5. The highest hazard quotient for any accidental exposure scenario for workers - i.e., 0.006 for the upper range of the hazard quotient for spill over the lower legs for one hour - is lower than the level of concern by a factor of over 150. Confidence in these assessments is reasonably high because of the availability of dermal absorption data in human as well as worker exposure studies. The Forest Service may apply glyphosate at a maximum rate of 7 lbs a.e./acre, a factor of 3.5 higher than the typical application rate of 2 lbs a.e./acre. This has essentially no impact of the risk characterization for workers. The highest hazard quotient for the typical application rate is 0.2. For an application rate of 7 lbs a.e./acre, the corresponding hazard quotient would be higher by a factor of 3.5 or 0.7, which is still below the level of concern.

From a practical perspective, the most likely accidental exposure for workers that might require medical attention involves accidental contamination of the eyes. Glyphosate and glyphosate formulations are skin and eye irritants. Quantitative risk assessments for irritation are not normally derived, and, for glyphosate specifically, there is no indication that such a derivation is warranted. Glyphosate with the POEA surfactant is about as irritating as standard dish washing detergents, all purpose cleaners, and baby shampoos. As with the handling of any chemical, including a variety of common household products, reasonable care should be taken to avoid contact of skin and eyes.

The only area of remarkable uncertainty involving worker exposures concerns the potential health effects during brown-and-burn operations. The combustion of wood and wood by-products may produce a number of toxic compounds. This is a concern with brown-and-burn operations but does not pertain to the use of glyphosate or any other herbicide. The potential effects of combustion products is common to all risk assessments of materials that might be subject to burning. With the exception of some plastics, the combustion products of which are known to pose a risk to fire fighters, the combustion products of most chemicals have not been examined in detail. The necessity of addressing this data gap must be weighed against the need to address other data gaps on glyphosate and other chemicals. The combustion products of burning wood and vegetation are respiratory irritants as well as carcinogens, and exposure to these combustion products should be avoided. There is no basis for believing that the presence of low or even high levels of glyphosate residues will have a significant impact on this hazard.

For members of the general public, none of the longer-term exposure scenarios exceed or even approach a level of concern. Although there are several uncertainties in the longer-term exposure assessments for the general public, the upper limits for hazard indices are below a level of concern

by factors of about 25 (longer term consumption of contaminated fruit) to over two million (2,500,000 for longer-term consumption of fish by the general population). The risk characterization is thus relatively unambiguous: based on the available information and under the foreseeable conditions of application and exposure, there is no route of exposure or exposure scenario suggesting that the general public will be at risk from longer-term exposure to glyphosate. As with the hazard characterization for workers, an application rate of 7.5 lbs a.e./acre makes no difference in the assessment of potential risks. At this application rate, the highest hazard quotient would be about 0.14 [0.04 × 3.5], which is still below a level of concern by a factor of about 7.

One acute exposure scenario does exceed the level of concern at the upper range at the typical application rate of 2 lbs a.e./acre. The exposure scenario for the consumption of contaminated water after an accidental spill into a small pond results in an excursion above the RfD at the upper limit of exposure – i.e, a hazard quotient of 2. This exposure scenario is extreme to the point of limited plausibility. This sort of scenario is routinely used in Forest Service risk assessments as an index of the measures that should be taken to limit exposure in the event of a relatively large spill into a relatively small body of water. For glyphosate, as well as for most other chemicals, this exposure assessment indicates that such an event would require measures to ensure that members of the general public do not consume contaminated water.

At the highest application rate that might be used in Forest Service programs, the accidental spill scenario is the only other scenario that results in a hazard quotient above unity. At this application rate, the associated dose is about 14 mg/kg, which is still below the dose of 184 mg/kg associated with no apparent overt effects in humans by a factor of over 10.

3.4.2. Workers. A quantitative summary of the risk characterization for workers is presented in Table 3-7 for the typical application rate of 2 lbs a.e./acre. The quantitative risk characterization is expressed as the hazard quotient. For both general and accidental exposures, the hazard index is calculated as the estimated doses from Table 3-1 divided by the RfD of 2 mg/kg/day. As discussed in Section 3.3.2, there is no substantial dose-duration-effect relationship for glyphosate and the acute and chronic RfDs are identical.

Given the very low hazard quotients for accidental exposure, the risk characterization is reasonably unambiguous. None of the accidental exposure scenarios approach a level of concern. 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. Given that the highest hazard quotient for any accidental exposure scenario - i.e., 0.0057 for the upper range of the hazard quotient for spill over the lower legs for one hour - is a factor of 175 lower than the level of concern, substantially more severe and much less plausible scenarios would be required to suggest a potential for systemic toxic effects from accidental exposures. Confidence in this assessment is reasonably high because of the availability of dermal absorption data in human. As

discussed in Section 3.2.2.2, the first-order dermal absorption rates used in this exposure scenario are taken from the study by Wester et al. (1991).

The hazard quotients for general or longer term exposures in workers are also unambiguous. Even at the upper range of plausible exposures all hazard quotients are below the level of concern. The highest hazard quotient – i.e., 0.2, the upper range for workers involved in broadcast ground spray – is below the level of concern by a factor of 5.

As noted in Section 2, the Forest Service may apply glyphosate at a maximum rate of 7 lbs a.e./acre, a factor of 3.5 higher than the typical application rate of 2 lbs a.e./acre. This has essentially no impact of the risk characterization for workers. As noted above, the highest hazard quotient for the typical application rate is 0.2. For an application rate of 7 lbs a.e./acre, the corresponding hazard quotient would be higher by a factor of 3.5 or 0.7, which is still below the level of concern.

As summarized in section 3.1.11, glyphosate and glyphosate formulations are skin and eye irritants. Quantitative risk assessments for irritation are not normally derived, and, for glyphosate specifically, there is no indication that such a derivation is warranted. As discussed by Maibach (1986), glyphosate with the POEA surfactant is about as irritating as standard dish washing detergents, all purpose cleaners, and baby shampoos. As with the handling of any chemical, including a variety of common household products, reasonable care should be taken to avoid contact of skin and eyes.

The only area of remarkable uncertainty concerns brown-and-burn operations. Glyphosate, like Roundup, does not appear to be very toxic by inhalation (Section 3.1.13). Although residues of glyphosate in air during brown-and-burn operations have not been measured, they are likely to be very low given that brown-and-burn operations take place about 30 to180 days after treatment with the herbicide and the foliar half-life is from 1.6 to 46 days. Consequently, there is no evidence to suggest that toxic levels of glyphosate are likely to be encountered.

The combustion of wood and wood by-products may produce a number of toxic compounds. This is a concern with brown-and-burn operations but does not pertain to the use of glyphosate or any other herbicide. Nevertheless, as discussed in section 3.1.13, glyphosate forms a polycondensate on combustion at temperatures ranging from 200 to 240°C. It is likely that other combustion products are formed under different combustion conditions. No information is available regarding the inhalation toxicity of the polycondensate or other possible combustion products.

The potential effects of combustion products is common to all risk assessments of materials that might be subject to burning. With the exception of some plastics, the combustion products of which are known to pose a risk to fire fighters, the combustion products of most chemicals have not been examined in detail. The necessity of addressing this data gap must be weighed against the need to address other data gaps on glyphosate and other chemicals. The combustion products

of burning wood and vegetation are respiratory irritants as well as carcinogens, and exposure to these combustion products should be avoided. There is no basis for believing that the presence of low or even high levels of glyphosate residues will have a significant impact on this hazard.

3.4.3. General Public. The quantitative hazard characterization for the general public is summarized in Table 3-8 for the typical application rate of 2 lbs a.e./acre. Like the quantitative risk characterization for workers, the quantitative risk characterization for the general public is expressed as the hazard quotient using the RfD of 2 mg/kg/day for both acute and longer-term exposures.

None of the longer-term exposure scenarios exceed or even approach a level of concern. 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 indices are below a level of concern by factors of about 25 (longer term consumption of contaminated fruit) to over two million (about 2,325,000 for longer-term consumption of fish by the general population). The risk characterization is thus relatively unambiguous: based on the available information and under the foreseeable conditions of application and exposure, there is no route of exposure or exposure scenario suggesting that the general public will be at risk from longer-term exposure to glyphosate. As with the hazard characterization for workers, an application rate of 7.5 lbs a.e./acre makes no difference in the assessment of potential risks. At this application rate, the highest hazard quotient would be 0.14 [0.04 × 3.5], which is still below a level of concern by a factor of about 7.

One acute exposure scenario does exceed the level of concern at the upper range at the typical application rate of 2 lbs a.e./acre. The exposure scenario for the consumption of contaminated water after an accidental spill into a small pond results in an excursion above the RfD at the upper limit of exposure – i.e, a hazard quotient of 2. As detailed in Section 3.2.3.4.1, this exposure scenario is extreme to the point of limited plausibility. This sort of scenario is routinely used in Forest Service risk assessments as an index of the measures that should be taken to limit exposure in the event of a relatively large spill into a relatively small body of water. For glyphosate, as well as for most other chemicals, this exposure assessment indicates that such an event would require measures to ensure that members of the general public do not consume contaminated water. As detailed in Table 3-3, the upper range of exposure scenario involves a dose of 4.1 mg/kg bw. While this is an unacceptable level of exposure, it is far below doses that would likely result in overt signs of toxicity. As detailed in Section 3.3.3, a dose of 184 mg/kg as Roundup – i.e., glyphosate plus surfactant – was not associated with any overt signs of toxicity in humans – and mild signs of toxicity were apparent at doses of 427 mg/kg, over 100 times higher than the upper range of 4.1 mg/kg in the accidental spill scenario.

At the highest application rate that might be used in Forest Service programs, the accidental spill scenario remains the only scenario that results in a hazard quotient above unity. At this application rate, the associated dose is about 14 mg/kg, which is still below the dose of 184 mg/kg associated with no apparent overt effects in humans.

3.4.4. Sensitive Subgroups. No reports were encountered in the literature leading to the identification of sensitive subgroups. There is no indication that glyphosate causes sensitization or allergic responses, which does not eliminate the possibility that some individuals might be sensitive to glyphosate as well as many other chemicals.

3.4.5. Connected Actions. There is very little information available on the interaction of glyphosate with other compounds. As summarized in Section 3.1.2, there are some data suggesting that glyphosate may inhibit hepatic mixed-function oxidases. This is a very important system of enzymes in the metabolism of many xenobiotics. While the inhibition of hepatic mixed-function oxidases is a plausible mechanism of interaction, this does not lead to any definite conclusions regarding the potential influence of glyphosate on the toxicity of other chemicals. In any event, this mechanism of action would probably be relevant only at very high doses, substantially above exposures that can be anticipated in Forest Service programs.

3.4.6. Cumulative Effects. As noted above, this risk assessment specifically considers the effect of repeated exposures and no adverse effects are anticipated. As discussed in the dose-response and dose-severity relationships (see section 3.3.3), the daily dose rather than the duration of exposure determines the toxicological response. Consequently, repeated exposure to levels below the toxic threshold should not be associated with cumulative effects.

It is possible and even likely that some individuals will be exposed to multiple sources of glyphosate as a result of Forest Service programs. For example, an individual consuming contaminated fish might also consume contaminated water and/or vegetation. For glyphosate, these multiple sources of exposure as inconsequential. As detailed in Table 3-8, the only substantial exposure scenario for acute exposures is the consumption of contaminated water after a spill into a small pond. All other plausible combinations of exposures would not exceed a level of concern. Similarly, for longer term exposures, the over-riding route of exposure is the consumption of contaminated vegetation. Adding all other sources of exposure would have no substantial impact on the hazard quotient.

Lastly, individuals may be exposed to glyphosate from other sources not related to Forest Service activities. For example, glyphosate has a number of approved uses on crops and some exposure to glyphosate in crop residues is likely. The U.S. EPA/OPP (2002) has estimated that residues of glyphosate on crops could account for about 1% of the RfD for the U.S. population overall (U.S. EPA/OPP 2002, p. 17726). This amounts to a hazard quotient of 0.01, substantially higher than any of the central estimates of the hazard quotients for longer term exposure scenarios associated with Forest Service programs (Table 3-8). Thus, except for the upper limit of exposure in the consumption of contaminated vegetation, the use of glyphosate by the Forest Service is not likely to substantially increase an individuals potential exposure to glyphosate from other sources. For the consumption of contaminated vegetation, the upper limit of exposure combined with the U.S. EPA estimate of other dietary exposures would not exceed the RfD – i.e., 0.14 + 0.01 = 0.15.

Table 3-1: Summary of Worker Exposure Scenarios

Scenario	Dose (mg/kg/day or event)			Exposure Assessment Worksheet
	Central	Lower	Upper	
General Exposures (dose in mg/kg/day)				
Directed ground spray (Backpack)	2.63e-02	9.00e-04	1.60e-01	C01a
Broadcast ground spray (Boom spray)	4.48e-02	1.32e-03	3.02e-01	C01b
Aerial applications	2.94e-02	4.80e-04	1.60e-01	C01c
Accidental/Incidental Exposures (dose in mg/kg/event)				
Immersion of Hands, 1 minute	7.20e-06	7.10e-07	6.05e-05	C02a
Contaminated Gloves, 1 hour	4.32e-04	4.26e-05	3.63e-03	C02b
Spill on hands, 1 hour	9.44e-04	1.20e-04	4.61e-03	C03a
Spill on lower legs, 1 hour	2.33e-03	2.95e-04	1.14e-02	C03b

Table 3-2: Occupational Exposure Rates used in risk assessments [a]			
Worker Group	Rate (mg/kg bw per lb applied)		
	Central	Lower	Upper
Directed foliar	0.003	0.0003	0.01
Broadcast foliar	0.0002	0.00001	0.0009
Aerial	0.00003	0.000001	0.0001
[a] Taken from SERA (2001a).			

Table 3-3**:** Summary of Exposure Scenarios for the General Public

Scenario	Target	Dose (mg/kg/day)			Worksheet
		Central	Lower	Upper	
Acute/Accidental Exposures					
Direct spray, entire body	Child	3.57e-02	4.53e-03	1.74e-01	D01a
Direct spray, lower legs	Woman	3.58e-03	4.55e-04	1.75e-02	D01b
Dermal, contaminated vegetation	Woman	2.19e-03	6.98e-04	5.31e-03	D02
Contaminated fruit	Woman	8.06e-03	8.06e-03	1.47e-01	D03
Contaminated water, spill	Child	1.37e+00	3.33e-01	4.10e+00	D05
Contaminated water, stream	Child	3.01e-03	9.17e-05	9.02e-02	D06
Consumption of fish, general public	Man	1.56e-02	6.23e-03	3.12e-02	D08a
Consumption of fish, subsistence populations	Man	7.59e-02	3.04e-02	1.52e-01	D08b
Chronic/Longer Term Exposures					
Contaminated fruit	Woman	4.41e-03	4.41e-03	8.04e-02	D04
Consumption of water	Man	5.71e-05	4.00e-06	5.49e-04	D07
Consumption of fish, general public	Man	1.09e-07	1.09e-08	8.69e-07	D09a
Consumption of fish, subsistence populations	Man	8.79e-07	8.79e-08	7.04e-06	D09b

Table 3-4: Glyphosate specific pesticide parameters used in GLEAMS modeling and estimation of concentrations in ambient water

Parameter	Clay	Loam	Sand	Comment/ Reference
Halftimes (days)				
Aquatic Sediment	203	203	203	Dix 1998
Foliar	10	10	10	Note 1
Soil	30	30	30	Note 2
Water	1000	1000	1000	Note 3
Ko/c	2000	2000	2000	Note 4
K_d	2600	2100	500	Note 5
Water Solubility, mg/L	12000	12000	12000	Note 6
Foliar wash-off fraction	0.5	0.5	0.5	Leung 1994

Note 1 Central value from Feng and Thompson 1990 and Newton et al. 1984.

Note 2 Typical value from Table 2-2

Note 3 Gyphosate is stable in water at neutral pH. Ignore microbial degradation for modeling.

Note 4 Highly variable. Used geometric mean from Gerritse et al. 1996

Note 5 Use ranges from USDA/ARS 1995. Central value for loam, lower value for sand, and upper value for clay.

Note 6 Value for acid given by Tomlin (1994) and USDA/ARS (1995)

Table 3-5: Estimated concentrations of glyphosate in a small (0.25 acre, 1 meter deep) pond adjacent to a 10 acre plot based on GLEAMS modeling with different soil types and annual rainfall rates and using a normalized application rate of 1 lb/acre.

Annual Rainfall	Concentrations in Ambient Water (µg/L per lb/acre)					
	Clay		Loam		Sand	
	Average	Maximum	Average	Maximum	Average	Maximum
5	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
10	0.00012	0.00030	0.09440	0.17565	1.10442	2.05992
15	0.13807	0.25089	0.34458	0.63596	3.18058	5.97802
20	0.29624	0.54061	0.73480	1.35134	5.60349	10.69358
25	0.47944	0.74475	1.14161	2.02281	8.10309	15.85858
50	0.75344	1.65665	1.39087	3.09125	4.34293	15.06299
100	0.97995	3.20707	1.53840	5.39600	3.30534	20.35153
150	1.03871	4.27997	1.49796	6.84364	2.73199	22.74196
200	1.03666	5.06852	1.41487	7.92040	2.33566	25.83345
250	1.01076	5.78976	1.32712	8.79284	2.04561	27.84026

Table 3-6: Estimated concentrations of glyphosate in a small stream (4,420 m^3/day) adjacent to a 10 acre plot based on GLEAMS modeling with different soil types and annual rainfall rates and using a normalized application rate of 1 lb/acre.

Annual Rainfall	Concentrations in Ambient Water (µg/L per lb/acre)					
	Clay		Loam		Sand	
	Average	Maximum	Average	Maximum	Average	Maximum
5	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
10	0.00001	0.00492	0.00703	0.62660	0.02064	2.13822
15	0.01267	1.12481	0.02556	2.33913	0.05947	6.64604
20	0.02713	2.44600	0.05435	5.10484	0.10512	12.47003
25	0.05311	4.88123	0.08585	8.26234	0.15311	19.10679
50	0.18321	18.06811	0.26291	28.05858	0.37979	56.63863
100	0.45951	52.78010	0.59880	77.47465	0.73684	140.44210
150	0.69588	92.44662	0.86220	132.26409	0.98828	227.07054
200	0.88933	135.15046	1.06546	190.09709	1.17292	314.68937
250	1.04689	180.02965	1.22476	250.14160	1.31401	402.83056

Table 3-7: Summary of risk characterization (HQ's[1]) for workers.

Acute RfD	2	mg/kg/day	Sect. 3.3.3.	
Chronic RfD	2	mg/kg/day	Sect. 3.3.3.	

Scenario	Hazard Quotient Based on Chronic RfD			Exposure Assessment Worksheet
	Central	Lower	Upper	
General Exposures [using Chronic RfD]				
Directed ground spray (Backpack)	1e-02	5e-04	8e-02	C01a
Broadcast ground spray (Boom spray)	2e-02	7e-04	2e-01	C01b
Aerial applications	1e-02	2e-04	8e-02	C01c
Accidental/Incidental Exposures [using Acute RfD]				
Scenario	Hazard Quotient Based on Acute RfD			Exposure Assessment Worksheet
	Central	Lower	Upper	
Immersion of Hands, 1 minute	4e-06	4e-07	3e-05	C02a
Contaminated Gloves, 1 hour	2e-04	2e-05	2e-03	C02b
Spill on hands, 1 hour	5e-04	6e-05	2e-03	C03a
Spill on lower legs, 1 hour	1e-03	1e-04	6e-03	C03b

[1] Hazard quotient is the level of exposure divided by the RfD then rounded to one significant decimal place or digit. See Table 3-1 for summary of exposure assessment.

Table 3-8: Summary of risk characterization (HQ's[1]) for the general public[1].

Chronic RfD		2	mg/kg/day	Sect. 3.3.3.	
Acute RfD		2	mg/kg/day	Sect. 3.3.3.	
Scenario	Target	Hazard Quotient			Worksheet
		Central	Lower	Upper	
Acute/Accidental Exposures					
Direct spray, entire body	Child	2e-02	2e-03	9e-02	D01a
Direct spray, lower legs	Woman	2e-03	2e-04	9e-03	D01b
Dermal, contaminated vegetation	Woman	1e-03	3e-04	3e-03	D02
Contaminated fruit	Woman	4e-03	4e-03	7e-02	D03
Contaminated water, spill	Child	7e-01	2e-01	**2**	D05
Contaminated water, stream	Child	2e-03	5e-05	5e-02	D06
Consumption of fish, general public	Man	8e-03	3e-03	2e-02	D08a
Consumption of fish, subsistence populations	Man	4e-02	2e-02	8e-02	D08b
Chronic/Longer Term Exposures					
Contaminated fruit	Woman	2e-03	2e-03	4e-02	D04
Consumption of water	Man	3e-05	2e-06	3e-04	D07
Consumption of fish, general public	Man	5e-08	5e-09	4e-07	D09a
Consumption of fish, subsistence populations	Man	4e-07	4e-08	4e-06	D09b

[1] Hazard quotient is the level of exposure divided by the RfD. See Table 3-3 for a summary of the exposure assessments.

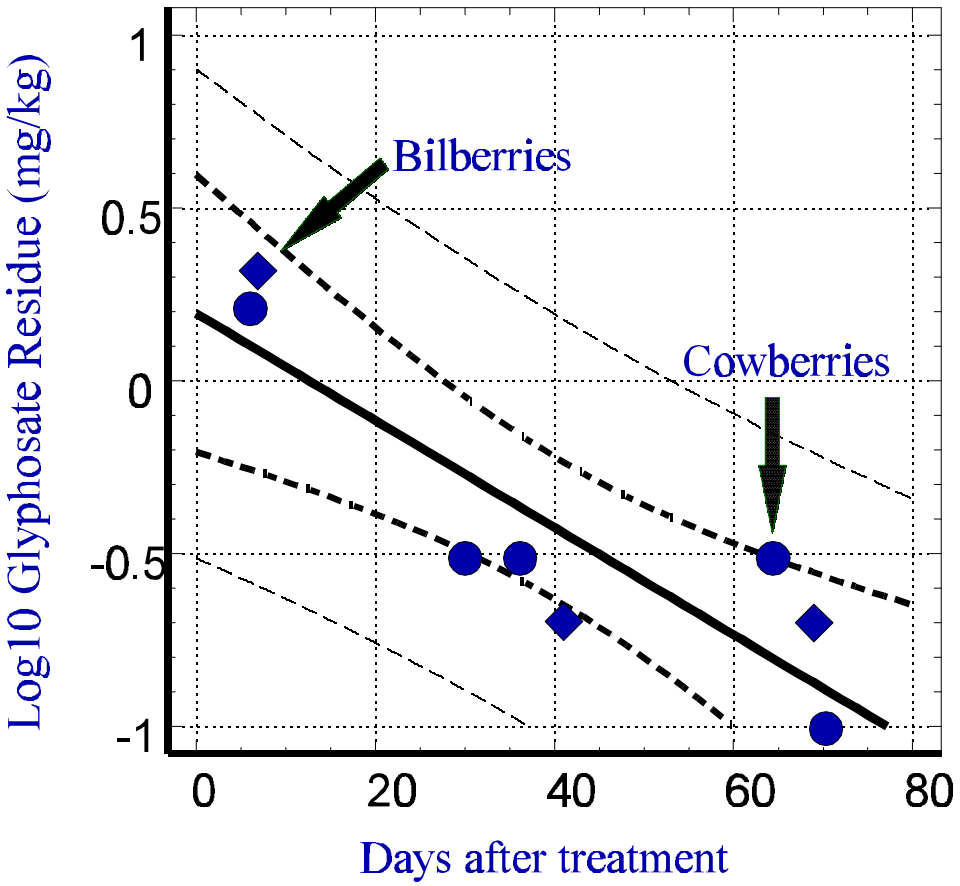


Figure 3-1: Residues of glyphosate on cowberries and bilberries after the application of glyphosate at 0.67 lb/acre (data from Siltanen et al. 1981).

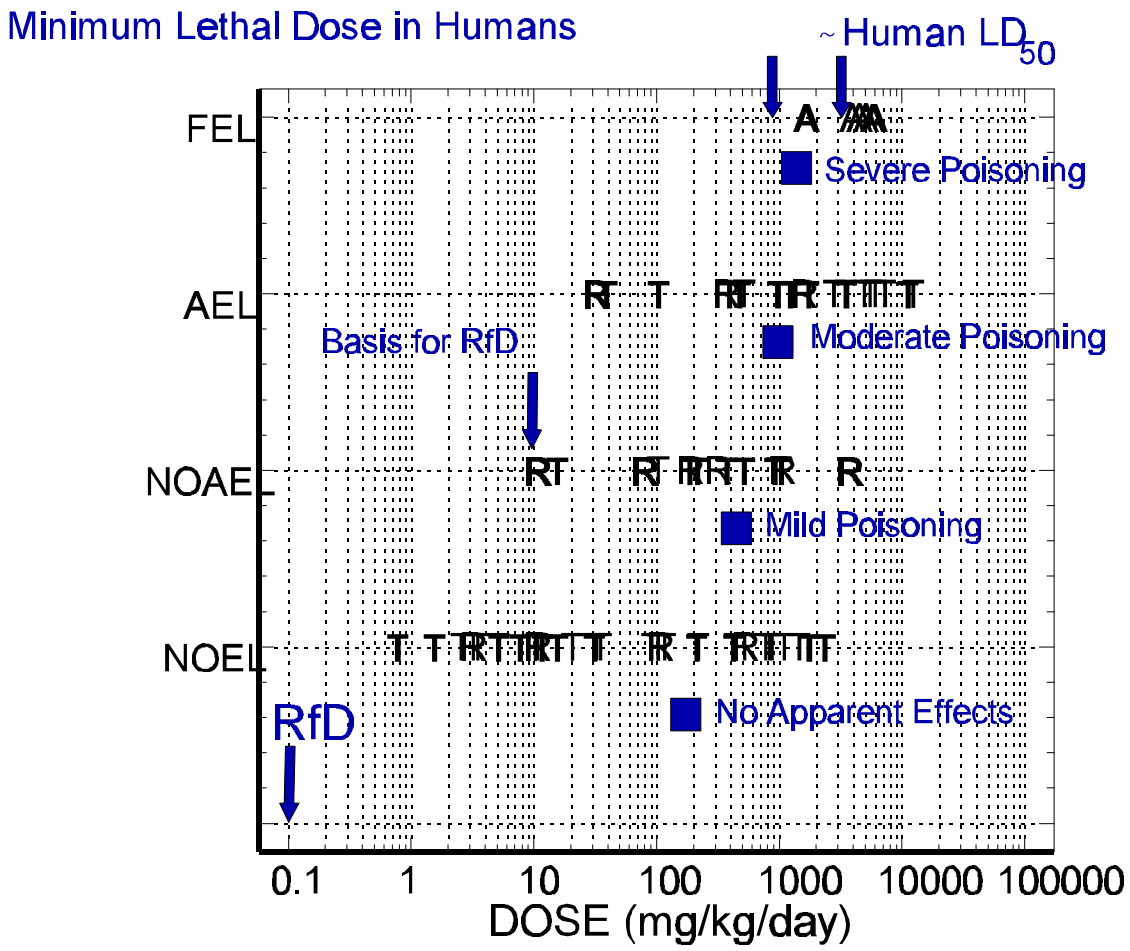


Figure 3-2: Dose-Severity Relationships for glyphosate [see text for details]

4. ECOLOGICAL RISK ASSESSMENT

4.1. HAZARD IDENTIFICATION

4.1.1. Overview. There are several standard toxicity studies in experimental mammals that were conducted as part of the registration process and there is a large body of published information on the toxicity of glyphosate to mammals. Just as these studies are used in the human health risk assessment to identify the potential toxic hazards associated with exposures to glyphosate, they can also be used to identify potential toxic effects in wildlife mammalian species. Loss of body weight is the most commonly seen effect of glyphosate in mammals. Inhibition of oxidative phosphorylation has been implicated as a possible mechanism by which glyphosate causes weight loss in experimental mammals; however, there is not adequate information about terrestrial wildlife from which to make a further assessment about the importance of this mechanism. As in the human health risk assessment, the potential significance of non-specific toxic effects can be assessed from the available toxicity studies in mammals. Because toxicity data in mammals are available in few species of experimental mammals, the use of these data to assess the potential hazards to large number of diverse mammalian wildlife species is an uncertain process. Nonetheless, there do not appear to be any systematic differences among mammalian species, including humans, when comparable toxicity values are expressed in units of mg/kg/day. While the available data are limited, this apparent consistency among species diminishes concern with the use of data based on a limited subset of species to characterize risk for terrestrial mammals in general.

In assessing potential effects in birds, the most relevant data for this risk assessment are the standard dietary and bird reproduction studies required for registration as well as the acute oral LD_{50} studies. The available toxicity studies do not suggest any specific or unique toxicity in birds compared to mammals. As in mammals, there is suggestive evidence that glyphosate may inhibit oxidative phosphorylation and consequently reduce food conversion efficiency. Also consistent with the data in experimental mammals is the apparent lack of teratogenic activity in birds.

The honey bee is the standard test organism for assessing the potential effects of pesticides on terrestrial invertebrates and there is a standard set of studies available on this species. In addition, studies are available on a relatively wide range of other terrestrial invertebrates including earthworms, isopods, snails, spiders, butterflies, and other terrestrial arthropods.

Glyphosate is readily metabolized by soil bacteria and many species of soil microorganisms can use glyphosate as sole carbon source. Nonetheless, microorganisms, like higher plants, do have the shikimate pathway for the production of aromatic amino acids. At the molecular level, glyphosate occupies the binding site of phosphoenol pyruvate, the second substrate of 5-enolpyruvylshikimate 3-phosphate synthase, mimicking an intermediate state of the ternary enzyme-substrate complex. This inhibits the shikimic acid pathway in plants, effectively blocking the synthesis of certain phenolic compounds and the synthesis of aromatic amino acids. This, in turn, leads to a variety of toxic effects in plants, including the inhibition of photosynthesis in plants as well as inhibition of respiration and nucleic acid synthesis in plants and microorganisms.

Since glyphosate inhibits this pathway, toxicity to microorganisms may be expected and glyphosate has been considered as an antimicrobial agent for human pathogens. Nonetheless, there is very little information suggesting that glyphosate will be harmful to soil microorganisms under field conditions and a substantial body of information indicating that glyphosate is likely to enhance or have no effect on soil microorganisms. Most field studies involving microbial activity in soil after glyphosate exposures note an increase in soil microorganisms or microbial activity and the application of glyphosate may cause transient increases in soil fungi that may be detrimental to some plants. While the mechanism of this apparent enhancement is unclear, it is plausible that glyphosate treatment resulted in an increase in the population of pathogenic fungi in soil because glyphosate was used as a carbon source by the fungi and/or treatment with glyphosate resulted in increased nutrients for fungi in the soil. There is no indication that the transient enhancement in populations of soil fungi or bacteria will result in any substantial or lasting damage to soil ecology.

In higher plants, inhibition of the shikimic acid pathway leads to an inhibition or cessation of growth, cellular disruption, and, at sufficiently high levels of exposure, plant death. The time course for these effects can be relatively slow, depending on the plant species, growth rate, climate, and application rate. Gross signs of toxicity include wilting and yellowing of the vegetation, followed by browning, breakdown of plant tissue, and, ultimately, root decomposition. Standard toxicity studies are available on seedling emergence and vegetative vigor in a number of different plant species. The drift studies are also highly relevant to the assessment of risk in that unintended drift is one of the more plausible exposure scenarios for nontarget terrestrial plant species. The lowest reported effect level in drift studies is 1/33 of an application rate of 1.121 kg/ha that was associated with transient damage in soybeans. This treatment corresponds to 0.034 kg/ha [1.121 kg/ha ÷ 33] or about 0.03 lb/acre. At much higher concentrations – in the range of 0.7 lbs/acre – there is a plausible basis for concern that exposure to substantial glyphosate drift may have long term impacts on bryophyte and lichen communities.

In addition to the laboratory bioassays or field observations on single species, there are a number field studies that have assessed the effects of glyphosate on groups of terrestrial organisms, both animals and plants. These studies indicate that effects on terrestrial animals are likely to be secondary to effects on vegetation when glyphosate is applied at application rates comparable to or greater than those contemplated by the Forest Service. In some cases, the effects noted in filed studies appeared to be beneficial to some species under study. In most cases, the effects noted were changes in population density that reflected changes in food availability or suitable habitat.

In aquatic species, the acute lethal potency of glyphosate and glyphosate formulations has been relatively well-defined. These values are typically expressed as time-specific LC_x values where *x* is the estimate of the proportion of fish that die – e.g., 96 hour LC_{50}. A large number of acute LC_{50} values have been determined in various species of fish. As in the human health risk assessment, the formulation of glyphosate with surfactants, especially the POEA surfactant commonly used in glyphosate formulations, has a pronounced effect on the acute lethal potency of glyphosate.

The U.S. EPA typically uses LC_{50} values or fractions of LC_{50} values as the basis for characterizing risk, as in the U.S. EPA RED on glyphosate. A common concern with this approach is that more subtle non-lethal effects that may impact of the stability of fish populations in the field may not be properly assessed. The available information on the sub-lethal effects associated with glyphosate is summarized in this risk assessment and NOEC (no observable effect concentration) values form the basis of the risk characterization.

Lastly, field studies are available on the effects of glyphosate applications on fish populations. As with the risk characterization for terrestrial species, these studies have limitations in terms of their quantitative use in a risk assessment but are nonetheless highly relevant to the risk assessment and may be used to further assess the quality of the risk characterization based on laboratory bioassay.

The toxicity of glyphosate to aquatic plants has been evaluated by U.S. EPA based on studies submitted for the registration of glyphosate. In addition, several studies are available from the open literature as well as more recent studies submitted to U.S. EPA. These studies are available for both algae and aquatic macrophytes. As would be expected from a herbicide, glyphosate is much more toxic to aquatic plants than animals.

4.1.2. Toxicity to Terrestrial Animals.

4.1.2.1. Mammals – As summarized in the human health risk assessment (Section 3.1), there are several standard toxicity studies in experimental mammals that were conducted as part of the registration process and there is a large body of published information on the toxicity of glyphosate to mammals. Just as these studies are used in the human health risk assessment to identify the potential toxic hazards associated with exposures to glyphosate, they can also be used to identify potential toxic effects in wildlife mammalian species.

Loss of body weight is the most commonly seen effect of glyphosate in mammals. Inhibition of oxidative phosphorylation has been implicated as a possible mechanism by which glyphosate causes weight loss in experimental mammals (see section 3.1.2); however, there is not adequate information about terrestrial wildlife from which to make a further assessment about the importance of this mechanism. As in the human health risk assessment, the potential significance of non-specific toxic effects can be assessed from the available toxicity studies (Appendices 3 through 6).

The WHO (1994) criteria document summarizes a study in heifers that is cited on several material safety data sheets (MSDS's in C&P Press, 2002) for glyphosate formulations. According to WHO (1994), this study involved dosing of Brahman-cross heifers with Roundup at 400, 500, 630 or 790 mg/kg body weight per day by nasogastric intubation. At 790 mg/kg, some animals died with labored breathing and pneumonia from the aspiration of rumen contents. This is consistent with lung damage seen in experimental mammals (Section 3.1.4). Additional signs of toxicity at 500, 630 and 790 mg/kg body weight included diarrhoea and decreased food intake. No adverse effects were observed at 400 mg Roundup/kg bw (equivalent to 215 mg a.i./kg bw or about 160 mg a.e./kg bw). Although this report is attributed to Monsanto Inc, this study was not

found in a search of the U.S. EPA studies submitted for registration. The MSDS for Glyphosate Original (C&P Press, 2002) is consistent with this summary but the MSDS's for for Aqua Neat, Debit TMF, Eagre, Forester's Non-Selective Herbicide, and Glyphosate contain a different summary:

> *This product was administered to Brahman-cross heifers by gavage at daily doses of 0, 540, 830, 1290, or 2000 mg/kg for 7 consecutive days. Clinical signs of toxicity, including loss of appetite, diarrhea, and death (1290 and 2000 mg/kg) were observed at 830 mg/kg or above. The no-effect level was considered to be 540 mg/kg/day.*

The reason for differences between these summaries is unclear.

A reported incident of fatal poisoning of a horse by drift from glyphosate was investigated by the Texas Department of Agriculture (1992), which made the determination that glyphosate was not the cause of death and that the horse died of natural causes.

Because toxicity data in mammals are available in few species of experimental mammals, the use of these data to assess the potential hazards to large number of diverse mammalian wildlife species is an uncertain process. One approach to this process involves identifying patterns of toxicity in mammals of various sizes (i.e., allometric relationships as discussed in SERA 2001a, Section 3.2.). As detailed in Section 4.3.2 (Dose Response Assessment for Terrestrial Species), there do not appear to be any systematic differences among mammalian species, including humans, when comparable toxicity values are expressed in units of mg/kg/day. While the available data are limited, this apparent consistency among species diminishes concern with the use of data based on a limited subset of species to characterize risk for terrestrial mammals in general.

4.1.2.2. Birds – The most relevant data for this risk assessment are the standard dietary and bird reproduction studies required for registration as well as the acute oral LD_{50} studies. The toxicity of glyphosate on acute gavage administration to birds is >2000 mg/kg (Fink et al. 1978), comparable to that seen in experimental mammals. No effects on reproduction have been seen in bobwhite quail (Fink 1975) and mallard ducks (Fink and Beavers 1978) at concentration of up to 1000 ppm.

While the available toxicity studies do not suggest any specific or unique toxicity in birds, the study in zebra finches by Evan and Batty (1986) noted pronounced weight loss in animals after dietary exposures to 5000 ppm glyphosate for 3 to 7 days accompanied by a 20-30% decrease in food consumption but a 30-60% decrease in body weight. This is consistent with observations in experimental mammals suggesting that glyphosate may inhibit oxidative phosphorylation and consequently reduce food conversion efficiency.

Also consistent with the data in experimental mammals is the apparent lack of teratogenic activity in birds. There is no indication that glyphosate or Roundup causes birth defects in birds (Batt et

al. 1980, Hoffman and Albers 1984). The study by Hoffman and Albers (1984) is somewhat difficult to interpret because of the way in which doses are expressed—lb/acre at 100 gallons/acre. In this study, eggs were immersed in various concentrations of several pesticides, including glyphosate, for approximately 30 seconds and observed throughout development. The reported LC_{50} for glyphosate from Roundup is 178 lbs/acre at 100 gallons/acre. This probably corresponds to a concentration of 80.1 kg ÷ 378.5 L

$$(178 \text{ lbs} \cdot 0.45 \text{ kg/lb}) \div (100 \text{ gallons} \cdot 3.785 \text{ L/gallon})$$

or approximately 200 g/L, which corresponds to a solution of about 20% (w/v). This is consistent with the NOEL reported by Batt et al. (1980), which involved a less severe exposure-immersion in a 5% solution for 5 seconds. It should also be noted that the apparent application rate of 178 lbs/acre is substantially higher than the maximum annual labeled application rate of 10.6 lbs/acre.

4.1.2.3. Invertebrates – The honey bee is the standard test organism for assessing the potential effects of pesticides on terrestrial invertebrates and there is a standard set of studies available on this species (Palmer and Beavers 1997c; Palmer and Krueger, 2001a; Palmer and Krueger, 2001b). In addition, studies are available on a relatively wide range of other terrestrial invertebrates including earthworms, isopods, snails, spiders, butterflies, and other terrestrial arthropods.

In standard oral and contact bioassay summarized by U.S. EPA/OPP (1993c), the LD_{50} values for bees was over 100 µg/bee. Three more recent studies have been submitted to the U.S. EPA that are consistent with these earlier reports. In an acute contact toxicity assay, no effects were seen at 100 µg/bee (Palmer and Beavers 1997c). Similar results have been reported recently for a newer formulation, MON 77360, in which the NOEC based on mortality in contact toxicity was also 100 µg (Palmer and Krueger 2001a). This dose is classified as a NOEC because mortality (3/60 animals) was not significantly different from mortality in the matched solvent control (0/60, p=0.12 using the Fisher exact test). Combining the matched solvent control (0/60) with the negative control (0/60) for a combined control response of 0/120, the mortality of 3/60 animals is statistically significant (p=0.0358 using the Fisher exact test) although low (3/60 = 5%). No mortality (0/60) was observed at the next lower dose (50 µg/bee) or at any of the other lower doses down to 6.25 µg/bee.

In an acute dietary study (Palmer and Krueger 2001b), the 48 h oral LD_{50} is reported as >100 µg/bee based on a 11.7% mortality (7/60) at the highest dose tested. The NOEC is reported as 50 µg/bee based on 5% mortality (3/60). Again, this response rate is not significant with respect to solvent matched controls (0/60) but is significant is solvent and negative controls are combined (0/120, p=0.0358 using the Fisher exact test). It should be notes that high mortality (26/60) was observed at 12.5 µg/bee but this was attributed to an unidentified failure in the test apparatus that resulted in apparently substantial direct contact with the test solution. While this sort of unexpected low dose response is noteworthy, the low mortality at higher doses (i.e., 1/60 at 25

µg/bee and 3/60 at 50 µg/bee) supports the assessment of Palmer and Krueger (2001b) that the high mortality at 12.5 µg/bee was an aberration.

Glyphosate has been tested as an insecticide for spider mites, *Tetranychus urticae*, a pest species on apple trees (Ahn et al. 1997) as well as for toxicity to *Typhlodromus pyri*, an important predator of spider mites (Weppleman 1998b). Direct foliar spray of glyphosate IPA at 0.593 to 4.74 mg ai per leaf (kidney bean plants) had no effect on the spider mite based on mortality in eggs, larva, nymphs or adults (Ahn et al. 1997) an was essentially ineffective as an insecticide.

Applications equivalent to 10 L/ha RoundUp ULTRA (glyphosate isopropylame salt at 360 g/L or an application rate of 3.6 kg a.i./ha) applied to glass slides caused 100% mortality in spider mites after 24 hours of contact and was classified as "harmful" (Weppleman 1998a) . In a similar assay using *Aphidius rhopalosiphi* (a beneficial wasp that is a parasite of the cereal aphid), the same contact exposure also resulted in 100% mortality after 24 hours. The relevance of the studies by Weppleman (1998a and 1998b) to the assessment of potential effects under normal use is unclear. As noted in Weppleman (1998a),

> *the 5% v/v test solution of Roundup ULTRA produced a wet sticky layer on the treated glass plates that resulted in alterations of the moving behavior of the wasps to the point of sticking.*

In other words, it appears the application of the glyphosate formulation to the glass slides cause the test organism to stick to the slides and this may have contributed to the observed mortality.

Haughton et al. (1999; 2001a; 2001b) have conducted a series of laboratory and field studies on the effects of glyphosate on the spider, *Lepthyphantes tenuis*. Direct spray laboratory bioassays at rates equivalent to 180, 360, 720, 1080 , 1440, and 2160 g/ha resulted in low rates of mortality that were not dose related (Haughton et al. 2001a). In the field, application rates of 360, 720, and 1440 g ae/ha resulted in decreased spider populations that were attributed to secondary effects from changes in the vegetation (Haughton et al. 2001b). No substantial effects were observed in spider populations at application rates of 90 or 180 g a.e./ha (Haughton et al. 1999).

Data on other arthropods are less detailed but also indicate a low potential for a direct toxic effect from glyphosate. In a laboratory study in which isopods were exposed to leaf litter at levels equivalent to application rates of 2.1 kg/ha, the effect on litter degradation depended on the tree species. Direct toxic effects—evidenced by increased mortality—could not be ruled out but were not statistically significant (Eijsackers 1992). Samsoe-Petersen (1995) report no measurable effect on rove beetle (mortality and egg production) after spray of substrate with 1% Roundup (3.6 g/L) at 6 µL/cm^2. Bramble et al. (1997) conducted a series of studies on effects of using herbicides (including glyphosate) in rights-of-way maintenance compared to using mechanical maintenance and noted no significant or substantial differences in butterfly populations.

Three studies are available relating to the potential effects of glyphosate on earthworms. In a laboratory study, effects on earthworm cultures treated at levels equivalent to application rates of 0.7 to 2.8 g glyphosate/ha included decreased growth rates and early mortality (Springett and Gray 1992). The direct relevance of this study is limited, however, because the exposure conditions (spraying twice weekly on culture dishes) do not closely approximate field conditions. Dalby et al. (1995) report no effects on earthworms in applications designed to mimic agricultural use. This study, however, does not report exposures either as g/ha or ppm soil and thus cannot be used directly in this risk assessment. The soil LC_{50} for glyphosate to *Aporrectodea caliginosa*, a worm common in Libya, has been reported to be 246 to 177 mg glyphosate/kg soil dry weight over exposure periods of 8 to 37 days (Mohamed et al. 1995).

One study is available on the toxicity of glyphosate to a terrestrial snail, *Helix aspersa*, Brown garden snail, in which diets containing 4994 ppm glyphosate resulted in no mortality over a 14 day exposure period. Assuming a 30% food consumption factor for this species (APHIS 1993), this corresponds to a dose of about 1,500 mg/kg (4994 ppm × 0.3 mg/kg bw ppm = 1498.2 mg/kg bw).

4.1.2.4. Soil Microorganisms. As noted in Section 3.1.15.1, glyphosate is readily metabolized by soil bacteria with AMPA as a major metabolite. In addition, many species of soil microorganisms can use glyphosate as sole carbon source (Dick and Quinn 1995a; Dick and Quinn 1995b; Dotson et al. 1996; Wardle and Parkinson 1992a). Microorganisms, like higher plants, do have the shikimate pathway for the production of aromatic amino acids. Since glyphosate inhibits this pathway, toxicity to microorganisms may be expected (Cox 2002; Issa 1999). As noted in Section 3.1.2, glyphosate has been considered as an antimicrobial agent for human pathogens. Nonetheless, there is very little information suggesting that glyphosate will be harmful to soil microorganisms under field conditions and a substantial body of information indicating that glyphosate is likely to enhance or have no effect on soil microorganisms (Busse et al. 2001; Wardle and Parkinson 1990a,b; Wardle and Parkinson 1991).

As reviewed by Cox (2002), a number of studies have demonstrated effects on soil microorganisms under laboratory conditions that are consistent with the ability of glyphosate to inhibit the shikimate pathway. For example, Issa (1999) noted that the growth of soil algae and cyanobacteria may be inhibited by glyphosate in artificial culture media at concentrations of 5 and 20 mM – i.e., about 845 and 3,380 mg/L. Roundup was a more potent inhibitor than glyphosate IPA, which was in turn a more potent inhibitor than the free acid of glyphosate. The decreased growth was associated with shikimate accumulation and was antagonized by excess aromatic amino acids. Thus, this inhibition is consistent with the inhibition of the shikimate pathway.

Wan et al. (1998) noted an inhibition of extraradical mycelial growth in *Glomus intraradices* after 14 days exposure in a preparation with carrot roots in a culture medium containing 0.5 ppm glyphosate. This effect, however, was attributed to an effect of glyphosate on the carrot roots rather than a direct toxic effect on the fungi. Direct toxic effects on soil fungi in culture medial have been demonstrated by Chakravarty and Sidhu (1987) at concentrations of 10 ppm or greater.

At application rates of 0.54 kg/ha, a transient decrease in populations of soil fungi and bacteria was noted after 2 months but no effect was apparent after 6 months. Similarly, at an application rate of 3.23 kg/ha, no effect was seen on soil fungi and bacteria after 10-14 months (Chakravarty and Chatarpaul 1990). A transient decrease in soil microbial activity was also noted by Wardle and Parkinson (1992b) after the application of glyphosate at 5 kg/ha. Sannino and Gianfreda (2001) report that glyphosate inhibited soil phosphatase activity at 20 mM. This inhibition, however, was attributed to competitive inhibition of p-nitrophenylphosphate, the substrate used in the phosphatase assay, by glyphosate. Thus, the inhibition of phosphatase activity was an artifact of the assay method rather than an indication of glyphosate toxicity.

Soil concentrations of 100 ppm of glyphosate or AMPA had no significant effect on soil denitrification (Pell et al. 1998). Bromilow et al. (1996) noted no effects on soil fertility in repeated applications over 14 years – 1980 to 1993 – of glyphosate at 1.4 kg/ha based on assays for microbial biomass and crop productivity.

Several field studies involving microbial activity in soil after glyphosate exposures note an increase rather than decrease in soil microorganisms or microbial activity (Haney et al. 2002; Hart and Brookes 1996; Laatikainen and Heinonen-Tanski 2002; Nicholson and Hirsch 1998). As discussed by Kremer (2002), the application of glyphosate may cause transient increases in soil fungi that may be detrimental to some plants. For example, Descalzo et al. (1996a,b) has shown that inoculation of soil with various pathogenic soil fungi may result in an apparent enhancement of glyphosate toxicity.

4.1.2.5. Toxicity to Terrestrial Plants. Studies on the mechanism of action of glyphosate are numerous (Anthelme and Marigo 1998; Green et al. 1992; Hernandez et al. 1999; Hernandez et al. 2000; Hetherington et al. 1998; Jain et al. 2002; Pline et al. 2002; Uotila et al. 1995; Singh and Shaner 1998; Schonbrunn et al. 2001). At the molecular level, glyphosate occupies the binding site of phosphoenol pyruvate, the second substrate of 5-enolpyruvylshikimate 3-phosphate synthase, mimicking an intermediate state of the ternary enzyme-substrate complex. This inhibits the shikimic acid pathway in plants, effectively blocking the synthesis of certain phenolic compounds and the synthesis of aromatic amino acids. This, in turn, leads to a variety of toxic effects in plants, including the inhibition of photosynthesis, respiration, and nucleic acid synthesis.

At the level of the whole plant, inhibition of the shikimic acid pathway leads to an inhibition or cessation of growth, cellular disruption, and, at sufficiently high levels of exposure, plant death. The time course for these effects can be relatively slow, depending on the plant species, growth rate, climate, and application rate. Gross signs of toxicity, which may not be apparent for 2–4 days in annuals or for more than 7 days in perennials, include wilting and yellowing of the vegetation, followed by browning, breakdown of plant tissue, and, ultimately, root decomposition.

There are a large number of efficacy studies on glyphosate (e.g., Bariuan et al. 1999). For the most part, this risk assessment is not concerned with efficacy studies and these studies are not

covered. Nonetheless, some efficacy studies focus on understanding the pharmacology of glyphosate in plants and such studies are germane to assessing potential effects in nontarget vegetation. Glyphosate is absorbed primarily through the foliage, and the absorption is rapid. Approximately 33% of the applied glyphosate is absorbed within a few hours after application. Glyphosate absorption by plants may be enhanced by high humidity (Schonherr 2002). Because glyphosate is strongly adsorbed to soil, relatively little if any absorption occurs through the roots (Smith and Oehme 1992). The production of ^{14}C from plant associated material does not appear to be correlated with soil microbial biomass (Von Wiren-Lehr et al. 1997). In actively growing plants, translocation involves cell to cell transport through the cuticle followed by long distance transport via vascular tissue. In dormant plants, transport is much slower and may be negligible. Glyphosate is not extensively metabolized or detoxified in plants. In plants that share a common seedpiece or propaglue node, such as sugar cane, translocation from plant to plant can result in injury to plants that are not treated directly (Dal Piccolo et al. 1980). At least in sugar beets, the difference between tolerant and susceptible strains is in the rate of excretion of glyphosate (Geiger et al. 1999). The retention of glyphosate on foliage is affected by the use of adjuvants with a wash off of about 50% with adjuvants and 64% without adjuvants (Leung 1994). As with many herbicides, glyphosate may produce a hormetic response in some species, causing a stimulation of growth at low concentrations and an inhibition only at higher concentrations (Schabenberger et al. 1999). This type of response has also been noted in other studies (e.g., yields of smartweed and soybeans in Figure 2, p. 1195 of Fletcher et al. 1996).

As noted in the U.S. EPA/OPP (1993c) RED for glyphosate, data submitted up to 1993 did not include bioassays for vegetative vigor (i.e., direct application to foliage after plants have emerged) or sufficient studies on the effects of drift on non-target species. The only data on toxicity to terrestrial plants summarized in the RED involved seedling emergence assays using a 50% solution of glyphosate IPA. In this assay (Bohn 1987), glyphosate applications of up to 10 lb a.i./acre resulted in <25 % effect on the monocots and dicots tested.

Since the publication of the RED, additional studies have been submitted to the U.S. EPA or published in the open literature on seedling emergence (Willard 1996; Everett et al. 1996a; Suma et al. 1995) and vegetative vigor (Chetram and Lucash 1994; Everett et al. 1996b). In addition, several studies have been conducted on the effects of drift on nontarget plant species (Al-Khatib and Peterson 1999; Bhatti et al. 1997; De Jong and de Haes 2001; Fletcher et al. 1996; Gilreath et al. 2001; Marrs and Frost 1997; Newmaster et al. 1999).

The studies on seedling emergence submitted to the U.S. EPA involve a water dispersible granule formulation (Willard 1996) and a wettable powder formulation (Everett et al. 1996a). Additional details on the formulations cannot be disclosed in this risk assessment. Both studies were consistent with earlier reports indicating no adverse effects in monocots and dicots at application rates of about 4.5 lb a.e./acre. In an open literature publication by Shuma e tal. (1995), a Roundup formulation (356 g a.i./L) was associated with complete inhibition of seed viability when applied to oats 15 days after anthesis (flowering or seed formation) at an application rate of 1.76 kg/ha (about 1.6 a.i. lb/acre) and applications as low as 0.44 kg/ha partially inhibited seed

germination. This study is not inconsistent with the studies by Everett et al. (1996a) or Willard (1996). These latter studies involved standard test protocols in which seeds were exposed directly rather than harvested from plants after anthesis.

The two vegetative vigor studies (Chetram and Lucash 1994; Everett et al. 1996b) both follow similar experimental designs. Various monocots and dicots are grown from seeds to emergence prior to any herbicide application. After the leaves emerge, the plants are sprayed at various rates – expressed in the same units as application rate – to assess the consequences of direct spray and drift. In the study by Everett et al. (1996b) glyphosate was applied as a wettable powder formulation. The most sensitive species was the dicot, oilseed rape *(Brassica napus)*, with an EC_{25} of 0.083 kg a.e./ha (0.07 lb a.e./acre) and EC_5 of 0.042 kg a.e./ha (0.037 lb a.e./acre). The least sensitive species was the monocot, Purple Nutsedge (*Cyperus rotundus*), with an EC_{25} of 0.891 kg a.e./ha (0.79 lb a.e./acre) and EC_5 of 0.58 kg a.e./ha (0.52 lb a.e./acre). The EC_5 values are essentially NOECs. In the study by Chetram and Lucash (1992), the most sensitive species based on reduced growth were tomato and radish, with a NOEC of 0.035 lb a.e./acre and the least sensitive species were ryegrass, corn, and onions with a NOEC of 0.56 lb a.e./acre.

The drift studies are also highly relevant to the assessment of risk in that unintended drift is one of the more plausible exposure scenarios for nontarget terrestrial plant species (Section 4.2). The lowest reported effect level in drift studies is the report by Al-Khatib and Peterson (1999) that 1/33 of an application rate of 1.121 kg/ha was associated with transient damage in soybeans, based on an assessment of visual injury, over a 30 day period after application but no net decrease in soybean production by the end of the season. This treatment corresponds to 0.034 kg/ha [1.121 kg/ha ÷ 33] or about 0.03 lb/acre. A study by the same authors found that grapes were much less sensitive, evidencing damage at exposures equivalent to one-third of the application rate. A grass (*Poa annua*) and a dicot (*Brassica napus*) both exhibited substantial damage at deposition rates of over 1000 $\mu g/m^2$ or about 1.8 lbs/acre. Fletcher et al. (1996) found that simulated drift in the range of 0.4% to 0.8% of an application rate of 0.43 kg/ha had no marked effect on canola, smartweed, soybean or sunflower plants.

The study by Newmaster et al. (1999) suggests that some bryophytes and fungi may be sensitive to long term effects after glyphosate exposure. The EC_{50} for a decrease in relative abundance two years after application is about 0.8 kg/ha or 0.7 lbs/acre (Newmaster et al. 1999, Figure 3, p. 1105). In addition, changes in relative abundance were apparent at six weeks after application (Newmaster et al. 1999, Figure 7, p. 1108). The statistical analyses presented by Newmaster et al. (1999) involves the use of a non-threshold polynomial model. While this may be a reasonable method for quantifying effects among the two herbicides studied (glyphosate and triclopyr), this may be less appropriate for risk assessment, as discussed further in Section 4.3 (dose-response assessment). Nonetheless, this study does appear to present a plausible basis for concern that exposure to substantial glyphosate drift may have long term impacts on bryophyte and lichen communities.

4.1.2.6. Field Studies – In addition to the laboratory bioassays or field observations on single species, there are a number field studies that have assessed the effects of glyphosate on groups of terrestrial organisms, both animal and plant (Appendix 8).

These studies indicate that at application rates comparable to or greater than those contemplated by the Forest Service effects on terrestrial animals are likely to be secondary to effects on vegetation. This has been demonstrated for moose (Santillo 1994), small mammals (Anthony and Morrison 1985; D'Anieri et al. 1987; Ritchie et al. 1987; Santillo et al. 1989a; Sullivan 1990; Sullivan et al. 1997; Sullivan et al. 1998a), rabbits (Hjeljord et al. 1988), birds (Cayford 1988; Easton and Martin 1998; Freemark and Boutin 1995; Linz et al. 1994 and 1996 ; Linz and Blixt 1997; MacKinnon and Freedman 1993; Solberg and Higgins 1993), carabid beetles (Brust 1990; Duchesne et al. 1999), and various other invertebrates (Byers and Bierlein 1984; Freemark and Boutin 1995; Moldenke 1992; Santillo et al. 1984; Yokoyama and Pritchard 1984).

In some cases, the effects noted in these studies appeared to be beneficial to the species under study [e.g., increased use by water fowl associated with an increase in open water after treatment with Rodeo (Solberg and Higgins 1993)]. In most cases, the effects noted were changes in population density that reflected changes in food availability or suitable habitat.

One report does indicate that use of glyphosate in conifer release will cause an initial decrease in leaves on deciduous trees that serve as a food source for white-tailed deer. This effect, however, is transient and followed by an increase in forb abundance (Vreeland et al. 1998). While glyphosate will certainly impact some plant species, no effects on plant diversity were noted in a study by Miller et al. (1999). Glyphosate residues or perhaps residues of adjuvants used with glyphosate have been shown to affect grazing preference in cattle (Jones and Forbes 1984) but not sheep (Kisseberth et al. 1986).

A concern with the direct use of field studies in a risk assessment is that field studies, like many epidemiology studies, may be difficult to interpret because of the nature of the "control group" and because some studies may not be sufficiently sensitive to detect subtle adverse effects. These concerns are reasonable. Nonetheless, it is worth noting that Sullivan et al. (1998b) was able to detect a decline in vole populations with an concomitant increase in chipmunk and deer mice populations due to a shift in the nature of the available food. While this is not to suggest that all of the field studies summarized in Appendix 8 are or would be highly sensitive to subtle changes and effects, it does support the qualitative use of these studies – along with the more quantitative use of laboratory toxicity studies – in the risk characterization (Section 4.4).

4.1.3. Aquatic Organisms

4.1.3.1. Toxicity to Fish

4.1.3.1.1. Overview – As with terrestrial species, the acute lethal potency of glyphosate and glyphosate formulations has been relatively well-defined. These values are typically expressed as time-specific LC_x values where *x* is the estimate of the proportion of fish that die – e.g., 96 hour LC_{50}. A large number of acute LC_{50} values have been determined in various species of fish.

These are summarized in Appendix 9 and discussed further in Section 4.1.3.1.2. As in the human health risk assessment (Section 3.1.14), the formulation of glyphosate with surfactants, especially the POEA surfactant commonly used in glyphosate formulations, has a pronounced effect on the acute lethal potency of glyphosate. These data are detailed in Section 4.1.3.1.3.

The U.S. EPA typically uses LC_{50} values or fractions of LC_{50} values as the basis for characterizing risk, as in the U.S. EPA/OPP (1993c) RED on glyphosate. A common concern with this approach is that more subtle non-lethal effects that may impact of the stability of fish populations in the field may not be properly assessed. The available information on the sub-lethal effects associated with glyphosate is summarized in Section 4.1.3.1.4 and, as discussed further in Section 4.3. (dose-response assessment), NOEC (no observable effect concentration) values form the basis of the risk characterization in this risk assessment.

Lastly, field studies are available on the effects of glyphosate applications on fish populations. As with the risk characterization for terrestrial species (Section 4.1.2.6), these studies have limitations in terms of their quantitative use in a risk assessment but are nonetheless highly relevant to the risk assessment and may be used to further assess the quality of the risk characterization based on laboratory bioassay. Thus, these studies are summarized in Section 4.1.3.1.5.

4.1.3.1.2. Standard Toxicity Studies – Glyphosate and glyphosate formulations have been tested in a large number of fish species and this information is summarized in Appendix 9. As summarized by U.S. EPA/OPP (1993c, p. 40), the 96-hour LC_{50} values in freshwater fish range from 86 (70-106) mg/L in rainbow trout for a 83% pure sample of technical grade glyphosate to 140 mg/L (120-170) mg/L in rainbow trout for a 97.6% pure sample of technical grade glyphosate (U.S. EPA/OPP 1993c, p. 40). Based on these bioassays, U.S. EPA/OPP (1993c) classified technical grade glyphosate as non-toxic to practically non-toxic in freshwater fish. Some bioassays of technical grade glyphosate resulted in much lower LC_{50} values – i.e., 10 mg/L for trout in soft-water (Wan et al. 1989) and about 3 mg/L for unfed flagfish (Holdway and Dixon 1988).

Some formulations of glyphosate can be much more toxic to fish than technical grade glyphosate. As also summarized by U.S. EPA/OPP (1993c) and detailed in Appendix 9, the 96-hour LC_{50} values for formulated glyphosate in freshwater fish range from 1.3 (1.1-16) mg/L in rainbow trout for a 41% glyphosate formulation to >1000 mg/L mg/L in rainbow trout and bluegill sunfish for a 62.4% glyphosate formulation (U.S. EPA/OPP 1993c, pp. 42-43). Based on these LC_{50} values, U.S. EPA/OPP (1993c) classified glyphosate formulations as moderately toxic to practically non-toxic in freshwater fish. The less toxic surfactants appear are identified only as "AA surfactant", "W" surfactant, and "x-77" surfactant. The "x-77" surfactant appears to be X-77®, a non-ionic alkylphenol ethoxylate-based surfactant supplied by Loveland Industries. As detailed in Appendix 9, this surfactant modestly increases the toxicity of Rodeo - e.g., decreases the LC_{50} value by about 30% (Mitchell and Chapman 1985a). The identity of the other surfactants in these formulations is not specified in U.S. EPA/OPP (1993c). Abdelghani et al. (1997) have noted that

Syndets surfactant, a surfactant used with glyphosate and other herbicides, is much more toxic to fish (as well as crawfish) than Roundup (Appendices 11 and 12).

Because of the high toxicity of some glyphosate formulations and some surfactants, the U.S. EPA/OPP (1993c) required testing of one surfactant used in glyphosate, MON0818. This surfactant was classified as highly toxic to slightly toxic, with LC_{50} values in the range of 0.65 (0.54-2.7) mg/L to 2.0 (1.5-2.7) mg/L in rainbow trout (U.S. EPA/OPP 1993c, p. 43). While the U.S. EPA/OPP (1993c) does not specifically identify MON0818, the study cited for the toxicity of this compound references Folmar et al. (1979). As discussed further in Section 4.1.3.1.3, Folmar et al. (1979) tested the POEA surfactant used in Roundup.

Based on the low acute toxicity of formulated glyphosate to marine organisms (as summarized in Section 4.1.3.3), the U.S. EPA/OPP (1993c, p. 49) waived the requirement for testing of marine or estuarine fish species.

In terms of the dose-response assessment for longer term exposures to glyphosate, the most relevant study remains the life cycle toxicity studies done in fathead minnow. As summarized in the U.S. EPA/OPP (1993c), no effect on mortality or reproduction was observed at a concentration of 25.7 mg/L using 87.3% pure technical grade glyphosate. No other chronic toxicity studies have been encountered in fish either in the published literature or the more recent studies submitted to U.S. EPA.

4.1.3.1.3. Effect of Surfactants – Most of the surfactant studies summarized in U.S. EPA (1993b) were conducted in the 1970's or 1980's and the formulations were identified in these studies by codes assigned by the registrant. Thus, while it is possible to specifically identify some formulation bioassays with some current formulations, the correspondence of other formulation bioassays to currently available formulations is unclear. Even with the more recent studies, the name of the formulation is not always clearly specified. For example, Roundup ULTRA (NOS) has a 96-hour LC_{50} value of 7.9 (6.2 - 10) mg/L with an NOEC of 6.2 mg/L in rainbow trout (Drottar and Swigert 1998b) and a 96-hour LC_{50} value of 7.7 (6.5 - 11) mg/L with an NOEC of 3.9 mg/L in bluegill sunfish (Drottar and Swigert 1998c). These studies, however, do not specifically identify the formulation as Roundup ULTRAMAX but do indicate that the formulation was a liquid. Because only two Roundup ULTRA formulations have been identified, Roundup ULTRAMAX as a liquid formulation and Roundup ULTRADRY as a granular formulation, it would appear that the studies by Drottar and Swigert involved ULTRAMAX. However, the composition of the Roundup ULTRA used in the Drottar and Swigert studies is different from the composition of Roundup ULTRAMAX given on the product label (Appendix 1). This difficulty is clearly associating formulation data with specific studies makes formulation specific assessments difficult.

In an attempt to clarify this issue, Appendix 3c summarizes the available ecological information from all of the MSDS's for the formulations that are labeled for forestry applications. It is apparent that these formulations fall into relatively clear groups. The most toxic formulations

appear to be Credit Systemic, Credit, Glyfos, Glyphosate, Glyphosate Original, Prosecutor Plus Tracker, Razor SPI, Razor, Roundup Original, Roundup Pro Concentrate, and Roundup UltraMax. It may be presumed that these formulations contain the most toxic surfactants. Other formulations such as Aqua Neat, Aquamaster, Debit TMF, Eagre, Foresters' Non-Selective Herbicide, Glyphosate VMF, and Roundup Custom are much less acutely toxic. Some of these, however, require or recommend the use of a surfactant and this would likely increase the toxicity of the formulation.

For this risk assessment, the uncertainties involving the presence or absence of a surfactant and the possibly differing effects of using various surfactants cannot be resolved with certainty. As detailed in the dose-response assessment, the toxicity of glyphosate is characterized based on the use of a surfactant, either in the formulation or added as an adjuvant in a tank mixture.

As noted in the previous subsection, the POEA surfactant used in some glyphosate formulations is substantially more toxic to aquatic species than glyphosate and substantially more toxic than other surfactants that may be used with glyphosate. Two aquatic toxicity studies (Folmar et al. 1979, Wan et al. 1989) have been conducted on glyphosate, the POEA surfactant, and a Roundup formulation which permit a quantitative assessment of the relative toxicities of glyphosate and POEA as well as an assessment of potential for toxicologic interactions (i.e., synergism or antagonism) in combined exposures to these agents. Both of these studies indicate that POEA is substantially more toxic than glyphosate and that POEA surfactant is the primary toxic agent of concern.

The study by Folmar et al. (1979) is summarized in Table 4-1. As indicated in the first column of this table, these investigators conducted bioassays on four species of fish and one invertebrate (midge larvae). The following three columns give the LC_{50} values for glyphosate, POEA, and Roundup, respectively. For fish, the 96-hour LC_{50} values are given in the table. Folmar et al. (1979) report LC_{50} values for 24 and 48 hours but these values are not substantially different from those at 96 hours. The fifth column calculates the relative potency (ρ) of POEA with respect to glyphosate as the LC_{50} of glyphosate divided by the corresponding LC_{50} for POEA. In other words, for rainbow trout at pH 6.5, the LC_{50} for POEA is 7.4 mg/L and the corresponding LC_{50} for glyphosate is 140 mg/L. Thus, the relative potency of POEA with respect to glyphosate is about 19 [$140 \div 7.4 = 18.92$].

In mixtures, the concept of relative potency provides an explicit tool for identifying the most significant toxic agent(s) in a mixture as well as for assessing potential interactions among agents in a mixture (Durkin 1981, Mumtaz et al. 1994). For example, for a mixture of two agents with the same potency present in a mixture in proportions of π_1 and π_2, the fractional contribution of each agent to the toxicity of the mixture is simply the proportion (π_1 or π_2) of the agent in the mixture. When the potencies differ, both agents contribute equally to the toxicity of the mixture when π_1 is equal to $\rho\pi_2$. As above, ρ is defined here as the LC_{50} of component 1 divided by the LC_{50} of component 2.

In Roundup, glyphosate is present at 356 g/L and POEA is present at 150 g/L. The proportion of glyphosate in Roundup (π_G), ignoring the only other constituent which is water, is about 0.7 [356÷(356+150)]. Similarly, the proportion of POEA (π_S for proportion of surfactant) in the mixture is about 0.3 [150÷ (356+150)]. Both constituents would contribute equally to the mixture if the relative potency of POEA was about 2.3 [0.7÷0.3]. The relative potency of POEA with respect to glyphosate is much greater than 2.3, at least for fish species (Table 4-1). Thus, POEA is the more significant toxic agent in the mixture.

The magnitude of the difference can be expressed in various ways, the simplest of which is the ratio of the concentrations or equivalently the ratios of the proportions adjusted for the difference in potency:

For example, if the relative potency is 70, as it is in Table 4-1 for rainbow trout at pH 7.2, POEA may be said to contribute 30 [70 · 0.3 ÷ 0.7] times more than glyphosate to the toxicity of the mixture.

This method of describing relative toxic contribution is based on the assumption that the components in the mixture do not affect one another (i.e., there are no toxicological interactions). For terrestrial plants, such interactions have been clearly documented. One method for assessing whether or not similar interactions are plausible in aquatic species is to compare the observed LC_{50} values for Roundup to the LC_{50} values that would be predicted by one model of non-interactive joint action, simple similar action (Finney 1971, Durkin 1981). Using this assumption, the expected LC_{50} can be calculated as:

$$LC_{50_{Roundup}} = \frac{LC_{50_{Glyphosate}}}{(\pi_G + \rho\pi_S)} \qquad \textbf{(4-2)}$$

where π and ρ are as defined above.

The predicted LC_{50} values for Roundup based on this assumption are presented in the second to the last column of Table 4-1, and the ratio of the predicted to observed LC_{50} values are given in the last column. Ratios >1 suggest some form of greater than additive toxicity, and, conversely, ratios <1 indicate less than additive toxicity. Note also that the observed LC_{50} values for Roundup are presented as the total concentration of glyphosate and POEA. In other words, the LC_{50} values for Roundup reported in Folmar et al. (1979) are multiplied by 1.42 ((352+150)÷352) and give the LC_{50} values in units of weight of both glyphosate and POEA. These units are required for the above equation 4-2.

As indicated in Table 4-1, there is a tendency for the toxicity of glyphosate to decrease (i.e., the LC_{50} values increase) as the pH increases, although the changes are not substantial. The effect of pH on POEA is also not substantial but the effect seems to be the opposite of the effect that pH has on glyphosate. In all of the bioassays, the surfactant is more toxic than glyphosate. Because

of the effect of pH on toxicity, the relative potency of POEA increases as pH increases. At all pH levels, the ratio of predicted to observed LC_{50} values for Roundup does not deviate remarkably or systematically from unity, suggesting that no substantial interactions take place between these two compounds.

A similar analysis of the results presented by Wan et al. (1989) are summarized in Table 4-2. In general, this study agrees well with the earlier study by Folmar et al. (1979). In all cases, the surfactant is substantially more toxic than glyphosate. The effect of pH is more consistent and more substantial: the toxicity of glyphosate decreases and the toxicity of the surfactant increases with increasing pH. This is discussed further by Wan et al. (1992) but no additional experimental data are provided. Consequently, the relative potency of the surfactant to glyphosate also increases with increasing pH. The LC_{50} values reported in Wan et al. (1989) for Roundup are expressed as "*mg product/L*." In calculating the expected LC_{50} values for Roundup in Table 4-2, it is assumed that these LC_{50} values include the concentrations of both glyphosate and the surfactant. As indicated in the last column of this table, the ratio of the predicted to observed LC_{50} values for Roundup are consistently <1, indicating a less than additive interaction. Similarly, Wan et al. (1991) found no significant interaction between glyphosate and an indicator dye, referred to as basacid blue.

The significance of this information on the toxicity of the POEA surfactant to the current risk assessment is that much of the toxicity and all of the available monitoring data used in the risk assessment for aquatic species is on glyphosate rather than the surfactant. Because POEA is the toxic agent of primary concern in some Roundup formulations, the monitoring data used in the exposure assessment and toxicity data used in the dose response assessment must be adjusted, as discussed in Section 4.3, to consider the differences in potency between these two agents.

The only reported potential adverse effect in fish associated with field applications of a glyphosate/surfactant mixture is given by Trumbo (2002). This report involved the application of Rodeo (1.5%) and the surfactant R-11 (0.5%) to three sites for the control of purple loosestrife. Water samples were collected from water near the application. At one site, glyphosate was monitored at 0.85 mg/L and the surfactant was monitored at 0.4 mg NPE/L and 0.0125 mg/L. When fathead minnows were exposed to this water in the laboratory, 30% mortality was noted after 96 hours and this mortality was significantly ($p<0.05$) greater than control mortality. As discussed by Trumbo (2002), it is unlikely that the mortality was associated directly with glyphosate but the 96-hour LC_{50} for R-11 is about 4 mg/L or one-tenth of the monitored concentration of NPE and it is likely that the mortality was attributable to the surfactant.

4.1.3.1.4. Sub-lethal Effects – The sub-lethal effects of glyphosate are less well characterized than its acute lethal potency. As noted in Appendix 9, non-lethal NOEC concentrations are available in many of the studies that report LC_{50} values. These NOEC values may be regarded as information on *"sub-lethal"* exposures in that no lethality was observed. In terms of this risk assessment, however, the term *sublethal* is not intended to apply to endpoints that may be precursor effects leading to mortality such as various forms of necrosis or other degenerative

changes in organs associated with the lethality. In addition, the term *sublethal* is not intended to apply to levels of exposure in which no mortality was observed. Such effects will be referred as *nonlethal* endpoints. Rather, *sublethal* will be used to designate endpoints that may lead to harmful but nonlethal effects that may impact the ability of wildlife species to maintain normal populations. In other words, the term *sub-lethal* is intended to designate effects that may impact reproduction, behavior, or the ability to respond to other stressors.

Six studies have reported and focused on acute effects other than mortality in fish (El-Gendy et al. 1998; Grisolia 2002; Janz et al. 1991; Morgan et al. 1991; Neskovic et al. 1996b; Szarek et al. 2000). The studies by Szarek et al. (2000) involve observations of nonlethal endpoints that do not substantially impact the hazard identification for fish. Janz et al. (1991) noted that short-term exposures at 5% to 85% of the 96 hour LC_{50} values of several glyphosate formulations do not induce indicators of physiological stress assayed as changes in biochemical parameters in blood. Morgan et al. (1991) noted that trout do not exhibit avoidance responses to glyphosate formulations at concentrations less than the 96-hour LC_{50}. Behavioral changes – i.e., changes in coughing and ventilation rates, changes in swimming, loss of equilibrium, and changes in coloration – were observed at 25% of the LC_{50} values over exposure periods of up to 96 hours. The study by Grisolia (2002) is of minimal relevance because it involved intra-abdominal injections in a erythrocyte micronucleus assay in *Tilapia rendalli*. The results of the assay were positive and the authors interpreted this as indicating that fish DNA might be more sensitive as an indicator of potential mutagenic effects. While this interpretation may have some merit, it does not add substantially to large data base available in a variety of mammalian systems, as discussed in Section 3.1.10. The study by Szarek et al. (2000) involved very brief exposures of carp to Roundup concentrations that are far greater than the LC_{50} values – i.e., 1 hour exposures to 205 mg a.e./L and one-half hour exposures to and 410 mg a.e./L. All fish died during these exposures. Changes were observed in the mitochondria of carp hepatocytes. The observed effects may be due to the uncoupling oxidative phosphorylation (Section 3.1.2). Conversely, given that all fish died during exposure, these effects may represent normal post-mortem pathology. In either event, this is not suggestive of a sub-lethal effect that is relevant to the assessment of population level effects.

The studies by Neskovic et al. (1996b) and El-Gendy et al. (1998) report effects that could be viewed as true sub-lethal toxicity. The study by Neskovic et al. (1996b) noted histologic changes in the gills, kidneys, and liver of carp, *Cyprinus carpio*. In this study, carp were exposed to *technical grade* glyphosate but the purity was only 62%, much lower than that used in current commercial formulations. Nonetheless, the 96-hour LC_{50} value for the technical grade glyphosate in carp is reported as 620 (607-638) mg/L, which is higher than values for more highly purified forms of glyphosate (Section 4.1.3.1.2) in trout and bluegill sunfish. The sub-lethal studies were conducted over 14-days of exposure to concentrations of 2.5, 5, 10 mg a.e./L. At 10 mg/L abnormal histopathologic changes were noted in the gills and liver. At 5 mg/L abnormal histopathologic changes were noted only in the gills. These changes were accompanied by increased alkaline phosphatase activity. While these effects cannot be directly associated with

potential longer term effects on fish populations, the histologic changes in the gills and liver would be classified as adverse.

In terms of impacting the risk assessment, however, it should be noted that a full life-cycle toxicity study has been conducted in fathead minnow, a standard chronic toxicity that was required by and accepted by the U.S. EPA (1993a). In this study, the NOEC was 25.7 mg/L (U.S. EPA, 1993a, p. 41). It is important to note that the NOEC from this full life-cycle toxicity study not only indicates a lack of mortality but also indicates that the fish were able to reproduce normally. Thus, it is conceivable, based on the work of Neskovic et al. (1996b), that the some at least transient histopathologic effects could occur at the NOEC was 25.7 mg/L. Nonetheless, in terms of the risk assessment, the life cycle NOEC of 25.7 mg/L remains the most appropriate basis for risk characterization.

El-Gendy et al. (1998) published a study on potential effects of glyphosate on immune function in fish. This is the only study that has reported any effect on immune function in any species. In this study, Bolti fish (*Tilapia nilotica*) were exposed for up to 4 weeks to glyphosate. However, neither the formulation of glyphosate nor the specific concentration used in the study are reported. Instead, exposure level was described as *"1/1000 of the field recommended concentration"* and the formulation is given only as "*glyphosate 48% SC*".

This study examined a number of important immunologic endpoints including:

- Proliferative response of splenocytes (LT) to the T-cell mitogens phytohemagglutinin (PHA) and concanavalin A (Con A) and to the B-cell mitogen lipopolysaccharide (LPS) using This is an *in vitro* assay for cell-mediated immunity.

- The Plaque Forming Cell (PFC) assay following *in vitro* immunization with sheep red blood cells (SRBC). This is a key assay to determine effects on humoral (antibody in circulation) immunity.

- The quantification of serum anti-SRBC levels. This endpoint is also an assay for humoral immunity.

- The electrophoretic evaluation of serum protein fractions. This is a general parameter for detection of overt/non-specific toxicity.

However, there are several aspects of this study that pose difficulties in interpreting the data.

Firstly, it is stated that the LT assay was performed on blood samples taken at 1 hr, 24 hr, 2 and 4 weeks from the time of treatment. It is assumed that for each of these treatment dates a new set of cultures would be set up. Therefore one would expect to have stimulation index (SI) values for the control for each of the mitogens tested at each time point. This is not the case since SI values for all three mitogens are presented only once. Furthermore, it is not clear for which time point the stated SI values are (see Table 1 in El-Gendy et al. 1998). Secondly, the authors report data

for the anti-SRBC titres (Table 3 in El-Gendy et al. 1998) at 1 hr, 24 hr, 2 and 3 weeks. No data are presented for optimizing the number of SRBC injected. The schedule of immunization (one injection vs multiple injections) with SRBC is not stated by the authors. It is rather odd that statistically significant depressed anti-SRBC titres are noted within one hr following treatment. Further, no data are presented on the preimmunization level of anti-SRBC in the control and treated. Also only one control value is presented and the time point to which this value applies is not specified. Finally, no control values are presented for each of the time points to which the treated groups should be compared.

The PFC assay is carried out in vitro using several treatment levels in µM quantities. Data from this assay is questionable for the following reasons: It is not clear whether the assay was performed in groups of fish separate from those which were immunized for anti-SRBC *in vivo*; there is evidence from Table 2 in El-Gendy et al. 1998 that the concentrations used in this assay are cytotoxic to spleen cells. Thus, the issue of direct toxicity of the chemicals in question on cells of the immune system is a very important issue. Ideally there should be very little toxicity when one deals with immunologic assays. In addition, the data on protein levels and serum fractions are inconclusive. Lastly, and most importantly, the authors do not mention any infections of the fish and have not challenged the fish with any infectious agent to test for a potential decrease in resistance to infection due to effects on the immune system. In terms of potential ecological effects, the failure to test for susceptibility to infections greatly reduces the utility of this study. Thus, it can not be concluded from the data presented in this study that the effects reported on the immune system represent a direct toxic effect on the immune parameters examined. Given the reported cytotoxicity, it is plausible that the reported immune effects are the result of general cytotoxicity rather than due to specific effects on immune function.

In addition to the above noted deficiencies, the study by El-Gendy et al. (1998) is inconsistent with a full life-cycle toxicity study conducted in fathead minnow (U.S. EPA, 1993a, p. 41), as discussed above. While El-Gendy et al. (1998) do not report the concentration tested in their study, the study required by U.S. EPA defines clearly a NOEC for an exposure over a life span. If glyphosate had caused any substantial impairment of immune function in this assay, signs of the immune impairment – i.e., increased infections – should have been apparent. Thus, in terms of the ecological risk assessment, the study by El-Gendy et al. (1998) has no substantial impact.

4.1.3.1.5. Field Studies – Several field studies are available indicating that the application of glyphosate to control aquatic weeds is beneficial to fish populations. Caffrey (1996) evaluated the efficacy of glyphosate in the control of emergent weeds along the river Boyne in Ireland. Glyphosate was applied as a "5L/ha" formulated product that is not otherwise specified. In other words, the information in this publication is not sufficient to calculate exposures either as lb/acre or concentration of glyphosate in water. While no rigorous studies of fish populations were conducted, anecdotal accounts from local anglers indicated that brown trout and salmon populations were enhanced and that the fish were observed to spawn in newly cleared areas. Similarly, Olaleye and Akinyemiju (1996) report a beneficial effect on fish populations in Nigeria when Roundup (360 g/L) was used for aquatic weed control and Kruger et al. (1996) report no

adverse effects when Roundup (360 g/L) was used for aquatic weed control in commercial carp production facilities. In an abstract, D'Silva et al. (1997) report that glyphosate was the least toxic herbicide, compared to 2,4-D, diquat, fluridone, endothall, in terms of sub-lethal effects in largemouth bass. This publication, however, provides little detail and a full publication has not been encountered in the literature.

4.1.3.2. Amphibians – The observation of hind limb deformities in free-living amphibians has substantially increased concern for the effects of xenobiotics on populations of amphibians (e.g., Quellet et al. 1997). Glyphosate IPA, Roundup, and the POEA surfactant used in Roundup have been specifically tested for malformations in the frog embryo teratogenesis assay (Perkins et al. 2000). In this assay, frog (*Xenopus laevis*) embryos are exposed to the test solution in petri dishes for 96-hours. As in the bioassay in fish, the least toxic agent was glyphosate IPA with an LC_{50} of 5407 mg a.e./L and an LC_5 of 3779 mg a.e./L, indicating that glyphosate IPA is less toxic to frog embryos than to fish. Also as with fish, the most toxic agent was the POEA surfactant with LC_{50} of 2.7 mg/L and an LC_5 of 2.2 mg/L. The Roundup formulation has an intermediate toxicity with an LC_{50} of 9.4 mg a.e./L and an LC_5 of 6.4 mg a.e./L. The LC_{50} values are comparable to the those of fish. No reported hind limb abnormalities were noted. The only abnormalities specified in the publication include uncoiling of the gut, edema, blistering, abnormal pigmentation, and axial twisting in control embryos. No statistically significant increase in abnormalities were seen in any groups exposed to glyphosate IPA, Roundup, and the POEA surfactant at levels that were not lethal. The precise number and nature of abnormalities in the groups exposed to lethal concentrations of glyphosate IPA, Roundup, and the POEA surfactant are, however, not specified.

Smith (2001) assayed another formulation of glyphosate, Kleeraway Grass and Weed Killer RTU (Monsanto), that contains glyphosate IPA at 0.75% as well as an ethoxylated tallowamine surfactant. Bioassays were conducted on tadpoles (1 week post-hatching) of the western chorus frog, *Pseudacris triseriata*, and the plains leopard frog (*Rana blairi*). The concentrations used in the bioassays are specified in the publication as 0.0001, 0.001, 0.01, 0.1 dilutions of the formulated product. A 0.75% formulation contains 7.5 g/L. Thus, the concentrations used in this study correspond to 0.75 mg IPA/L, 7.5 mg IPA/L, 75 mg IPA/L, and 750 mg IPA/L or 0.56 mg a.e./L, 5.6 mg a.e/L, 56 mg a.e./L, 560 mg a.e./L. The test protocol involved a 24-hour exposure period followed by a two week observation period to detect sub-lethal toxicity. In *Pseudacris triseriata*, 100% mortality was observed at all concentrations above 0.56 mg a.e./L and 55% mortality was observed at this concentration. During the post-exposure observation period, 4/9 animals died in first 2 days. In an initial experiment with *Rana blairi*, all tadpoles died at all concentrations. In a repeat experiment using older tadpoles (not otherwise specified), all animals survived at 0.56 mg a.e./L. In both species, normal growth and development was observed over the two week observation period in all survivors.

This very high sensitivity of tadpoles reported by Smith (2001) is not consistent with the study by Bidwell and Gorrie (1995), who assayed the toxicity of glyphosate and "Roundup 360" in four species of frogs from western Australia. For juvenile frogs, 48-hour LC_{50} values were 51.8 mg

a.e./L for Roundup 360 and 83.6 mg/L for technical grade glyphosate. For tadpoles, 48-hour LC_{50} values were 11.6 mg a.e./L for Roundup 360 and 121 mg/L for technical grade glyphosate. Thus, while the tadpoles were somewhat more sensitive than juveniles, the reported LC_{50} values are in the range of those seen in fish.

An additional formulation of glyphosate, Roundup Biactive is available in Australia (Monsanto Australia Limited, 2000). This formulation is less toxic than Roundup to aquatic species based on bioassays in various species of frogs (Mann and Bidwell 1999).

Cole et al. (1997) report no effect on populations of six species of amphibians (based on capture rates) among clearcut sites with and without glyphosate applications. Species included rough-skin newt, ensatina, Pacific giant salamander, Dunn's salamander, western redback salamander, and re-legged frog. Removal of red alder from the habitat, reduced amphibian populations regardless of the method used to remove the alder.

4.1.3.3. Aquatic Invertebrates – As with the toxicity data on fish, the U.S. EPA (1993c) summarizes a standard set of bioassays of toxicity to aquatic invertebrates. For aquatic invertebrates, however, the LC_{50} values are typically given based on a 48 hour rather than 96 hour exposure period. The 48-hour LC_{50} of technical grade glyphosate (83%) to *Daphnia magna* is listed as 780 mg/L, substantially higher than the 96-hour LC_{50} values in freshwater fish. For the common midge, *Chironomus plumosus*, the 48-hour LC_{50} of 96.7% technical grade glyphosate is listed as 55 (31-97) mg/L (U.S. EPA/OPP 1993c, p. 44). As with fish, the toxicity of some formulated glyphosate products is much greater, with LC_{50} values as low as 3 mg/L (U.S. EPA/OPP 1993c, p. 46). These and other more recent studies submitted to U.S. EPA (e.g., Long et al. 1996a; Long et al. 1996b; Drottar and Swigert 1998a) on the toxicity of glyphosate and glyphosate formulations are summarized in Appendix 3 (comparison of formulations) and Appendix 10 (toxicity to aquatic invertebrates).

In addition to registrant submitted studies, Alberdi et al. (1996) has published a comparative study on the toxicity of a glyphosate formulation to two species of daphnids, *Daphnia magna* and *Daphnia spinulata*. The formulation of glyphosate tested in this study contained glyphosate IPA 48% and a different surfactant - characterized as a oxide-coco-amide-propyl dimethyl-amine (15%). The 48 hour EC_{50}s at IPA are reported as 66.18 mg/L in *D. spinulata* and 61.72 (58.8-64.2) mg/L in *D. magna*. These are comparable to the LC_{50} of 72 mg/L for a glyphosate formulation containing the "W" surfactant (U.S. EPA/OPP 1993c).

One chronic life cycle toxicity study with *Daphnia magna* is reported in U.S. EPA/OPP (1993c) with an MATC of between 50 and 96 mg/L. This is comparable to the NOEC of 25.7 mg/L in the life-cycle study in fish (Section 4.1.3.1.2). As with the fish study, this is the most relevant bioassay in aquatic invertebrates for assessing the longer term effects of glyphosate in ambient water.

The effects of glyphosate have also been determined in an aquatic snail, *Pseudosuccinea columella*, intermediate host of the sheep liver fluke. Tate et al. (1997) assayed glyphosate acid for sub-lethal effects on egg production at concentrations of 0.1, 1, and 10 mg a.e./L for 3-generations. No marked effects were noted on the first or second generations. In the third generation, snail embryos exposed to 1 mg/L developed much faster than those exposed at 0.1 or 10 mg/L and faster than control snails. Hatching, however, was inhibited at 10 mg/L and inhibited slightly at 0.1 mg/L but egg-laying capacity increased at both of these concentrations. In a follow up study, Tate et al. (2000) noted effects on concentrations of amino acids in snails (specifically alanine, glycine, glutamic acid and threonine) at the same concentrations. Effects on concentrations of some proteins have also been noted by Christian et al. (1993) for this species of snail. The mechanism for the effect of glyphosate on amino acid and protein metabolism is not known. In terms of reproductive effects that might be significant, the Tate et al. (1997) study suggests that some changes could be observed at concentrations as low as 0.1 mg/L but that the mixed effects of glyphosate on egg-laying capacity and hatching could be off-setting in terms of total reproductive capacity.

Various field studies have not noted any remarkable effects on aquatic invertebrates. At application rates of 1 L Rodeo/ha for the control of purple loosestrife, Gardner and Grue (1996) noted no adverse effects on aquatic invertebrates. At application rates of 0.94 or 1.48 kg a.i./ha as glyphosate IPA (Rodeo), Hagg (1986) found no indication of lethality in two water hyacinth weevils, *Neochetin eichhorniae* and *N. bruchi*. In a forest pond mesocosm, Hildebrand et al. (1980) found no differences in invertebrate survival over an 8 day period after sprays of 2.2 kg/ha, 22 kg/ha and 220 kg/ha. Lastly, no indication of short or long term (119 days) effects were noted after the application of a Rodeo and X-77 mixture in control of smooth cordgrass in a marine estuary. In this study, Rodeo was applied at a rate of 4.7 L/ha and X-77 was applied at a rate of 1 L/ha (Simenstad et al. 1996).

4.1.3.4. Aquatic Plants – The toxicity of glyphosate to aquatic plants has been evaluated by U.S. EPA/OPP (1993c) based on studies submitted for the registration of glyphosate. In addition, several studies are available from the open literature as well as more recent studies submitted to U.S. EPA. These studies are detailed in Appendix 11 for both algae and aquatic macrophytes. As would be expected from a herbicide, glyphosate is much more toxic to aquatic plants than animals. EC_{50} values for technical grade glyphosate in algae reported by U.S. EPA/OPP (1993c, p. 51) are as low as 0.85 mg/L for *Skeletonema costatum* (a marine species). The lower value of 0.85 mg/L for *Skeletonema costatum* appears to be the most sensitive bioassay reported. In a more recent study on this species, Smyth et al. (1996c) report an EC_{50} of 12 (7.6-19) mg/L a 5-day with an NOEC of 1.8 mg/L and a LOEC of 3.2 mg/L.

Some species appear to be much more tolerant than *Skeletonema costatum*. Smyth et al. (1996d) report EC_{50} of 17 (13-24) mg/L for a freshwater diatom *Navicula pelliculosa*, with growth enhancement observed at 1.8 mg/L and no inhibition observed at concentrations below 32 mg/L – i.e., the EC_{50} was estimated by extrapolation. The EC_{50} value reported for this species in EPA/OPP (1993c, p. 51) is to 39.9 mg/L. At stimulation of chlorophyll-a synthesis has also been

reported by Wong (2000) in *Scenedesmus quadricauda* at low (0.02 mg/L) concentrations. The most tolerant species of algae appears to be *Chlorella fusca*, with an EC_{50} of 377 mg/L for growth inhibition (Faust et al. 1994).

Saenz et al. (1997) have reported that a commercial formulation of glyphosate, referred to as "Ron-do", is about equitoxic in *Scenedesmus acutus* and *Scenedesmus quadricauda* with glyphosate EC_{50} values of about 7.2 to 10.2 mg/L and EC_{50} values for Ron-do of about 99 mg/L when expressed as glyphosate concentrations. No information on this formulation, however, has been encountered and it does not appear to be distributed in the United States.

Freshwater aquatic macrophytes appear to be as sensitive to glyphosate as algae. The U.S. EPA/OPP (1996c) report a 7-day EC_{50} of 21.5 mg/L in duckweed for technical grade glyphosate, very similar to the EC_{50} reported for the freshwater diatom, *Navicula pelliculosa*. More recently, Smyth et al. (1996a) reported an EC_{50} in duckweed for frond number 12 (11-14) mg/L, with a NOEC of 3 mg/L and a LOEC of 6 mg/L.

Austin et al. (1991) studied the effects of glyphosate on periphyton in artificial streams and noted an increase in periphyton concentrations at concentrations of 0.0019 - 0.2874 mg/L. The authors suggest that algae are using glyphosate as a phosphorous source and that glyphosate could contribute to eutrophication of coastal oligotrophic (nutrient poor and oxygen rich) waterways and this could effect salmonid populations. No specific data supporting this supposition, however, is reported. In a pond study, Perschbacher et al. (1997) report no adverse effect on plankton after an application of glyphosate at a rate of 0.43 kg/ha or about 0.4 lbs/acre.

4.2. EXPOSURE ASSESSMENT

4.2.1. Overview. Terrestrial animals might be exposed to any applied herbicide from direct spray, the ingestion of contaminated media (vegetation, prey species, or water), grooming activities, or indirect contact with contaminated vegetation. The highest exposures for terrestrial vertebrates will occur after the consumption of contaminated vegetation or contaminated insects. In acute exposure scenarios, doses as high as 225 mg/kg are estimated. Other routes of exposure, like the consumption of contaminated water or direct spray, lead to lower levels of exposure. In chronic exposure scenarios, the estimated daily doses at the upper limits of exposure are in the range of about 50 to 80 mg/kg/day and are associated with highly conservative assumptions regarding the consumption of contaminated vegetation.

The primary hazards to non-target terrestrial plants are associated with unintended direct deposition or spray drift. Unintended direct spray will result in an exposure level equivalent to the application rate. At least some plants that are sprayed directly with glyphosate at or near the recommended range of application rates will be damaged. Based on the AgDRIFT model, no more than 0.0058 of the application rate would be expected to drift 100 m offsite after low boom ground applications. In order to encompass a wide range of field conditions, GLEAMS simulations were conducted for clay, loam, and sand at annual rainfall rates from 5 to 250 inches. Under arid conditions (i.e., annual rainfall of about 10 inches or less), there is no or very little runoff. Under these conditions, degradation, not dispersion, accounts for the decrease of glyphosate concentrations in soil. At higher rainfall rates, plausible offsite movement of glyphosate results in runoff losses that range from about negligible up to about 45% of the application rate, depending primarily on the amount of rainfall rather than differences in soil type.

The potential for effects on aquatic species are based on estimated concentrations of glyphosate in water that are identical to those used in the human health risk assessment without further elaboration. For an accidental spill, the central estimate for the concentration of glyphosate in a small pond is estimated at about 18.2 mg/L with a range from 1.8 to 127 mg/L. For longer term exposure scenarios, the expected concentrations of glyphosate in ambient water range from 0.0001 to 0.008 mg/L with a central value of 0.001 mg/L.

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

In this exposure assessment, estimates of oral exposure are expressed in the same units as the available toxicity data (i.e., oral LD_{50} and similar values). 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 body weight. For dermal exposure, the units of measure usually are expressed in mg of agent per cm^2 of surface area of the organism and abbreviated as mg/cm^2. In estimating dose, however, a distinction is made between the exposure dose and the absorbed dose. The *exposure dose* is the amount of material on the organism (i.e., the product of the residue level in mg/cm^2 and the amount of surface area exposed), which can be expressed either as mg/organism or mg/kg body

weight. The *absorbed dose* is the proportion of the exposure dose that is actually taken in or absorbed by the animal.

For the exposure assessments discussed below, general allometric relationships are used to model exposure. In the biological sciences, allometry is the study of the relationship of body size or mass to various anatomical, physiological, or pharmacological parameters (e.g., Boxenbaum and D'Souza 1990). Allometric relationships take the general form:

$$y = aW^x$$

where ***W*** is the weight of the animal, ***y*** is the variable to be estimated, and the model parameters are **a** and **x**. For most allometric relationships used in this exposure assessment, **x** ranges from approximately 0.65 to 0.75. These relationships dictate that, for a fixed level of exposure (e.g., levels of a chemical in food or water), small animals will receive a higher dose, in terms of mg/kg body weight, than large animals.

Estimates of exposure are given for both a small and a large mammal as well as a small and a large bird. For many compounds, allometric relationships for interspecies sensitivity to toxicants indicate that for exposure levels expressed as mg toxicant per kg body weight (mg/kg body weight), large animals, compared with small animals, are more sensitive.

As discussed in Section 3.1.4 and 3.1.5, the limited data on glyphosate do suggest that larger mammals, specifically the dog, appear to be more sensitive to glyphosate than smaller mammals (i.e., rats and mice) but the data are not adequate to support the development of quantitative allometric relationships for toxicity. There are no data to assess species sensitivity in small and large birds.

The exposure assessments for terrestrial animals are summarized in Table 4-3. As with the human health exposure assessment, the computational details for each exposure assessment presented in this section are provided in the attached worksheets (worksheets F01 through F14).

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 extent of dermal contact 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 3.1.7). 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 glyphosate.

Other, perhaps more substantial, uncertainties affect the estimates for absorbed dose. For example, the estimate based on first-order dermal absorption does not consider fugitive losses from the surface of the animal and may overestimate the absorbed dose. Conversely, some animals, particularly birds and mammals, groom frequently, and grooming may contribute to the total absorbed dose by direct ingestion of the compound residing on fur or feathers. Furthermore, other vertebrates, particularly amphibians, may have skin that is far more permeable than the skin of most mammals (Moore 1964).

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 F02a, 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 glyphosate 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). Because there is no information regarding the dermal absorption rate of glyphosate by bees or other invertebrates, this exposure scenario, detailed in worksheet F02b, also assumes complete absorption over the first day of exposure.

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

4.2.2.2. Indirect Contact – As in the human health risk assessment (see section 3.2.3.3), the only approach for estimating the potential significance of indirect dermal contact is to assume a relationship between the application rate and dislodgeable foliar residue. The study by Harris and Solomon (1992) 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. Species of wildlife are likely to spend longer periods of time, compared to humans, in contact with contaminated vegetation.

It is reasonable to assume that for prolonged exposures a steady-state may be reached between levels on the skin, rates of absorption, and levels on contaminated vegetation, although there are no data regarding the kinetics of such a process. The bioconcentration data on glyphosate (section 3.2.3.5) as well as its high water solubility and low octanol/water partition coefficient suggest that glyphosate is not likely to partition from the surface of contaminated vegetation to the surface of skin, feathers, or fur. Thus, a plausible but conservative 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 far below those of toxicological concern. Consequently, details of the indirect exposure scenarios for contaminated vegetation are not further elaborated in this document.

4.2.2.3. Ingestion of Contaminated Vegetation or Prey – Since glyphosate 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).

A small mammal is used because allometric relationships indicate that small mammals will ingest greater amounts of food per unit body weight, compared with large mammals. The amount of food consumed per day by a small mammal (i.e., an animal weighing approximately 20 g) is equal to about 15% of the mammal's total body weight (U.S. EPA/ORD 1989). When applied generally, this value may overestimate or underestimate exposure in some circumstances. For example, a 20 g herbivore has a caloric requirement of about 13.5 kcal/day. If the diet of the herbivore consists largely of seeds (4.92 kcal/g), the animal would have to consume a daily amount of food equivalent to approximately 14% of its body weight [(13.5 kcal/day ÷ 4.92 kcal/g)÷20g = 0.137]. Conversely, if the diet of the herbivore consists largely of vegetation (2.46 kcal/g), the animal would have to consume a daily amount of food equivalent to approximately 27% of its body weight [(13.5 kcal/day ÷ 2.46 kcal/g)÷20g = 0.274] (U.S. EPA/ORD 1993, pp.3-5 to 3-6). For this exposure assessment, the amount of food consumed per day by a small mammal weighing 20 g is estimated at about 3.6 g/day from the general allometric relationship for food consumption in rodents (U.S. EPA/ORD 1993, p. 3-6).

A large herbivorous mammal is included because empirical relationships of concentrations of pesticides in vegetation, discussed below, indicate that grasses may have substantially higher pesticide residues than other types of vegetation such as forage crops or fruits (Worksheet A04). Grasses are an important part of the diet for some large herbivores, but most small mammals do not consume grasses as a substantial proportion of their diet. Thus, even though using residues from grass to model exposure for a small mammal is the most conservative approach, it is not generally applicable to the assessment of potential adverse effects. Hence, in the exposure

scenarios for large mammals, the consumption of contaminated range grass is modeled for a 70 kg herbivore, such as a deer. Caloric requirements for herbivores and the caloric content of vegetation are used to estimate food consumption based on data from U.S. EPA/ORD (1993). Details of these exposure scenarios are given in worksheets F10 for acute exposures as well as Worksheets F11a and F11b for longer-term exposures.

For the acute exposures, the assumption is made that the vegetation is sprayed directly – i.e., the animal grazes on site – and that the animal consumes 100% of the animals diet is contaminated. While appropriately conservative for acute exposures, neither of these assumptions are plausible for longer-term exposures. Thus, for the longer-term exposure scenarios for the large mammal, two sub-scenarios are given. The first is an on-site scenario that assumes that a 70 kg herbivore consumes short grass for a 90 day period after application of the chemical. The contaminated vegetation accounts for 10 to 100% of the diet assuming that the animal would spend 10 to 100% of the grazing time at the application site. 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 12a. The second sub-scenario is similar except the assumption is made that the animal is grazing at distances of 25 to 100 feet from the application site (lowing risk) but that the animal consumes 100% of the diet from the contaminated area (increasing risk). For this scenario, detailed in Worksheet F12b, AgDRIFT is used to estimate deposition on the off-site vegetation. Drift estimates from AgDrift are summarized in Worksheet A06 and this model is discussed further in Section 4.2.3.2.

The consumption of contaminated vegetation is also modeled for a large bird. For these exposure scenarios, the consumption of range grass by a 4 kg herbivorous bird, like a Canada Goose, is modeled for both acute (Worksheet F12) and chronic exposures (Worksheets F13a and F13b). As with the large mammal, the two chronic exposure scenarios involve sub-scenarios for on-site as well as off-site exposure.

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

Similarly, the consumption of contaminated insects is modeled for a small (10g) bird. No monitoring data have been encountered on the concentrations of glyphosate in insects after applications of glyphosate. The empirical relationships recommended by Fletcher et al. (1994) are used as surrogates as detailed in Worksheet F14. 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. As detailed in Worksheet F14, this approach yields dose estimates of about 20 to 800 mg/kg bw for a small bird. This is higher than any monitored residues in terrestrial animals by factors or about 10 to 400 and is likely to be grossly conservative (Newton et al. 1984, p. 1148, Table II).

As indicated in Section 3.2.3.6, the empirical relationships recommended by Fletcher et al. (1994) for fruit may somewhat overestimate concentrations on fruit based on the study by Siltanen et al. (1981). As indicated in Worksheet A04, Fletcher et al. (1994) estimate residue rates on leaves at 45 to 135 ppm per lb applied and on short grasses as 85 to 240 ppm per lb applied. Newton et al. (1994) found that initial residues on "herbaceous vegetation" were typically in the range of 360 to 1273 ppm after the application of glyphosate at a rate of 4.12 kg/ha or about 3.7 lb/acre (Newton et al. 1994, , p. 1798, Table 3). This corresponds to residue rates of about 97 to 344 ppm per lb applied per acre [360ppm to 1273 ppm ÷ 3.7 lb/acre]. This suggests that the estimates of glyphosate on grasses could be somewhat underestimated using the residue rates from Fletcher et al. (1994). The potential impact of this underestimate is discussed further in the risk characterization.

In addition to the consumption of contaminated vegetation and insects, glyphosate may reach ambient water and bioconcentrate in 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.

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

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

4.2.3.2. Off-Site Drift – Because off-site drift is more or less a physical process that depends on droplet size and meteorological conditions rather than the specific properties of the herbicide, estimates of off-site drift can be modeled using AgDRIFT (Teske et al. 2001). AGDRIFT is a model developed as a joint effort by the EPA Office of Research and Development and the Spray Drift Task Force, a coalition of pesticide registrants. 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 applications is given in Worksheet A06. In ground broadcast applications, glyphosate 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. This is discussed further in the risk characterization.

Drift distance can be estimated using Stoke's law, which describes the viscous drag on a moving sphere. According to Stoke's law:

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

or

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

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

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

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

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

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

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

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

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

4.2.3.3. Runoff – Glyphosate 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 is similar to the approach used by U.S. EPA (1995) in their exposure assessment for terrestrial plants. The approach is reasonable because off-site runoff will contaminate the off-site soil surface and could impact non-target plants. Percolation, on the other hand, represents the amount of the herbicide that is transported below the root zone and thus may impact water quality but should not affect off-site vegetation.

Based on the results of the GLEAMS modeling (Section 3.2.3.4.2), the proportion of the applied glyphosate 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 but may reach up to about 30% to 45% of the applied amount at high rainfall rates.

4.2.3.4. Wind Erosion – Wind erosion is a major transport mechanism for soil (e.g., Winegardner 1996) and is associated with the environmental transport of herbicides (Buser 1990). Although numerous models were developed for wind erosion (e.g., Strek and Spaan 1997, Strek and Stein 1997), the quantitative aspects of soil erosion by wind are extremely complex and site specific. Field studies conducted on agricultural sites found that annual wind erosion may account for 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.

This risk assessment uses average soil losses ranging from 1 to 10 tons/ha·year, with a typical value of 5 tons/ha·year. The value of 5 tons/ha·year is equivalent to 500 g/m^2 [1 ton=1000 kg and 1 ha = 10,000 m^2] or 0.05 g/cm^2 [1m^2=10,000 cm^2]. Thus, using a soil bulk density of 1.5 g/cm^3 (Knisel et al. 1992, p. 56), the depth of soil removed from the surface per year would be 0.033 cm[(0.05 g/cm^2)÷ (1.5 g/cm^3)]. The average amount per day would be about 0.00007 cm/day [0.033 cm per year ÷ 365 days/year]. The upper range of the typical daily loss would thus be about 0.00009 cm/day.

The amount of glyphosate 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 glyphosate would be neither substantial or nor significant.

Any number of undesirable exposure scenarios could be constructed. As a reasonable 'worst case' scenario, it is assumed that glyphosate is applied to arid soil, that it is incorporated into the top 1 cm of soil, that minimal rainfall occurs for a 2-month period, that the degradation and dispersion of glyphosate in the soil is negligible over the 2-month period, and that local conditions favor a high rate of soil loss (i.e., smooth, sandy surface with high wind speeds) that is a factor at the upper limit of the typical rate (i.e., 0.00009 cm/day). Under those conditions, 0.0054 [0.00009 cm/day × 60 days ÷ 1 cm] of the applied glyphosate would be lost due to wind erosion. This is virtually identical to the estimates of off-site contamination from low-boom applications at a distance of 100 feet from the application site and is greater than drift that would be expected 500 feet offsite (0.0016 for low-boom applications from Worksheet A06) by a factor about 3 [0.0054 ÷ 0.0016 = 3.375]. Thus, in areas where wind erosion of soil may occur, wind erosion could be a more important mode of offsite movement than drift during application.

The deposition of the glyphosate contaminated soil also will vary substantially with local conditions. Under desirable conditions, the soil might be dispersed over a very large area and be of no toxicological consequence. In some cases, however, local topographical conditions might favor the deposition and concentration of contaminated dust from a large treated area into a relatively small off-site area. An objective approach for modeling these types of events was not available in the literature. For this risk assessment, neither concentration nor dispersion is considered quantitatively.

4.2.4. Aquatic Organisms. The potential for effects on aquatic species are based on estimated concentrations of glyphosate in water that are identical to those used in the human health risk assessment (Section 3.2.3.4). Thus, for an accidental spill, the central estimate for the concentration of glyphosate in a small pond is estimated at about 18.2 mg/L with a range from 1.8 to 127 mg/L (Worksheet D05). For longer term exposure scenarios, the expected concentrations of glyphosate in ambient water range from 0.0001 to 0.008 mg/L with a central value of 0.001 mg/L (Worksheet B06).

4.3. DOSE-RESPONSE ASSESSMENT

4.3.1. Overview. For mammals, the toxicity data used to characterize risk are identical to those used in the human health risk assessment – i.e., a NOAEL of 175 mg/kg with an associated LOAEL of 350 mg/kg. The 175 mg/kg NOAEL and 350 mg/kg LOAEL values are used for both the acute and chronic risk assessments. This approach is taken because of the lack of a substantial dose-duration or dose-severity relationship for glyphosate. For birds, a dose of 100 mg/kg is used as a NOAEL for characterizing chronic risks. It should be noted that this dose is very close to the NOAEL of 175 mg/kg used for mammals and is consistent with the apparent lack of variability in the toxicity of glyphosate among species. As in the assessment for mammals, this NOAEL is based on a repeated dose study for reproductive effects. The acute NOAEL is taken as 562

mg/kg from a five-day dietary studies in bobwhite quail and mallard ducks. Toxicity to terrestrial invertebrates is characterized using a standard set of studies in honey bees. The NOEC used in this risk assessment is taken as 50 µg/bee.

The assessment of potential effects in plants is based on standard toxicity studies required for pesticide registration involving pre-emergence and post-emergence exposures. In seedling emergence assays, very high concentrations – i.e., 10 lb a.i./acre or about 7.5 lbs a.e./acre – will modestly inhibit seed germination in both monocots and dicots. The NOEC for seed germination is 4.5 lb a.e./acre in both monocots and dicots. This value is used to assess the consequences of off-site movement of glyphosate in runoff. Glyphosate appears to be more toxic in vegetative vigor assays – i.e., direct application to the foliage of growing plants. The lowest reported NOEC for growth in standard bioassays required for registration is 0.035 lb a.e./acre. The highest reported NOEC for growth is 0.56 lb a.e./acre. This range of values for sensitive and relatively insensitive species is used to assess the consequences of off-site drift of glyphosate.

The dose-response assessment for fish is substantially complicated by information indicating that some fish species such as salmonids are more sensitive to glyphosate than other species of fish and by information indicating that some surfactants are very toxic to fish and may substantially increase to the toxicity of glyphosate to fish. These factors are further complicated by gaps in the available data. Given the apparently high sensitivity of some salmonids to glyphosate, it would be desirable to have a life cycle toxicity study or at least an egg-and-fry study available on salmonids. In addition, given the apparently high toxicity of surfactant formulations compared to technical grade glyphosate, a life cycle toxicity study on at least one formulation containing a toxic surfactant would be desirable. Such studies, however, are not available. Consequently, an approximation method commonly used is mixtures risk assessment (the relative potency method) is employed to estimate a chronic NOEC of 2.57 mg/L for technical grade glyphosate in sensitive species of fish based on an observed NOEC value of 25.7 mg/L in tolerant species of fish. Similarly, NOEC values for glyphosate formulations containing toxic surfactants are estimated at 0.36 mg/L for sensitive species and 0.64 mg/L for tolerant species. A similar approach is used estimate the potential for acute effects based on 96-hour LC_{50} values. LC_{50} values rather than data on sublethal effects are used to characterize risks from acute exposures because most of the data on sublethal effects are based on very short-term exposures to concentrations in the range of 96-hour LC_{50} values. Most of the available toxicity data suggest that amphibians are no more sensitive to glyphosate than fish. Consequently, a separate dose-response assessment for amphibians is not conducted in this risk assessment.

The issues in the dose-response assessment for aquatic invertebrates are very similar to those encountered in the dose-response assessment for fish. There is sufficient data to assert that some glyphosate formulations that contain toxic surfactants may be much more toxic to aquatic invertebrates than technical grade glyphosate. There is only one chronic study on technical grade glyphosate and no chronic studies on glyphosate formulations. Similar to the approach used in the dose-response assessment for fish, a chronic NOEC of 50 mg/L for technical grade glyphosate is used to estimate a chronic NOEC of 0.7 mg/L for glyphosate formulations containing toxic

surfactants. The potential for acute effects in aquatic invertebrates are based on LC_{50} values of 780 mg/L for technical grade glyphosate and 11mg/L for glyphosate formulations containing toxic surfactants.

Glyphosate appears to be about equally toxic to both algae and aquatic macrophytes. In terms of growth inhibition, the NOEC of 3 mg/L in duckweed is used to characterize risk due to inhibition. At lower concentrations – i.e., in the range of 0.002 mg/L to 0.3 mg/L or higher – stimulation of algal growth may be a more common response and has been noted in several studies.

4.3.2. Toxicity to Terrestrial Organisms.

4.3.2.1. Mammals– As summarized in the dose-response assessment for the acute and chronic human health risk assessment (Section 3.3.3.), the NOAEL in experimental mammals is taken as 175 mg/kg with an associated LOAEL of 350 mg/kg.

The application of these NOAEL and LOAEL values to small rodents is clearly appropriate, since the NOAEL and LOAEL come from a study in rabbits (Rodwell et al. 1980b). Ecological risk assessments, however, are intended to encompass a wide range of mammalian species, from very small animals such as mice and voles to large mammals such as deer. For many chemicals, systematic differences in species sensitivity are apparent and generally indicate that small animals are less sensitive (i.e., have higher toxicity values) than large animals. This is not the case for glyphosate. Toxicity values for rats are very similar to the toxicity estimates in humans. For example, as discussed in Section 3.3.3, the threshold for toxicity based on an analysis of lethality data is about 445 mg/kg, virtually identical to the LOAEL of 350 mg/kg in rabbits from the study by Rodwell et al. (1980b). The estimated LD_{50} in humans is approximately 3,000 mg/kg which is consistent with oral LD_{50} values of glyphosate in mammals which range from approximately 2,000 to 6,000 mg/kg (Williams et al. 2000). Thus, for the ecological risk assessment, NOAEL of 175 mg/kg is used directly for both small and large mammals.

The 175 mg/kg NOAEL and 350 mg/kg LOAEL values are used for both the acute and chronic risk assessments. This approach is taken because of the lack of a substantial dose-duration or dose-severity relationship for glyphosate. It may be argued that this approach is somewhat conservative in that the 175 mg/kg/day NOAEL is based on a teratology study in rabbits involving a 21-day exposure period – i.e., days 6-27 of gestation – in which the compound was administered by gavage. Most acute exposure scenarios considered in this risk assessment will involve peak exposures that will occur over a much shorter period – i.e., a 1-day maximum concentration in water or on vegetation. Shorter-term toxicity values that might be used, however, would have very little impact on the risk characterization. As summarized above, the threshold for acute lethality is about 445 mg/kg, virtually identical to the LOAEL of 350 mg/kg in rabbits from the study by Rodwell et al. (1980b). Because of concern for nonlethal adverse effects, the estimated NOAEL for lethality would not be an appropriate basis for risk characterization.

4.3.2.2. Birds – As noted in Section 4.1.2.2, glyphosate has been classified by the U.S. EPA/OPP 1993c as no more than slightly toxic to birds. As an index of potential toxicity from acute exposure, the U.S. EPA/OPP 1993c uses the gavage study by Fink et al. (1978) in which the LD_{50} was >2000 mg/kg in bobwhite quail. The more recent studies by Palmer and Beavers (1997a,b) indicate five day dietary LC_{50} values of greater than 5620 ppm in both bobwhite quail and mallard ducks. These dietary values are actually an NOEC in that no mortality or signs of toxicity were observed in any test animals.

For longer-term effects, U.S. EPA/OPP 1993c uses the dietary NOAELs of 1000 ppm in bobwhite quail (Fink 1975) and mallard ducks (Fink and Beavers 1978). Both of these studies were assays for reproductive toxicity, a relevant and sensitive endpoint for the ecological risk assessment. In this risk assessment, the acute dietary studies by Palmer and Beavers (1997a,b) will be used to assess the effects from acute exposures. For longer term exposures, the reproductive NOAEL of 1000 ppm (Fink 1975; Fink and Beavers 1978) will be used in the risk characterization.

The dietary concentrations will be converted to doses expressed as mg/kg body weight. This approach is taken because the direct use of dietary concentrations from laboratory studies may be under-protective. Laboratory diets generally involve the use of dry food. Dry laboratory chow usually has a higher caloric content than food consumed in the wild, if only because most food consumed in the wild has a high water content. In addition, most reported concentrations of a pesticide in environmental samples are given on a wet (natural) weight rather than a dry (dedicated) weight basis. Consequently, animals tend to eat greater amounts of food in the wild than they do under laboratory conditions (U.S. EPA/ORD 1993) and thus ingested doses expressed as mg/kg bw/day will be higher in free living animals than in laboratory animals for a fixed concentration in food.

Because of these relationships, Forest Service risk assessments use doses expressed as mg/kg body weight for both the exposure and dose-response assessments. As detailed in the worksheets, information on caloric requirements and caloric values of different foods is used to estimate the amount of a particular food that an animal will use.

Based on average measured food consumption and body weight from other laboratory toxicity studies on mallard ducks and pheasant, the daily food consumption rates of the birds are approximately 10% to 20% of the body weight. Taking a conservative value of 10% (i.e., a value that leads to the lowest estimate of dose), the 1000 ppm benchmark dietary concentration cited by U.S. EPA corresponds to a daily dose of 100 mg/kg bw.

For the current risk assessment, the dose of 100 mg/kg bw will be used as a NOAEL for characterizing chronic risks to for birds. It should be noted that this dose is very close to the NOAEL of 175 mg/kg used for mammals and is consistent with the apparent lack of variability in the toxicity of glyphosate among species. As in the assessment for mammals, this NOAEL is based on a repeated dose study for reproductive effects but will be applied to both acute and

longer-term exposures. The acute NOAEL will be taken as 562 mg/kg bw from the acute dietary studies by Palmer and Beavers (1997a,b).

4.3.2.3. Terrestrial Invertebrates – As discussed in Section 4.1.2.3, a standard set of studies are available on the toxicity of glyphosate to honey bees (Palmer and Beavers 1997c; Palmer and Krueger, 2001a; Palmer and Krueger, 2001b). Palmer and Krueger (2001a) report an NOEC of 100 µg/bee and the U.S. EPA/OPP (1993c) classifies glyphosate as practically non-toxic based on an LD_{50} of >100 µg/bee. The NOEC used in this risk assessment, however, will be taken as 50 µg/bee. As detailed in Section 4.1.2.3, the dose of 100 µg/bee from the study by Palmer and Krueger (2001a) was associated with 5% mortality (3/60) and this response was statistically significant when untreated and solvent controls are pooled.

Taking the NOEC of 50 µg/bee and using a body weight of 0.093 g for the honey bee (USDA/APHIS 1993), the 50 µg/bee dose corresponds to about 540 mg/kg bw [0.050 mg/0.000093 kg = 537.6 mg/kg]. This value will be used in the risk characterization for assessing effects of direct contact on terrestrial invertebrates.

Given the large number of species of terrestrial invertebrates, the use of data from a single species for the risk characterization obviously leads to uncertainty in the risk assessment. As noted in Section 4.1.2.3, several additional studies are available on other terrestrial invertebrates. These studies, however, cannot be used quantitatively in the dose-response assessment either because of the way in which exposures were conducted or characterized. Nonetheless, they provide information that can be used in the risk characterization and these studies are discussed further in Section 3.4.

4.3.2.4. Soil Microorganisms. As noted in Section 4.1.2.4, soil microorganisms posses the shikimate pathway and a number of studies have demonstrated inhibition of microbial growth in laboratory culture. This is consistent with transient decreases in the populations of soil fungi and bacteria in the field after the application of glyphosate at application rates that are substantially less than those used in Forest Service programs – i.e., 0.54 kg/ha or about 0.5 lbs/acre from Chakravarty and Chatarpaul (1990). As also discussed in Section 4.1.2.4, several field studies note an increase rather than decrease in soil microorganisms or microbial activity, including populations of fungal plant pathogens, in soil after glyphosate exposures. While the mechanism of this apparent enhancement is unclear, it is plausible that glyphosate treatment resulted in an increase in the population of microorganisms in soil because glyphosate was used as a carbon source and/or treatment with glyphosate resulted in increased nutrients for microorganisms in the soil secondary to damage to plants.

4.3.2.5. Terrestrial Plants (Macrophytes) – As discussed in Section 4.1.2.5., standard toxicity studies required for pesticide registration are available on pre-emergence and post-emergence exposures. In seedling emergence assays, very high concentrations – i.e., 10 lb a.i./acre or about 7.5 lbs a.e./acre – will modestly inhibit seed germination in both monocots and dicots (Bohn 1987). The NOEC for seed germination is 4.5 lb a.e./acre in both monocots and dicots (Everett

et al. 1996a; Willard 1996). This value is used in Worksheet G04 to assess the consequences of off-site movement of glyphosate in runoff.

Glyphosate appears to be more toxic in vegetative vigor assays – i.e., direct application to the foliage of growing plants. The lowest reported NOEC for growth in standard bioassays required for registration is 0.035 lb a.e./acre, reported for tomato and radish in the study by Chetram and Lucash (1992). The highest reported NOEC for growth is 0.56 lb a.e./acre for ryegrass, corn, and onions, also from the study by Chetram and Lucash (1992). This range of values for sensitive and relatively insensitive species is very similar to the range of LC_5 values reported in the vegetative vigor assay of Everett et al. (1996b). The report by Al-Khatib and Peterson (1999) that transient visual injury occurs in soybeans at an application rate of about 0.03 lb a.e./acre is not consistent with the study by Chetram and Lucash (1992), in which no visual damage to soybeans was evident at 0.07 lb a.e./acre. Nonetheless, variations among studies is not uncommon and the study by Al-Khatib and Peterson (1999) appears to have been well-conducted.

In terms of the risk assessment, growth is a more relevant functional endpoint and will be used in preference to transient visual damage for the quantitative characterization of risk. Thus, as indicated in Worksheet G05, the NOEC values for sensitive and tolerant species are taken from the study by Chetram and Lucash (1992).

As also noted in Section 4.1.2.5, exposures substantially above the NOEC of 0.07 lb/acre - i.e., in the range of 0.7 lbs/acre – may have long term impacts on bryophyte and lichen communities (Newmaster et al. 1999). This is not a highly sensitive endpoint compared to the much lower NOEC values used above for the quantitative dose-response assessment.

4.3.3. Aquatic Organisms.

4.3.3.1. Fish – As detailed in Section 4.1.3.1.2, U.S. EPA/OPP (1993c) classified technical grade glyphosate as non-toxic to practically non-toxic in freshwater fish and LC_{50} values for glyphosate are in the range of 70 to 170 mg/L. In addition, the U.S. EPA/OPP (1993c) used the NOEC of 25.7 mg/L from life cycle toxicity study on technical grade glyphosate using fathead minnow and concluded that: *"technical glyphosate should not cause acute or chronic adverse effects to aquatic environments. Therefore, minimal risk is expected to aquatic organisms from the technical glyphosate"*.

The selection of the toxicity values by U.S. EPA/OPP (1993c), however, does not explicitly address the higher toxicity of some glyphosate formulations containing surfactants nor does it address the higher sensitivity of some species of fish to technical grade glyphosate. As discussed in Section 4.1.3.1.3, some formulations of glyphosate contain surfactants which are highly toxic to fish and the 96-hour LC_{50} values for these formulations can be in the range of 1 mg/L, substantially below the NOEC for glyphosate in the fathead minnow life cycle toxicity study. In terms of sensitive species, trout and other salmonids have much lower LC_{50} than those cited by

U.S. EPA/OPP (1993c), with the lowest LC_{50} value for salmonids of 10 mg glyphosate/L, for trout in soft-water (Table 4-2).

The data necessary to address these issues directly are not available. Given the apparently high sensitivity of some salmonids to glyphosate, it would be desirable to have a life cycle toxicity study or at least an egg-and-fry study available on salmonids. In addition, given the apparently high toxicity of surfactant formulations compared to technical grade glyphosate, a life cycle toxicity study on at least one formulation containing a toxic surfactant would be desirable.

In the absence of these types of studies, the relative potency method is the only remaining approach to assessing the potential consequences of longer-term exposures of more toxic formulations to more sensitive species. As discussed in U.S. EPA/ORD (2000), the relative potency method involves the assumption that the ratio of toxicity values are equal among differing bioassays. As applied to the current problem, the relative potency method involves the assumption that the ratios of the available data on acute LC_{50} values for glyphosate and glyphosate formulations can be used to assess the chronic NOEC for a glyphosate formulation.

Specifically, the LC_{50} values of a glyphosate formulation containing a surfactant to the fathead minnow is 2.3 (1.9-2.8) mg/L (U.S. EPA/OPP 1993c, p. 42). The LC_{50} value of technical grade glyphosate (96.7%) to the fathead minnow is 97 (79-120) mg/L (U.S. EPA/OPP 1993c, p. 40). Using the central estimates, the formulated product is more toxic than technical grade glyphosate by a factor of about 40 [97 mg/L ÷ 2.3 mg/L = 42.2]. Taking the life cycle NOEC of 25.7 mg/L for technical grade glyphosate in the fathead minnow and using the relative potency method, the life cycle NOEC for the formulation is estimated at 0.64 mg/L [25.7 mg/L ÷ 40].

The issue of species sensitivity may be addressed in a similar manner. As noted above, the lowest LC_{50} value for technical grade glyphosate in salmonids of 10 mg/L – rainbow trout in soft-water (Wan et al. 1989 as summarized in Table 4-2 of this risk assessment). Thus, salmonids may be more sensitive than fathead minnows to technical grade glyphosate by a factor of about 10 [97 mg/L ÷ 10 mg/L]. Taking the life cycle NOEC of 25.7 mg/L for technical grade glyphosate in the fathead minnow and using the relative potency method for species sensitivity, the life cycle NOEC for technical grade glyphosate in rainbow trout is estimated at about 2.57 mg/L [25.7 mg/L ÷ 10].

A similar approach may be taken to estimate the life cycle NOEC for trout. As discussed above, the life cycle NOEC for the surfactant formulation in fathead minnow is estimated at 0.64 mg/L. The lowest LC_{50} value in the fathead minnow is 2.3 mg/L. In salmonids, the lowest reported LC_{50} value for a surfactant formulation is 1.3 mg/L (U.S. EPA/OPP 1993c, rainbow trout, p. 42). This is lower than any of the LC_{50} values for surfactant formulations of glyphosate published in the open literature. Thus, for surfactant containing formulations, the sensitivity of salmonids relative to minnows is a factor of about 1.8 [2.3 mg/L ÷ 1.3 mg/L= 1.77]. Thus, the NOEC for the surfactant formulation in salmonids is estimated at 0.36 mg/L [0.64 mg/L ÷ 1.8 = 0.355].

Thus, the following chronic NOEC values are used in Worksheet G03 to characterize risk to fish:

typical fish, technical grade glyphosate:	25.7	mg/L [observed]
sensitive fish, technical grade glyphosate:	2.57	mg/L [estimated]
typical fish, glyphosate with surfactant:	0.64	mg/L [estimated]
sensitive fish, glyphosate with surfactant:	0.36	mg/L [estimated]

For acute toxicity, the data on sub-lethal effects, summarized in Section 4.1.3.1.4, could be considered but reported concentrations are generally above the LC_{50} values. Most of the studies summarized in Section 4.1.3.1.4 involve very short-term exposures to relatively high concentrations and are focused on understanding the mechanism of action of glyphosate. These studies, however, are not appropriate for the acute dose-response assessment.

As an alternative, the LC_{50} values will be used to characterize the risk of observing mortality in fish associated with peak concentrations of glyphosate. While the use of LD_{50} and LC_{50} values is generally avoided, the use of 96-hour LC_{50} values to assess the risks of peak exposure is inherently conservative in that most peak exposures will occur for a period of time much shorter than 96-hours. Thus, the following 96-hour LC_{50} values are used for characterizing the risks of short-term exposures in Worksheet G03:

typical fish, technical grade glyphosate:	97	mg/L
sensitive fish, technical grade glyphosate:	10	mg/L
typical fish, glyphosate with surfactant:	2.3	mg/L
sensitive fish, glyphosate with surfactant:	1.3	mg/L

The application of the relative potency method to the available toxicity data in fish is attended by substantial uncertainties. By definition, the relative potency method is used only when significant information is lacking and no better methods are available. The assumption that relative potencies are constant across species and different endpoints – i.e., LC_{50} values and chronic NOECs – cannot be supported by data because no such data are available. If the data were available to support this assumption, the data would be used in preference to the relative potency method. In addition, the application of the relative potency method to estimating the chronic toxicity of glyphosate-surfactant mixtures assumes that the surfactant will coexist with glyphosate and exert an influence on the toxicity of glyphosate as environmental dissipation and degradation occur. This is not likely to be the case and the use of the relative potency method for chronic toxicity of glyphosate-surfactant mixtures may be grossly conservative. Nonetheless, in the absence of data on the chronic toxicity of surfactant formulations to potentially sensitive fish species, this approach will be used in the current risk assessment.

4.3.3.2. Amphibians – No separate dose-response assessment is conducted in this risk assessment for amphibians. As detailed in Section 4.1.3.2, glyphosate and glyphosate formulations have been tested in a number of different bioassays with amphibians and there is no indication that glyphosate or glyphosate formulations induce deformities in amphibians. Most of the available

toxicity data suggest that amphibians are no more sensitive to glyphosate than fish. The report by Smith (2001) does suggest a greater sensitivity of tadpoles to a specific formulation. However, this study is not supported by the other available amphibian studies on glyphosate and glyphosate formulations. In addition, this study involves a formulation that is not used in Forest Service programs.

4.3.3.3. Aquatic Invertebrates – The issues in the dose-response assessment for aquatic invertebrates are very similar to those encountered in the dose-response assessment for fish (Section 4.3.3.1). There is sufficient data to assert that some glyphosate formulations that contain toxic surfactants may be much more toxic to aquatic invertebrates than technical grade glyphosate. There is only one chronic study on technical grade glyphosate and no chronic studies on glyphosate formulations.

One quantitative difference, however, involves the apparent magnitude of the differences in toxicity among technical grade glyphosate and various glyphosate formulations. The 48-hour LC_{50} value for technical grade glyphosate to *Daphnia magna* is listed in U.S. EPA (1993c, p. 45) as 780 mg/L. The 48-hour LC_{50} values for *Daphnia magna* of various glyphosate formulations, however, range from 3 mg/L (surfactant not specified) to >1000 mg/L (glyphosate with X-77 surfactant). The one chronic life cycle toxicity study with *Daphnia magna* using technical grade glyphosate reports an MATC of between 50 and 96 mg/L, similar to the NOEC of 25.7 mg/L in the life-cycle study in fish.

The application of the relative potency method to the invertebrate data on surfactant formulations of glyphosate can be done as with fish, as detailed in Section 4.3.3.1. However, the high variability in toxicity of the surfactant formulations to daphnids must be acknowledged.

As summarized in Appendix 3c, the formulations of glyphosate that are registered for forestry uses have a wide but narrower range of toxicity than the range reported in U.S. EPA (1993c). Based on the data presented in Appendix 3c, the acute toxicity of glyphosate formulations to *Daphnia magna* ranges from 11 mg/L (e.g., Roundup Pro, Roundup Pro Concentrate, Roundup UltraMax) to 930 mg/L (e.g., Aqua Neat, Aquatmaster).

The 48-hour LC_{50} value for technical grade glyphosate to *Daphnia magna* will be taken as 780 mg/L. Recognizing that some surfactant formulations may be at least somewhat less toxic than technical grade glyphosate, it will be assumed that formulations summarized in Appendix 3c that have a low toxicity – i.e., 930 mg/L – are either technical grade glyphosate or glyphosate with a surfactant of low toxicity. It will be assumed that the formulations with a substantially lower LC_{50} contain a toxic surfactant. The extremely toxic product reported in U.S. EPA/OPP (1993c) that has an LC_{50} value of 3 mg/L will not impact the dose-response assessment because none of the products that might be used in Forest Service programs (Appendix 3c) have an LC_{50} value that is this low.

Thus, the relative potency of the most toxic formulations that might be used in Forest Service programs is estimated as 71 [780 mg/L ÷ 11 mg/L = 70.91] and the MACT for the chronic toxicity of these formulations is estimated as 0.7 mg/L [50 mg/L ÷ 71]. Consequently, the values used to characterize risk to aquatic invertebrates in Worksheet G03 are:

Acute LC_{50}, non-toxic formulation:	780	mg/L
Acute LC_{50}, toxic formulation:	11	mg/L
Chronic NOEC, non-toxic formulation:	50	mg/L
Chronic NOEC, toxic formulation:	0.7	mg/L

It should be noted that the toxicities on other intermediate formulations could be calculated in the same manner as above. The potential need for such calculations is discussed further in Section 3.4 (Risk Characterization).

4.3.3.4. Aquatic Plants **–** As discussed in Section 3.1.3.4 and detailed in Appendix 11, glyphosate appears to be about equally toxic to both algae and macrophytes. A greater complication in the characterization of ecological effects may involve the enhancement of algal populations at low concentrations of glyphosate. It is unclear whether this is a hormetic effect or simply a stimulation of algal growth due to the utilization of glyphosate as a nutrient source by algae.

In terms of growth inhibition, the NOEC of 3 mg/L in duckweed (Smyth et al. 1996a) will be used to characterize risk due to inhibition. At lower concentrations – i.e., in the range of 0.002 mg/L to 0.3 mg/L or higher – stimulation of algal growth may be a more common response and has been noted in several studies (Austin et al. 1991; Smyth et al. 1996d; Wong 2000).

4.4. RISK CHARACTERIZATION

4.4.1. Overview. The current risk assessment for glyphosate generally supports the conclusions reached by U.S. EPA: *Based on the current data, it has been determined that effects to birds, mammals, fish and invertebrates are minimal.* At the typical application rate of 2 lbs a.e./acre, none of the hazard quotients for acute or chronic scenarios reach a level of concern even at the upper ranges of exposure for terrestrial organisms. For the application rate of 7 lbs a.e./acre, central estimates of the hazard quotients somewhat exceed the level of concern for the direct spray of a honey bee. That the upper range of the hazard quotients, the level of concern is exceeded modestly in acute scenarios for a large mammal consuming contaminated vegetation and a small bird consuming insects. In the chronic exposure scenarios, the hazard quotient for a large bird consuming contaminated vegetation on site exceeds the level of concern by a factor of about 3. As with all longer term exposure scenarios involving the consumption of contaminated vegetation, the plausibility of this exposure scenario is limited because damage to the treated vegetation – i.e., vegetation directly sprayed at the highest application rate – would reduce and perhaps eliminate the possibility of any animal actually consuming this vegetation over a prolonged period.

For relatively tolerant nontarget species of plants, there is no indication that glyphosate is likely to result in damage at distances as close as 25 feet from the application site. For sensitive species at the upper range of application rates, there is a modest excursion about the NOEC at offsite distances of 100 feet or less. It should be noted, however, that all of these drift estimates are based on low-boom ground sprays. Many applications of glyphosate are conducted by directed foliar applications using backpacks. In such cases, little if any damage due to drift would be anticipated. Nontarget terrestrial plants are not likely to be affected by runoff of glyphosate under any conditions.

The primary hazards to fish appear to be from acute exposures to the more toxic formulations. At the typical application rate of 2 lbs a.e./acre, the hazard quotients for the more toxic formulations at the upper ranges of plausible exposure indicate that the LC_{50} values for these species will be not reached or exceeded under worst-case conditions. At an application rate of 7 lbs a.e./acre, the acute exposures are estimated to slightly exceed the LC_{50} value for typical species and exceed the LC_{50} value for sensitive species by a factor of about 2. In these worst-case scenarios, the exposure estimates are based on a severe rainfall (about 7 inches over a 24 hour period) in an area where runoff is favored – a slope toward a stream immediately adjacent to the application site. This is a standard worst-case scenario used in Forest Service risk assessments to guide the Forest Service in the use of herbicides. This risk characterization strongly suggests that the use of the more toxic formulations near surface water is not prudent.

The use of less toxic formulations result in acute hazard quotients that do not approach a level of concern for any species. Nonetheless, the hazard quotient of 0.08 for sensitive species at an application rate of 2 lbs/acre is based on an LC_{50} value rather than a NOEC. Thus, the use of glyphosate near bodies of water where sensitive species of fish may be found (i.e., salmonids) should be conducted with substantial care to avoid contamination of surface water. Concern for

potential effects on salmonids is augmented by the potential effects of low concentrations of glyphosate on algal populations.

The likelihood of direct acute toxic effects on aquatic invertebrates or longer term direct effects on any fish species seems extremely remote based on central estimates of the hazard quotient and unlikely base on upper ranges of the hazard quotient. The hazard quotient of 0.044 for longer term effects of the more toxic formulations on sensitive fish is based on an estimated NOEC and thus is not, in itself, of substantial concern. Aquatic plants appear to be somewhat less sensitive to glyphosate than the most sensitive aquatic animals. There is no indication that adverse effects on aquatic plants are plausible.

4.4.2. Terrestrial Organisms

4.4.2.1. Terrestrial Animals– The quantitative risk characterization for terrestrial animals is summarized in Table 4-4. These hazard quotients are calculated by dividing the exposure assessments summarized in Table 4-1 by the toxicity values specified at the bottom of Table 4-4. As indicated at the bottom of Table 4-4, all of the hazard quotients are based on NOEC values. In addition, all hazard quotients are based on an application rate of 2 lbs a.e./acre, the typical application rate use in Forest Service programs. At this application rate, the level of concern is unity – i.e. at a hazard quotient of 1.0 or less, there is no plausible basis for asserting that adverse effects are likely to occur. As indicated in Section 2.4, the upper range of the application rate that is proposed in Forest Service programs is 7 lbs a.e./acre. At this application rate, the level of concern for the hazard quotients in Table 4-4 is about 0.3 [2 lbs a.e./acre ÷ 7 lbs a.e./acre = 0.2857]. Levels of concern for other application rates may be similarly calculated.

Based on the typical application rate of 2 lbs a.e./acre, none of the hazard quotients for acute or chronic scenarios reach a level of concern even at the upper ranges of exposure. This is consistent with the risk characterization given by U.S. EPA/OPP (1993c, p. 53): *Based on the current data, it has been determined that effects to birds, mammals, fish and invertebrates are minimal.*

For the application rate of 7 lbs a.e./acre, central estimates of the hazard quotients somewhat exceed the level of concern – i.e., the hazard quotient exceeds 0.3 – for the direct spray of a honey bee. That the upper range of the hazard quotients, the level of concern is exceeded modestly in acute scenarios for a large mammal consuming contaminated vegetation and a small bird consuming insects. In the chronic exposure scenarios, the hazard quotient for a large bird consuming contaminated vegetation on site exceeds the level of concern by a factor of about 2.8 [0.83 ÷ 0.3].

The direct spray of a honey bee at an application rate of 7 lbs a.e./acre corresponds to a dose of 1120 mg/kg bw. It is unclear if this would be associated with detectable toxic effects. Based on the study by Palmer and Krueger (2001a) , a dose of 100 µg/bee, corresponding to about 1080 mg/kg bw, was associated with 5% mortality (3/60). It should also be noted that this risk characterization applies only to bees that are directly sprayed at the maximum application rate (7

lbs/acre) and does not consider the effects of foliar interception. Thus, under actual field conditions, substantial mortality in bees would not be expected.

For a large mammal, dose associated with the acute consumption of contaminated vegetation at an application rate of 7 lbs a.e./acre is about 340 mg/kg (97.1 mg/kg from Table 4-3 × 7 lbs/acre ÷ 2 lbs/acre). This dose is below the LD_{50} value for mammals (2,000 to 6,000 mg/kg) by a factor of about 6 to 18. Thus, it is not likely that substantial mortality would be observed. For mammals, however, the NOEL of 175 mg/kg is associated with a LOAEL of 350 mg/kg, nearly identical with the upper range of exposure – i.e., 340 mg/kg. As detailed in Section 3.3.2 (the dose-response assessment for the human health risk assessment), the dose of 350 mg/kg/day results in some mortality in pregnant rabbits (Rodwell et al. 1980b). Thus, while *substantial* mortality would not be anticipated – i.e., the exposure is well below the LD_{50} – mortality in some animals would be plausible.

For a small bird consuming contaminated insects after the application of 7 lbs a.e./acre, the estimated dose is about 787 mg/kg [225 mg/kg from Table 4-3 × 7 lbs/acre ÷ 2 lbs/acre]. This dose is well below the LD_{50} but somewhat higher than the acute NOAEL of 562 mg/kg. As discussed in Section 4.2.2.3, this exposure assessment may be extremely conservative. The residue rates from small insects are used rather than the residue rates from large insects and this makes a substantial difference. In addition, as detailed in Worksheet F14, this exposure scenario assumes that 100% of the insects consumed by the bird on the day of exposure (i.e, no dissipation is assumed) were directly sprayed.

In the longer term exposure scenario for a large bird consuming vegetation at the application site, the average daily dose is about 291 mg/kg/day [83.2 mg/kg × 7 lbs/acre ÷ 2 lbs/acre]. This is a standard exposure scenario used in all Forest Service risk assessments. Nonetheless, as with all longer term exposure scenarios involving the consumption of contaminated vegetation, the plausibility of this exposure scenario is limited because damage to the treated vegetation – i.e., vegetation directly sprayed at the highest application rate – would reduce and perhaps eliminate the possibility of any animal actually consuming this vegetation over a prolonged period. On the other hand, as discussed in Section 4.2.2.3, residue rates estimated by Fletcher et al. (1994) and used in the exposure assessment are below some monitored values for glyphosate on herbaceous vegetation (Newton et al. 1994). Thus, while the longer term estimates of exposure may be overestimated by not considering damage to vegetation, this may be somewhat offset by an underestimate of initial residues.

Another factor that must be considered in the interpretation of these hazard quotients is the information from field studies. As discussed in Section 4.1.2.6, several field studies report effects on terrestrial animals that appear to be associated with changes in habitat and, in some cases, the effects appear to be beneficial.

4.4.2.2. Terrestrial Plants– The quantitative risk characterizations for terrestrial plants are summarized in Worksheet G04 for the offsite movement of glyphosate in runoff and Worksheet G05 for offsite movement of glyphosate by drift and wind erosion.

The runoff estimates are based on GLEAMS modeling using three different soils (clay, loam, and sand) at annual rainfall rates of 5 to 250 inches and using the typical application rate that the Forest Service is considering, 2 lb/acre. The toxicity index is based on the pre-emergence NOAEL of 4.5 lb/acre. As with the corresponding assessment of effects in terrestrial mammals, the level of concern is unity for an application rate of 2 lbs/acre and about 0.3 for an application rate of 7 lbs/acre. Based on this index of toxicity, plant species are not likely to be affected by runoff of glyphosate under any conditions.

Hazard quotients for offsite drift (Worksheet G05) are based on the NOEC value of 0.035 lb/acre for sensitive plant species as well as the NOAEL of 0.56 lb/acre for tolerant plant species, as detailed in Section 4.3.2.5. The estimates for offsite drift encompass plausible exposures attributable to wind erosion, as discussed in Section 4.2.2.4. For relatively tolerant species, there is no indication that glyphosate is likely to result in damage at distances as close as 25 feet from the application site. For sensitive species at the upper range of application rates, there is a modest excursion about the NOEC (hazard quotients of 0.3 to 1.1 with a level of concern of 0.3) at offsite distances of 100 feet or less. It should be noted, however, that all of these drift estimates are based on low-boom ground sprays. Many applications of glyphosate are conducted by directed foliar applications using backpacks. In such cases, little if any damage due to drift would be anticipated.

4.4.3. Aquatic Organisms. The quantitative risk characterization for aquatic species is summarized in Table 4-5. As in the corresponding tables for terrestrial species, the exposure component of the hazard quotients are based on the typical application rate of 2 lbs a.e./acre. Thus, the level of concern for this application rate is unity and the level of concern for the maximum application rate of 7 lbs a.e./acre is 0.3.

As discussed in previous sections of this risk assessment, some formulations of glyphosate are much more acutely toxic to fish and aquatic invertebrates than technical grade glyphosate or other formulations of glyphosate. This difference in acute toxicity among formulations appears to be due largely to the use of surfactants that are toxic to fish and invertebrates.

The primary hazards to fish appear to be from acute exposures to the more toxic formulations. As summarized in Table 4-5, the hazard quotients for the more toxic formulations at the upper ranges of exposure – i.e., 0.35 for typical species and 0.62 for sensitive species – indicate that the LC_{50} values for these species will be not reached or exceeded under worst-case conditions due to runoff after a high rainfall event into a small stream. At an application rate of 7 lbs a.e./acre, the acute exposures are estimated to slightly exceed the LC_{50} value for typical species and exceed the LC_{50} value for sensitive species by a factor of about 2. In these worst-case scenarios, the exposure estimates are based on a severe rainfall (about 7 inches over a 24 hour period) in an area

where runoff is favored – a slope toward a stream immediately adjacent to the application site. This, again, is a standard worst-case scenario used in Forest Service risk assessments to guide the Forest Service in the use of herbicides. Although this scenario is not likely to occur, the study by Trumbo (2002) found monitored concentrations of glyphosate at 0.85 mg/L, virtually identical to the modeled value of 0.8 mg/L at an application rate of 2 lbs a.e./acre. Thus, this risk characterization strongly suggests that the use of the more toxic formulations near surface water is not prudent.

The use of less toxic formulations result in hazard quotients that do not approach a level of concern for any species. Nonetheless, the hazard quotient of 0.08 for sensitive species at an application rate of 2 lbs/acre is based on an LC_{50} value rather than a NOEC. Thus, the use of glyphosate near bodies of water where sensitive species of fish may be found (i.e., salmonids) should be conducted with substantial care to avoid contamination of surface water.

Concern for potential effects on salmonids is augmented by the potential effects of low concentrations of glyphosate on algal populations. As discussed in Section 4.1.3.4, glyphosate may stimulate rather than inhibit algal growth at low concentrations. While this might not be classified as an adverse effect on algae, Austin et al. (1991) has suggested that this stimulation could contribute to eutrophication of waterways with salmonid populations. No field studies have been encountered in the literature suggesting that this effect has been observed. Nonetheless, the central estimate of the projected longer-term concentrations of glyphosate in water is 0.002 mg/L with an upper range of 0.056 mg/L at and application rate of 2 lbs a.e./acre. At an application rate of 7 lbs a.e./acre, the corresponding concentrations are about 0.007 mg/L to 0.2 mg/L. An increase in periphyton concentrations in artificial streams has been reported by Austin et al. (1991) at concentrations which encompass these ranges – i.e., 0.0019 - 0.2874 mg/L. This is supported by Wong (2000), who reported an increase in chlorophyll-a synthesis by *Scenedesmus quadricauda* at a concentration of 0.02 mg/L.

The likelihood of direct acute toxic effects on aquatic invertebrates or longer term direct effects on any fish species seems extremely remote based on central estimates of the hazard quotient and unlikely base on upper ranges of the hazard quotient. The hazard quotient of 0.044 for longer term effects of the more toxic formulations on sensitive fish is based on an estimated NOEC and thus is not, in itself, of substantial concern.

A very important limitation to this risk characterization, however, is that no chronic studies are available on the formulations that appear to have a very high acute toxicity. Thus, as detailed in Section 4.3.3.1 on fish and Section 4.3.3.3 on aquatic invertebrates, the relative potency method was used in an attempt to quantify potential chronic effects from exposure to for both sensitive species, primarily salmonids, as well as the chronic effects of formulations that contain the more toxic surfactants. While the relative potency method is the most reasonable approach that is apparent given the lack of more directly relevant data, it increases uncertainty in the risk characterization for longer term exposures.

Aquatic plants appear to be somewhat less sensitive to glyphosate than the most sensitive aquatic animals. There is no indication that adverse effects on aquatic plants are plausible. Unlike the case with aquatic animals, even short-term toxicity studies in aquatic plants use endpoints involving changes in population density. Thus, both the short-term and longer-term hazard quotients given in Table 4-3 can be legitimately used to characterize risk.

Table 4-1. Estimates of relative potency and toxicological interaction of glyphosate and POEA[a]

Species/Assay/Study	Observed LC_{50} values					
	Glyphosate	POEA	Roundup[b]	ρ	Predicted LC_{50}	Pred.÷ Obs.
			pH 6.5			
Rainbow trout	140	7.4	10.8	19	22	2.0
Bluegills	140	1.3	6.0	108	3.1	0.5
			pH 7.2, 96 hr unless specified			
Midge larvae, 48 hr.	55	13	25	4.2	28	1.1
Rainbow trout	140	2	11.8	70	6.5	0.6
Fathead minnow	97	1.0	3.2	97	3.2	1.0
Channel catfish	130	13	18	10	35	1.9
Bluegills	140	3.0	7.1	47	9.5	1.3
			pH 9.5			
Rainbow trout	240	0.65	2.0	369	2.1	1.1
Bluegills	220	1.0	2.6	220	3.3	1.3

[a]Data from Folmar et al. (1979).

[b]Value reported by Folmar as mg a.i multiplied 1.42 to account for added mass of surfactant.

ρ = LC_{50} of glyphosate ÷ LC_{50} of POEA.

Table 4-2. Estimates of relative potency and toxicological interaction of glyphosate and POEA in five species of salmonids [a]

Species/Assay/Study	Observed 96-hour LC_{50} Values					
	Glyphosate	POEA	Roundup[a]	ρ	Predicted LC_{50}	Pred.÷ Obs.
			Soft Water pH 6.3			
Coho	27	4.6	32	5.9	10.9	0.34
Chum	10	2.7	20	3.7	5.5	0.28
Chinook	19	2.8	33	6.8	6.9	0.21
Pink	14	4.5	33	3.1	8.5	0.26
Rainbow	10	2	33	5	4.5	0.13
			Soft Water pH 7.2			
Coho	36	3.2	27	11.3	8.8	0.33
Chum	22	4.2	19	5.2	9.7	0.51
Chinook	30	2.8	27	10.7	7.5	0.28
Pink	23	2.8	31	8.2	7.2	0.23
Rainbow	22	2.5	15	8.8	6.6	0.44
			Hard Water pH 8.2			
Coho	210	1.8	13	117	5.9	0.45
Chum	202	1.4	11	144	4.6	0.41
Chinook	220	1.7	17	129	5.6	0.32
Pink	380	1.4	14	261	4.6	0.33
Rainbow	220	1.7	14	129	5.6	0.40

[a] Data from Wan et al. (1989)

[b] As reported by Wan et al. (1989) in units of mg product/L.

Table 4-3: Summary of Exposure Scenarios for Terrestrial Animals for an Application Rate of 2 lbs a.e./acre.

Scenario	Dose (mg/kg/day)			Worksheet
	Central	Lower	Upper	
Acute/Accidental Exposures				
Direct spray				
small mammal, first-order absorption	4.75e-01	1.51e-01	1.15e+00	F01
small animal, 100% absorption	4.85e+01	4.85e+01	4.85e+01	F02a
bee, 100% absorption	3.21e+02	3.21e+02	3.21e+02	F02b
Contaminated vegetation				
small mammal	8.57e-01	8.57e-01	2.11e+00	F03
large mammal	3.44e+01	3.44e+01	9.71e+01	F10
large bird	5.38e+01	5.38e+01	1.52e+02	F12
Contaminated water				
small mammal, spill	2.66e+00	1.06e+00	5.32e+00	F05
stream	5.86e-03	2.93e-04	1.17e-01	F06
Contaminated insects				
small bird	7.50e+01	7.50e+01	2.25e+02	F14
Contaminated fish				
predatory bird, spill	9.45e-01	1.89e-01	2.83e+00	F08
Longer-term Exposures				
Contaminated vegetation				
small mammal, on site	4.69e-02	2.35e-02	2.31e-01	F04a
off-site	4.74e-04	1.36e-04	4.31e-03	F04b
large mammal, on site	5.65e+00	1.88e+00	5.32e+01	F11a
off-site	1.90e-01	1.09e-01	9.94e-01	F11b
large bird, on site	8.84e+00	2.95e+00	8.32e+01	F13a
off-site	2.98e-01	1.71e-01	1.56e+00	F13b
Contaminated water				
small mammal	2.93e-04	2.93e-05	2.34e-03	F07
Contaminated fish				
predatory bird	1.04e-04	5.20e-06	1.25e-03	F09

Table 4-4: Summary of quantitative risk characterization for terrestrial animals at an application rate of 2 lbs a.e./acre [1]

Scenario	Hazard Quotient[2] Central	Lower	Upper
Acute/Accidental Exposures			
Direct spray			
small mammal, first-order absorption	3e-03	9e-04	7e-03
small animal, 100% absorption	3e-01	3e-01	3e-01
bee, 100% absorption	6e-01	6e-01	6e-01
Contaminated vegetation			
small mammal	5e-03	5e-03	1e-02
large mammal	2e-01	2e-01	6e-01
large bird	1e-01	1e-01	3e-01
Contaminated water			
small mammal, spill	2e-02	6e-03	3e-02
small mammal, stream	3e-05	2e-06	7e-04
Contaminated insects			
small bird	1e-01	1e-01	4e-01
Contaminated fish			
predatory bird, spill	2e-03	3e-04	5e-03
Longer-term Exposures			
Contaminated vegetation			
small mammal, on site	3e-04	1e-04	1e-03
off-site	3e-06	8e-07	2e-05
large mammal, on site	3e-02	1e-02	3e-01
off-site	1e-03	6e-04	6e-03
large bird, on site	9e-02	3e-02	8e-01
off-site	3e-03	2e-03	2e-02
Contaminated water			
small mammal	2e-06	2e-07	1e-05
Contaminated fish			
predatory bird	1e-06	5e-08	1e-05

Toxicity Indices [3]

Acute toxicity value for mammal - NOAEL	175	mg/kg
Chronic toxicity value for mammal - NOAEL	175	mg/kg/day
Acute toxicity value for bird - NOAEL	562	mg/kg
Chronic toxicity value for birds - NOAEL	100	mg/kg/day
Honey Bee Acute toxicity - NOEC	540	mg/kg

[1] See Table 4-1 for summary of exposure assessments.
[2] Estimated dose ÷ toxicity index
[3] See chemical specific worksheet notes for a discussion of the dose-response assessments.

Table 4-5: Quantitative Risk Characterization for Aquatic Species at an Application Rate of 2 lbs a.e./acre.

Hazard Quotients	**Central**	**Lower**	**Upper**	**Toxicity Value (mg/L)**	**End-point**
Fish, Acute Exposures					
Typical species, less toxic formulation	4.1e-04	2.1e-05	8.2e-03	97	LC_{50}
Sensitive species, less toxic formulation	4.0e-03	2.0e-04	8.0e-02	10	LC_{50}
Typical species, more toxic formulation	1.7e-02	8.7e-04	3.5e-01	2.3	LC_{50}
Sensitive species, more toxic formulation	3.1e-02	1.5e-03	6.2e-01	1.3	LC_{50}
Fish, Chronic Exposures					
Typical species, less toxic formulation	7.8e-05	7.8e-06	6.2e-04	25.7	NOEC
Sensitive species, less toxic formulation	7.8e-04	7.8e-05	6.2e-03	2.57	NOEC
Typical species, more toxic formulation	3.1e-03	3.1e-04	2.5e-02	0.64	NOEC
Sensitive species, more toxic formulation	5.6e-03	5.6e-04	4.4e-02	0.36	NOEC
Aquatic Invertebrates, Acute Exposures					
Less toxic formulation	5.1e-05	2.6e-06	1.0e-03	780	LC_{50}
Most toxic formulation	3.6e-03	1.8e-04	7.3e-02	11	LC_{50}
Aquatic Invertebrates, Chronic Exposures					
Less toxic formulation	4.0e-05	4.0e-06	3.2e-04	50	NOEC
Most toxic formulation	2.9e-03	2.9e-04	2.3e-02	0.7	NOEC
Aquatic Plants					
Acute	1.3e-02	6.7e-04	2.7e-01	3	NOEC
Chronic	6.7e-04	6.7e-05	5.3e-03	3	NOEC

Exposures (mg/L)	Central	Lower	Upper	Worksheets	
Acute	0.04	0.002	0.8	F06	Stream
Longer-term	0.002	0.0002	0.016	F09	Pond

See Sections 4.3.3.2, 4.3.3.3, and 4.3.3.4 for a discussion and derivation of the toxicity values for fish, invertebrates, and aquatic plants, respectively. See Worksheets F06 and F09 for the derivation of the concentrations in streams and ponds, respectively.

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APPENDICES

Appendix 1: Glyphosate Formulations with Forestry Applications (C&P Press Database)		
Brand Name Company/Composition	**Application Rate (Specified by Label)**	**Inerts (Specified)**
Accord SP **DOW AGROSCIENCES** 41.0% glyphosate (**isopropylamine salt**) 59.0% inert ingredients 4 lbs a.i./gallon 3 lbs a.e./gallon liquid formulation **No additional surfactant needed or recommended** ***recommended for aerial application by helicopter only***	**FORESTRY SITE PREPARATION:** BROADCAST: **AERIAL OR GROUND:** 2-10 qt/acre SPRAY-TO-WET:**HANDGUN OE BACKPACK:** 1-2% by volume LOW VOLUME DIRECTED SPRAY:**HANDGUN OE BACKPACK:** 1-2% by volume	not specified
	WOODY BRUSH AND TREE RATES: 2 qt/acre (Birch) to 4 qt/acre (Kudzu)	
	PERENNIAL WEEDS: 0.5-5.0 qt/acre (Bindweed) to 4-5 qt/acre (Torpedograss)	
	INJECT AND FRILL APPLICATION: 25-100% concentration to continuous frill around tree or as cuts evenly spaced around tree below all branches	
	ANNUAL WEEDS: 12 to 48 fl oz/acre	
Aqua Neat **RIVERDALE** 53.8% glyphosate (**isopropylamine salt**) 46.2% inert ingredients 5.4 lbs a.i./gallon 4 lbs a.e./gallon liquid formulation **Recommends use of nonionic surfactant labeled for herbicide use** ***labeled for aerial application (NOS)***	**ANNUAL WEED CONTROL:** **BROADCAST APPLICATON**: 1 ½ pints/acre to 3 pints/acre (Italian Ryegrass) **HAND-HELD HIGH-VOLUME APPLICATION**: 3/4 percent solution	not specified MSDS indicates no hazardous chemicals under OSHA Hazard Communication Standard
	PERENNIAL WEEDS: 3 pints/acre (Quackgrass) to 7 ½ pints/acre (Bermudagrass)	
	WOODY BRUSH AND TREE RATES: 3 pints/acre (Birch) to 7 ½ pints/acre (Poison Ivy or Poison Oak)	
	AQUATIC AND OTHER NON-CROP SITES: Maximum application rate is 7 ½ pints/acre in any single broadcast application made over water	
	WEEDS CONTROLLED OR SUPPRESSED: 12 to 48 fl oz/acre	
	INJECTION AND FRILL APPLICATION: 25-100% concentration to continuous frill around tree or as cuts evenly spaced around tree below all branches	
	CUT STUMP APPLICATION: 50-100% solution to freshly cut surface	

Appendix 1: Glyphosate Formulations with Forestry Applications (C&P Press Database)		
Brand Name Company/Composition	**Application Rate (Specified by Label)**	**Inerts (Specified)**
Aquamaster **MONSANTO** 53.8% glyphosate (**isopropylamine salt**) 46.2% inert ingredients 5.4 lbs a.i./gallon 4 lbs a.e./gallons liquid formulation **Requires use of nonionic surfactant labeled for herbicide use** ***labeled for aerial application (NOS)***	**ANNUAL WEED CONTROL:** **BROADCAST APPLICATION**: 1 ½ pints/acre to 3 pints/acre (Italian Ryegrass) **HAND-HELD HIGH-VOLUME APPLICATION**: 3/4 to 1 ½ percent solution	water CAS No. 7732-18-5 MSDS indicates no hazardous chemicals under OSHA Hazard Communication Standard
	AQUATIC AND OTHER NON-CROP SITES: Maximum application rate is 7 ½ pints/acre in any single broadcast application made over water	
	PERENNIAL WEEDS: 3 pints/acre (Quackgrass) to 7 ½ pints/acre (Bermudagrass)	
	WOODY BRUSH AND TREE RATES : 3 pints/acre (Birch) to 7 ½ pints/acre (Poison Ivy or Poison Oak)	
	WEEDS CONTROLLED OR SUPPRESSED: 12 to 48 fl oz/acre	
	INJECTION AND FRILL APPLICATION: 25-100% concentration to continuous frill around tree or as cuts evenly spaced around tree below all branches	
	CUT STUMP APPLICATION: 50-100% solution to freshly cut surface	
Cornerstone **AGRILLIANCE** 41.0% glyphosate (**isopropylamine salt**) 59.0% inert ingredients 4 lbs a.i./gallon 3 lbs a.e./gallons liquid formulation **Nonionic surfactants labeled for use with herbicides may be used** ***labeled for aerial application by fixed wing and helicopter***	**ANNUAL WEED CONTROL:** **Low-Volume Broadcast Application**: 8 oz/acre (Foxtail) to 48 oz/acre (Fliaree) **HIGH-VOLUME BROADCAST APPLICATION:** 1 to 1 ½ qt/acre	not specified
	PERENNIAL WEEDS:1 qt/acre (Alfalfa) to 5 qt/acre (Bermudagrass)	
	WOODY BRUSH AND TREES: 2 qt/acre (Birch) to 5 qt/acre (Poison Ivy or Oak)	
	WEEDS CONTROLLED OR SUPPRESSED: 12 to 64 fluid ounces/acre	
	INJECTION AND FRILL APPLICATION: 50-100% concentration of product either to continuous frill around the tree or as cuts evenly spaced around the tree below all branches	
	TREE AND VINE CROPS: 8 fl oz/acre (Barley) to 16 fl oz/acre (Crabgrass)	

Appendix 1: Glyphosate Formulations with Forestry Applications (C&P Press Database)		
Brand Name Company/Composition	**Application Rate (Specified by Label)**	**Inerts (Specified)**
Credit **NUFARM** 41.0% glyphosate (**isopropylamine salt**) 59.0% inert ingredients 4 lbs a.i./gallon 3 lbs a.e./gallons liquid formulation **Nonionic surfactants labeled for use with herbicides may be used** ***labeled for aerial application by fixed wing and helicopter***	**ANNUAL WEED CONTROL:** **Low-Volume Broadcast Application**: 8 oz/acre (Foxtail) to 48 oz/acre (Fliaree) **HIGH-VOLUME BROADCAST APPLICATION:** 1 to 1 ½ qt/acre	exthoxylated tallowamines CAS No. 61791-83-6 (SARA Title III) MSDS indicates that this inert is a hazardous chemical under OSHA Hazard Communication Standard
	PERENNIAL WEEDS:1 qt/acre (Alfalfa) to 5 qt/acre (Bermudagrass)	
	WOODY BRUSH AND TREES: 2 qt/acre (Birch) to 5 qt/acre (Poison Ivy or Oak)	
	CONIFER RELEASE: 1 to 1 ½ qt/acre	
	SILVICULTURAL SITES AND RIGHTS-OF-WAY: where repeat applications are necessary do not exceed 10.6 qt/acre per year	
	WEEDS CONTROLLED OR SUPPRESSED: 12 to 64 fl oz/acre	
Credit Systemic **NUFARM** 41.0% glyphosate (**isopropylamine salt**) 59.0% inert ingredients 4 lbs a.i./gallon 3 lbs a.e./gallons liquid formulation **Nonionic surfactants labeled for use with herbicides may be used** ***labeled for aerial application by fixed wing and helicopter***	**ANNUAL WEED CONTROL:** **Low-Volume Broadcast Application**: 8 oz/acre (Foxtail) to 48 oz/acre (Fliaree) **HIGH-VOLUME BROADCAST APPLICATION:** 1 to 1 ½ qt/acre	exthoxylated tallowamines CAS No. 61791-83-6 (SARA Title III) MSDS indicates that this inert is a hazardous chemical under OSHA Hazard Communication Standard
	PERENNIAL WEEDS:16 fl oz/acre (Leafy spurge) to 5 qt/acre (Bermudagrass)	
	WOODY BRUSH AND TREES: 2 qt/acre (Birch) to 5 qt/acre (Poison Ivy or Oak)	
	WEEDS CONTROLLED OR SUPPRESSED: 12 to 64 fl oz/acre	
	MIDDLES MANAGEMENT (ANNUAL WEEDS): 8 (Barley) to 32 fl oz/acre (Filaree)	

Appendix 1: Glyphosate Formulations with Forestry Applications (C&P Press Database)		
Brand Name Company/Composition	**Application Rate (Specified by Label)**	**Inerts (Specified)**
Debit TMF **NUFARM** 53.8% glyphosate (**isopropylamine salt**) 46.2% inert ingredients 5.4 lbs a.i./gallon 4 lbs a.e./gallons liquid formulation **Requires use of nonionic surfactant labeled for herbicide use** ***labeled for aerial application by fixed wing and helicopter***	**ANNUAL WEED CONTROL:** **BROADCAST APPLICATION**: 1 ½ pints/acre to 3 pints/acre (Italian Ryegrass) **HAND-HELD HIGH-VOLUME APPLICATION**: 3/4 percent solution	not specified MSDS indicates no hazardous chemicals under OSHA Hazard Communication Standard
	PERENNIAL WEEDS: 3 pints/acre (Quackgrass) to 7 ½ pints/acre (Bermudagrass)	
	WOODY BRUSH AND TREE RATES : 3 pints/acre (Birch) to 7 ½ pints/acre (Poison Ivy or Poison Oak)	
	FARM DITCHES : 4 ½ to 6 fl oz/acre **DORMANT RANGELAND** : 6 to 12 fl oz/acre	
	WEEDS CONTROLLED OR SUPPRESSED: 6 to 48 fl oz/acre	
Eagre *Aquatic Herbicide* **GRIFFIN** 53.8% glyphosate (**isopropylamine salt**) 46.2% inert ingredients 5.4 lbs a.i./gallon 4 lbs a.e./gallons liquid formulation **Requires use of nonionic surfactant labeled for herbicide use** ***labeled for aerial application (NOS)***	**PERENNIAL WEEDS**: 3 pints/acre (Quackgrass) to 7 ½ pints/acre (Bermudagrass)	not specified
	WOODY BRUSH AND TREE RATES: 3 pints/acre (Birch) to 7 ½ pints/acre (Poison Ivy or Poison Oak)	
	AQUATIC AND OTHER NON-CROP SITES: Maximum application rate is 7 ½ pints/acre in any single broadcast application made over water	
	WEEDS CONTROLLED OR SUPPRESSED: 6 to 48 fl oz/acre	
	INJECTION AND FRILL APPLICATION: 25-100% concentration of product either to continuous frill around the tree or as cuts evenly spaced around the tree below all branches	
	CUT STUMP APPLICATION: 50-100% solution to freshly cut surface	

Appendix 1: Glyphosate Formulations with Forestry Applications (C&P Press Database)		
Brand Name Company/Composition	**Application Rate (Specified by Label)**	**Inerts (Specified)**
Foresters' *Non-Selective Herbicide* **RIVERDALE** 53.8% glyphosate (**isopropylamine salt**) 46.2% inert ingredients 5.4 lbs a.i./gallon 4 lbs a.e./gallons liquid formulation **Recommends use of nonionic surfactant labeled for herbicide use** ***labeled for aerial application by fixed wing and helicopter***	**ANNUAL WEED CONTROL:** **BROADCAST APPLICATION**: 1 ½ pints/acre to 3 pints/acre (Italian Ryegrass) **HAND-HELD HIGH-VOLUME APPLICATION**: 3/4 percent solution	not specified MSDS indicates no hazardous chemicals under OSHA Hazard Communication Standard
	PERENNIAL WEEDS: 3 pints/acre (Quackgrass) to 7 ½ pints/acre (Bermudagrass)	
	WOODY BRUSH AND TREE RATES: 3 pints/acre (Birch) to 7 ½ pints/acre (Poison Ivy or Poison Oak)	
	INJECT AND FRILL APPLICATION: 25-100% concentration of product either to continuous frill around the tree or as cuts evenly spaced around the tree below all branches	
	CUT STUMP APPLICATION: 50-100% solution to freshly cut surface	
	WETLAND SITES: not to exceed maximum application rate of 3 3/4 qt/acre	
Glyfos **CHEMINOVA** 41.0% glyphosate (**isopropylamine salt**) 59.0% inert ingredients 4 lbs a.i./gallon 3 lbs a.e./gallon liquid formulation **Requires use of nonionic surfactant labeled for herbicide use** ***labeled for aerial application by fixed wing and helicopter***	**ANNUAL WEEDS**: 8 fl oz/acre (Foxtail) to 48 fl oz/acre (Filaree)	exthoxylated tallowamines CAS No. 61791-83-6 (SARA Title III) MSDS indicates that this inert is a hazardous chemical under OSHA Hazard Communication Standard
	HIGH-VOLUME BROADCAST APPLICATION: 1 to 1 ½ qt/acre **LOW-VOLUME BROADCAST APPLICATION**: 1 to 1 ½ qt/acre	
	PERENNIAL WEEDS: 1 qt/acre (Alfalfa) to 5 qt/acre (Bermudagrass)	
	WOODY BRUSH AND TREES: 2 qt/acre (Birch) to 5 qt/acre (Poison Ivy or Oak)	
	MIDDLES MANAGEMENT (ANNUAL WEEDS): 8 (Barley) to 32 fl oz/acre (Filaree)	
	WEEDS CONTROLLED OR SUPPRESSED: 8 to 64 fl oz/acre	
	INJECT ION AND FRILL APPLICATION: 50-100% concentration of product either to continuous frill around the tree or as cuts evenly spaced around the tree below all branches	
	CONIFER RELEASE: 1 to 1 ½ qt/acre	

Appendix 1: Glyphosate Formulations with Forestry Applications (C&P Press Database)		
Brand Name Company/Composition	**Application Rate (Specified by Label)**	**Inerts (Specified)**
Glyfos Aquatic **CHEMINOVA** 53.8% glyphosate (**isopropylamine salt**) 46.2% inert ingredients 5.4 lbs a.i./gallon 4 lbs a.e./gallons liquid formulation **Recommends use of nonionic surfactant labeled for herbicide use** ***labeled for aerial application by fixed wing and helicopter***	**ANNUAL WEED CONTROL:** **BROADCAST APPLICATION**: 1 ½ pints/acre to 3 pints/acre (Italian Ryegrass) **HAND-HELD HIGH-VOLUME APPLICATION**: 3/4 percent solution	water included in otherwise unidentified inert ingredients
	PERENNIAL WEEDS: 3 pints/acre (Quackgrass) to 7 ½ pints/acre (Bermudagrass)	
	WOODY BRUSH AND TREE RATES: 3 pints/acre (Birch) to 7 ½ pints/acre (Poison Ivy or Poison Oak)	
	WEEDS CONTROLLED OR SUPPRESSED: 6 to 48 fl oz/acre	
	INJECT AND FRILL APPLICATION: 25-100% concentration to continuous frill around tree or as cuts evenly spaced around tree below all branches	
	CUT STUMP APPLICATION: 50-100% solution to freshly cut surface	
Glyfos Pro (No Surfactant Needed) **CHEMINOVA** 41.0% glyphosate (**isopropylamine salt**) 59.0% inert ingredients 4 lbs a.i./gallon 3 lbs a.e./gallon liquid formulation **No additional surfactant needed or recommended** ***labeled for aerial application (NOS)***	**CUT STUMP APPLICATION**: 50-100% solution to freshly cut surface	MSDS specifies surfactants and water @ 59% by weight and tallow alkylamine ethoxylate @ 3-7% by wt
	CHEMICAL MOWING-PERENNIALS: 6 fl oz/acre	
	CHEMICAL MOWING-ANNUALS: 4 to 5 fl oz/acre	
	DORMANT TURFGRASS: 8 to 64 fl oz/acre	
	INJECTION AND FRILL APPLICATION: 50-100% concentration to continuous frill around tree or as cuts evenly spaced around tree below all branches	
	ANNUAL WEED CONTROL: 1 to 4 qt/acre **BROADCAST APPLICATION**: 1 pint/acre **SPRAY-TO-WET APPLICATION**: 0.5 to 2 percent solution	
	PERENNIAL WEEDS: 1 qt/acre (Alfalfa) to 5 qt/acre (Bermudagrass)	
	WOODY BRUSH AND TREES: 2 qt/acre (Birch) to 5 qt/acre (Poison Ivy or Oak)	

Appendix 1: Glyphosate Formulations with Forestry Applications (C&P Press Database)		
Brand Name Company/Composition	**Application Rate (Specified by Label)**	**Inerts (Specified)**
Glyfos X-TRA **CHEMINOVA** 41.0% glyphosate (**isopropylamine salt**) 59.0% inert ingredients 4 lbs a.i./gallon 3 lbs a.e./gallon liquid formulation **No additional surfactant needed or recommended** ***labeled for aerial application by fixed wing and helicopter***	**CONIFER RELEASE:** 1 to 1 ½ qt/acre	MSDS indicates that product contains surfactant @ 10-30% by wt and that surfactant has EU classification: harmful is swallowed; irritating to eyes; toxic to aquatic organisms, may cause long-term adverse effects in aquatic environment. Product contains tallow alkylamine exthoxylate.
	CUT STUMP APPLICATION: 50-100% solution to freshly cut surface	
	INJECTION AND FRILL APPLICATION: 50-100% concentration to continuous frill around tree or as cuts evenly spaced around tree below all branches	
	WEEDS CONTROLLED OR SUPPRESSED: 8 to 64 fl oz/acre	
	WOODY BRUSH AND TREES: 2 qt/acre (Birch) to 5 qt/acre (Poison Ivy or Oak)	
Glyphomax **DOW AGROSCIENCES** 41.3% glyphosate (**isopropylamine salt**) 58.7% inert ingredients 4 lbs a.i./gallon 3 lbs a.e./gallon liquid formulation **Recommends use of nonionic surfactant labeled for herbicide use** ***labeled for aerial application by fixed wing and helicopter***	**ANNUAL WEED CONTROL:** **LOW-VOLUME BROADCAST APPLICATON**: 8 fl oz/acre (Foxtail) to 48 fl oz/acre (Filaree) **HIGH-VOLUME BROADCAST APPLICATON**: 1 to 1.5 qt/acre	not specified
	PERENNIAL WEEDS: 1 qt/acre (Alfalfa) to 5 qt/acre (Bermudagrass)	
	WOODY BRUSH AND TREES: 2 qt/acre (Birch) to 5 qt/acre (Poison Ivy or Oak)	
	CUT STUMP APPLICATION: 50-100% solution to freshly cut surface	

Appendix 1: Glyphosate Formulations with Forestry Applications (C&P Press Database)		
Brand Name Company/Composition	**Application Rate (Specified by Label)**	**Inerts (Specified)**
Glyphomax Plus **DOW AGROSCIENCES** 41.0% glyphosate (**isopropylamine salt**) 59.0% inert ingredients 4 lbs a.i./gallon 3 lbs a.e./gallon liquid formulation **No additional surfactant needed or recommended** ***labeled for aerial application by fixed wing and helicopter***	**ANNUAL WEEDS**: 12 fl oz/acre (Foxtail) to 48 fl oz/acre (Filaree)	not specified
	PERENNIAL WEEDS: 0.5 qt/acre (Johnsongrass) to 5 qt/acre (Bermudagrass)	
	WOODY BRUSH AND TREES: 2 qt/acre (Birch) to 5 qt/acre (Poison Ivy or Oak)	
	CUT STUMP APPLICATION: 50-100% solution to freshly cut surface	
Glyphosate **DUPONT** 41.0% glyphosate (**isopropylamine salt**) 59.0% inert ingredients 4 lbs a.i./gallon 3 lbs a.e./gallon liquid formulation **Recommends use of nonionic surfactant labeled for herbicide use** ***labeled for aerial application by fixed wing and helicopter (see additional instructions at end of label for California and Arkansas)***	**ANNUAL WEEDS**: 12 fl oz/acre (Foxtail) to 48 fl oz/acre (Filaree)	exthoxylated tallowamines (MSDS)
	PERENNIAL WEEDS: 1 qt/acre (Alfalfa) to 5 qt/acre (Bermudagrass)	
	WEEDS CONTROLLED OR SUPPRESSED: 8 to 64 fl oz/acre	
	WOODY BRUSH AND TREES: 2 qt/acre (Birch) to 5 qt/acre (Poison Ivy or Oak)	
	CONIFER RELEASE: 1.5 to 2 qt/acre	
	TREE AND VINE CROPS: 8 fl oz/acre (Barley) to 32 fl oz/acre (Filaree)	
	INJECTION AND FRILL APPLICATION: 50-100% concentration to continuous frill around tree or as cuts evenly spaced around tree below all branches	

Appendix 1: Glyphosate Formulations with Forestry Applications (C&P Press Database)		
Brand Name Company/Composition	**Application Rate (Specified by Label)**	**Inerts (Specified)**
Glyphosate Original **GRIFFIN** 41.0% glyphosate (**isopropylamine salt**) 59.0% inert ingredients 4 lbs a.i./gallon 3 lbs a.e./gallon liquid formulation **Recommends use of nonionic surfactant labeled for herbicide use** ***labeled for aerial application by fixed wing and helicopter (see additional instructions at end of lable for California and Arkansas)***	**ANNUAL WEEDS**: 8 fl oz/acre (Foxtail) to 48 fl oz/acre (Filaree)	not specified
	HIGH-VOLUME AND LOW-VOLUME BROADCAST APPLICATION: 1 to 1 ½ qt/acre	
	PERENNIAL WEEDS: 1 qt/acre (Alfalfa) to 5 qt/acre (Bermudagrass)	
	WEEDS CONTROLLED OR SUPPRESSED: 8 to 64 fl oz/acre	
	WOODY BRUSH AND TREES: 2 qt/acre (Birch) to 5 qt/acre (Poison Ivy or Oak)	
	TREE AND VINE CROPS: 8 fl oz/acre (Barley) to 32 fl oz/acre (Filaree)	
	INJECTION AND FRILL APPLICATION: 50-100% concentration to continuous frill around tree or as cuts evenly spaced around tree below all branches	
	CONIFER RELEASE: 1 ½ to 2 qt/acre	
Glyphosate VMF **DUPONT** 53.8% glyphosate (**isopropylamine salt**) 46.2% inert ingredients 5.44 lbs a.i./gallon 4 lbs a.e./gallons liquid formulation **Requires use of nonionic surfactant labeled for herbicide use** ***recommended for aerial application in all uses by helicopter. Fixed wing may be used for applications to industrial rangeland and pastures in CO, ID, IA, KS, MT, NE, ND, OR, SD, UT, WA, and WY***	**GROUND BROADCAST EQUIPMENT:** **ANNUAL WEEDS:** 3/4 to 1 ½ qt/acre **PERENNIAL WEEDS:** 1 ½ to 3 3/4 qt/acre **WOODY BRUSH AND TREES:** 3 3/4 to 7 ½ qt/acre	not specified
	HANDHELD DIRECTED SPRAY EQUIPMENT: **SPRAY-TO-WET** (HANDGUN OR BACKPACK): 3/4% to 1 ½% by volume **DIRECTED SPRAY** (BACKPACK): 3 3/4% to 7 ½ % by volume (MODIFIED HIGH VOLUME): 1 ½ % to 3% by volume	
	WEEDS CONTROLLED OR SUPPRESSED: 6 to 48 fl oz/acre	
	CONIFER RELEASE: 3/4 to 1 ½ qt/acre as broadcast spray (outside Southeastern US) **CONIFER RELEASE:** 1 1/8 to 1 7/8 qt/acre as broadcast spray (in Southeastern US)	
	WETLAND SITES: not to exceed maximum application rate of 7 ½ pints/acre in a single over-water broadcast application (see exceptions on pg 5 of label)	
	AQUATIC AND OTHER NON-CROP SITES: apply as directed under conditions described in "Weeds Controlled" section of label	

Appendix 1: Glyphosate Formulations with Forestry Applications (C&P Press Database)		
Brand Name Company/Composition	**Application Rate (Specified by Label)**	**Inerts (Specified)**
Glypro **DOW AGROSCIENCES** 53.8% glyphosate (**isopropylamine salt**) 46.2% inert ingredients 5.44 lbs a.i./gallon 4 lbs a.e./gallons liquid formulation **Recommends use of nonionic surfactant labeled for herbicide use** ***recommended that Glypro be applied by helicopter only in forestry site and utility rights-of-way***	**ANNUAL WEED CONTROL:** **BROADCAST APPLICATION**: 1 ½ pints/acre to 3 pints/acre (Italian Ryegrass) **HAND-HELD HIGH-VOLUME APPLICATION**: 3/4 percent solution	not specified
	PERENNIAL WEEDS: 3 pints/acre (Quackgrass) to 7 ½ pints/acre (Bermudagrass)	
	BRUSH OR TREE CONTROL: 3 pints/acre (Birch) to 7 ½ pints/acre (Poison Ivy or Poison Oak)	
	AQUATIC AND OTHER NON-CROP SITES: Maximum application rate is 7 ½ pints/acre in any single broadcast application made over water	
	FORESTRY SITE PREPARATION: BROADCAST: **AERIAL OR GROUND:** 1 ½ to 7 ½ qt/acre SPRAY-TO-WET: **HANDGUN, BACKPACK, OR MISTBLOWER:** 0.75-2% by volume LOW VOLUME DIRECTED SPRAY: **HANDGUN, BACKPACK, OR MISTBLOWER:** 5-10% by volume	
Glypro Plus **DOW AGROSCIENCES** 41% glyphosate (**isopropylamine salt**) 59% inert ingredients 4 lbs a.i./gallon 3 lbs a.e./gallons liquid formulation **No additional surfactant needed or recommended** ***labeled for aerial application by fixed wing and helicopter***	**ANNUAL WEEDS**: 12 fl oz/acre (Foxtail) to 48 fl oz/acre (Filaree)	not specified
	PERENNIAL WEEDS: 1 qt/acre (Alfalfa) to 5 qt/acre (Bermudagrass)	
	WOODY BRUSH AND TREES: 2 qt/acre (Birch) to 5 qt/acre (Poison Ivy or Oak)	
	INJECT ION AND FRILL APPLICATION: 50-100% concentration of product either to continuous frill around the tree or as cuts evenly spaced around the tree below all branches	
	CUT STUMP APPLICATION: 50-100% solution to freshly cut surface immediately after cutting	

Appendix 1: Glyphosate Formulations with Forestry Applications (C&P Press Database)		
Brand Name Company/Composition	**Application Rate (Specified by Label)**	**Inerts (Specified)**
Honcho **MONSANTO** 41% glyphosate (**isopropylamine salt**) 59% inert ingredients 4 lbs a.i./gallon 3 lbs a.e./gallons liquid formulation **Recommends use of nonionic surfactant labeled for herbicide use** ***labeled for aerial application by fixed wing and helicopter***	**ANNUAL WEEDS**: 8 fl oz/acre (Foxtail) to 48 fl oz/acre (Filaree)	**Composition on MSDS:** 41 % glyphosate 8% surfactant **tallow amine exthoxylate (CAS No. 61791-26-2)** 51% water MSDS also states that this product is hazardous according to the OSHA Hazard Communication Standard
	HIGH-VOLUME BROADCAST APPLICATION: 1 to 1 ½ qt/acre **LOW-VOLUME BROADCAST APPLICATION**: 1 to 1 ½ qt/acre	
	PERENNIAL WEEDS: 1 qt/acre (Alfalfa) to 5 qt/acre (Bermudagrass)	
	WEEDS CONTROLLED OR SUPPRESSED: 8 to 64 fl oz/acre	
	WOODY BRUSH AND TREES: 2 qt/acre (Birch) to 5 qt/acre (Poison Ivy or Oak)	
	INJECT ION AND FRILL APPLICATION: 50-100% concentration of product either to continuous frill around the tree or as cuts evenly spaced around the tree below all branches	
	CUT STUMP APPLICATION: 50-100% solution to freshly cut surface	
Mirage **UAP** 41% glyphosate (**isopropylamine salt**) 59% inert ingredients 4 lbs a.i./gallon 3 lbs a.e./gallons liquid formulation **Recommends use of nonionic surfactant labeled for herbicide use** ***labeled for aerial application by fixed wing and helicopter***	**ANNUAL WEEDS**: 8 fl oz/acre (Foxtail) to 48 fl oz/acre (Filaree)	exthoxylated tallowamines CAS No. 61791-83-6 (SARA Title III) MSDS indicates that this inert is a hazardous chemical under OSHA Hazard Communication Standard
	HIGH-VOLUME AND LOW-VOLUEMBROADCAST APPLICATION: 1 to 1 ½ qt/acre	
	PERENNIAL WEEDS: 1 qt/acre (Alfalfa) to 5 qt/acre (Bermudagrass)	
	WEEDS CONTROLLED OR SUPPRESSED: 8 to 64 fl oz/acre	
	WOODY BRUSH AND TREES: 2 qt/acre (Birch) to 5 qt/acre (Poison Ivy or Oak)	
	CUT STUMP APPLICATION: 50-100% solution to freshly cut surface	
	INJECT ION AND FRILL APPLICATION: 50-100% concentration of product either to continuous frill around the tree or as cuts evenly spaced around the tree below all branches	
	CONIFER RELEASE: 1.5 to 2 qt/acre	

Appendix 1: Glyphosate Formulations with Forestry Applications (C&P Press Database)		
Brand Name Company/Composition	**Application Rate (Specified by Label)**	**Inerts (Specified)**
Prosecutor **LESCO** 41% glyphosate (**isopropylamine salt**) 59% inert ingredients 4 lbs a.i./gallon 3 lbs a.e./gallons liquid formulation **Recommends use of nonionic surfactant labeled for herbicide use** ***labeled for aerial application by fixed wing and helicopter***	**ANNUAL WEEDS**: 8 fl oz/acre (Foxtail) to 48 fl oz/acre (Filaree)	**59% inerts including exthoxylated tallowamines** CAS No. 61791-83-6 (SARA Title III) MSDS indicates that this inert is a hazardous chemical under OSHA Hazard Communication Standard
	HIGH-VOLUME AND LOW-VOLUME BROADCAST APPLICATION: 1 to 1 ½ qt/acre	
	PERENNIAL WEEDS: 1 qt/acre (Alfalfa) to 5 qt/acre (Bermudagrass)	
	WEEDS CONTROLLED OR SUPPRESSED: 8 to 64 fl oz/acre	
	WOODY BRUSH AND TREES: 2 qt/acre (Birch) to 5 qt/acre (Poison Ivy or Oak)	
	CONIFER RELEASE: 1.5 to 2 qt/acre	
	INJECT ION AND FRILL APPLICATION: 50-100% concentration of product either to continuous frill around the tree or as cuts evenly spaced around the tree below all branches	
	CUT STUMP APPLICATION: 50-100% solution to freshly cut surface	
Prosecutor Plus Tracker **LESCO** 41% glyphosate (**isopropylamine salt**) 59% inert ingredients 4 lbs a.i./gallon 3 lbs a.e./gallons liquid formulation **Recommends use of nonionic surfactant labeled for herbicide use** ***labeled for aerial application by fixed wing and helicopter***	**ANNUAL WEEDS**: 8 fl oz/acre (Foxtail) to 48 fl oz/acre (Filaree)	**59% inerts including exthoxylated tallowamines** CAS No. 61791-83-6 (SARA Title III) MSDS indicates that this inert is a hazardous chemical under OSHA Hazard Communication Standard
	HIGH-VOLUMEAND LOW-VOLUME BROADCAST APPLICATION: 1 to 1 ½ qt/acre	
	PERENNIAL WEEDS: 1 qt/acre (Alfalfa) to 5 qt/acre (Bermudagrass)	
	WEEDS CONTROLLED OR SUPPRESSED: 8 to 64 fl oz/acre	
	WOODY BRUSH AND TREES: 2 qt/acre (Birch) to 5 qt/acre (Poison Ivy or Oak)	
	CONIFER RELEASE: 1.5 to 2 qt/acre	
	INJECT ION AND FRILL APPLICATION: 50-100% concentration of product either to continuous frill around the tree or as cuts evenly spaced around the tree below all branches	
	CUT STUMP APPLICATION: 50-100% solution to freshly cut surface	

Appendix 1: Glyphosate Formulations with Forestry Applications (C&P Press Database)		
Brand Name Company/Composition	**Application Rate (Specified by Label)**	**Inerts (Specified)**
Rattler **HELENA CHEMICAL CO.** 41% glyphosate (**isopropylamine salt**) 59% inert ingredients 4 lbs a.i./gallon 3 lbs a.e./gallons liquid formulation **Recommends use of nonionic surfactant labeled for herbicide use** ***labeled for aerial application by fixed wing and helicopter***	**ANNUAL WEEDS**: 8 fl oz/acre (Foxtail) to 48 fl oz/acre (Filaree)	not specified
	HIGH-VOLUME AND LOW-VOLUME BROADCAST APPLICATION: 1 to 1 ½ qt/acre	
	PERENNIAL WEEDS: 1 qt/acre (Alfalfa) to 5 qt/acre (Bermudagrass)	
	WEEDS CONTROLLED OR SUPPRESSED: 8 to 64 fl oz/acre	
	WOODY BRUSH AND TREES: 2 qt/acre (Birch) to 5 qt/acre (Poison Ivy or Oak)	
	CONIFER RELEASE: 1.5 to 2 qt/acre	
	INJECT ION AND FRILL APPLICATION: 50-100% concentration of product either to continuous frill around the tree or as cuts evenly spaced around the tree below all branches	
	CUT STUMP APPLICATION: 50-100% solution to freshly cut surface	
Razor **RIVERDALE.** 41% glyphosate (**isopropylamine salt**) 59% inert ingredients 4 lbs a.i./gallon 3 lbs a.e./gallons liquid formulation **Recommends use of nonionic surfactant labeled for herbicide use** ***labeled for aerial application by fixed wing and helicopter***	**ANNUAL WEEDS**: 8 fl oz/acre (Foxtail) to 48 fl oz/acre (Filaree)	**59% inerts including exthoxylated tallowamines** CAS No. 61791-83-6 (SARA Title III) MSDS indicates that this inert is a hazardous chemical under OSHA Hazard Communication Standard
	HIGH-VOLUME AND LOW-VOLUME BROADCAST APPLICATION: 1 to 1 ½ qt/acre	
	PERENNIAL WEEDS: 1 qt/acre (Alfalfa) to 5 qt/acre (Bermudagrass)	
	WEEDS CONTROLLED OR SUPPRESSED: 8 to 64 fl oz/acre	
	WOODY BRUSH AND TREES: 2 qt/acre (Birch) to 5 qt/acre (Poison Ivy or Oak)	
	CHEMICAL MOWING-PERENNIALS: 6 fl oz/acre (Kentucky bluegrass) to 8 fl oz/acre (tall fescue, fine fescue, orchardgrass, or quackgrass covers)	
	CHEMICAL MOWING-ANNUALS: 4 to 5 fl oz/acre	
	CUT STUMP APPLICATION: 50-100% solution to freshly cut surface	
	INJECT ION AND FRILL APPLICATION: 50-100% concentration of product either to continuous frill around the tree or as cuts evenly spaced around the tree below all branches	
	CONIFER RELEASE: 1.5 to 2 qt/acre	

Appendix 1: Glyphosate Formulations with Forestry Applications (C&P Press Database)		
Brand Name Company/Composition	**Application Rate (Specified by Label)**	**Inerts (Specified)**
Razor SPI **RIVERDALE.** 41% glyphosate (**isopropylamine salt**) 59% inert ingredients 4 lbs a.i./gallon 3 lbs a.e./gallons liquid formulation *Contains a temporary blue colorant to assist in accurate and uniform applications.* **Recommends use of nonionic surfactant labeled for herbicide use** ***labeled for aerial application by fixed wing and helicopter***	**ANNUAL WEEDS**: 8 fl oz/acre (Foxtail) to 48 fl oz/acre (Filaree)	**59% inerts including exthoxylated tallowamines** CAS No. 61791-83-6 (SARA Title III) MSDS indicates that this inert is a hazardous chemical under OSHA Hazard Communication Standard
	HIGH-VOLUME AND LOW-VOLUME BROADCAST APPLICATION: 1 to 1 ½ qt/acre	
	PERENNIAL WEEDS: 1 qt/acre (Alfalfa) to 5 qt/acre (Bermudagrass)	
	WEEDS CONTROLLED OR SUPPRESSED: 8 to 64 fl oz/acre	
	CONIFER RELEASE: 1.5 to 2 qt/acre	
	CUT STUMP APPLICATION: 50-100% solution to freshly cut surface	
	INJECT ION AND FRILL APPLICATION: 50-100% concentration of product either to continuous frill around the tree or as cuts evenly spaced around the tree below all branches	
	WOODY BRUSH AND TREES: 2 qt/acre (Birch) to 5 qt/acre (Poison Ivy or Oak)	
	CHEMICAL MOWING-PERENNIALS: 6 fl oz/acre (Kentucky bluegrass) to 8 fl oz/acre (tall fescue, fine fescue, orchardgrass, or quackgrass covers)	
	CHEMICAL MOWING-ANNUALS: 4 to 5 fl oz/acre	

Appendix 1: Glyphosate Formulations with Forestry Applications (C&P Press Database)		
Brand Name Company/Composition	**Application Rate (Specified by Label)**	**Inerts (Specified)**
Rodeo **DOW AGROSCIENCES** 53.8% glyphosate (**isopropylamine salt**) 46.2% inert ingredients 5.44 lbs a.i./gallon 4 lbs a.e./gallons liquid formulation **Requires use of nonionic surfactant labeled for herbicide use** ***labeled for aerial application (NOS). In California, aerial application may be made in aquatic sites and noncrop areas, including aquatic sites present in noncrop areas that are part of the intended treatment.***	**ANNUAL WEED CONTROL:** **BROADCAST APPLICATION**: 1 ½ pints/acre to 3 pints/acre (Italian Ryegrass) **HAND-HELD HIGH-VOLUME APPLICATION**: 3/4 percent solution	not specified
	PERENNIAL WEEDS: 3 pints/acre (Quackgrass) to 7 ½ pints/acre (Bermudagrass)	
	BRUSH OR TREE CONTROL: 3 pints/acre (Birch) to 7 ½ pints/acre (Poison Ivy or Poison Oak)	
	AQUATIC AND OTHER NON-CROP SITES: Maximum application rate is 7 ½ pints/acre in any single broadcast application made over water	
	CUT STUMP APPLICATION: 50-100% solution to freshly cut surface	
	INJECT ION AND FRILL APPLICATION: 50-100% concentration of product either to continuous frill around the tree or as cuts evenly spaced around the tree below all branches	

Appendix 1: Glyphosate Formulations with Forestry Applications (C&P Press Database)		
Brand Name Company/Composition	**Application Rate (Specified by Label)**	**Inerts (Specified)**
Roundup CUSTOM **MONSANTO** 53.8% glyphosate (**isopropylamine salt**) 46.2% inert ingredients 5.4 lbs a.i./gallon 4 lbs a.e./gallons liquid formulation **Requires use of nonionic surfactant labeled for herbicide use** ***labeled for aerial application by fixed wing and helicopter***	**PERENNIAL WEEDS**: 1.5 pints/acre (Paragrass) to 7 ½ pints/acre (Bermudagrass)	water CAS No. 7732-18-5 MSDS indicates no hazardous chemicals under OSHA Hazard Communication Standard
	CUT STUMP APPLICATION: 50-100% solution to freshly cut surface	
	ANNUAL WEEDS: 12 fl oz/acre (Foxtail) to 36 fl oz/acre (Filaree)	
	WOODY BRUSH AND TREE RATES: 3 pints/acre (Birch) to 7 ½ pints/acre (Poison Ivy or Poison Oak)	
Roundup ORIGINAL **MONSANTO** 41% glyphosate (**isopropylamine salt**) 59% inert ingredients 4 lbs a.i./gallon 3 lbs a.e./gallons liquid formulation **Recommends use of nonionic surfactant labeled for herbicide use** ***labeled for aerial application by fixed wing and helicopter***	**ANNUAL WEEDS**: 8 fl oz/acre (Foxtail) to 48 fl oz/acre (Filaree)	**Composition on MSDS:** 41 % glyphosate 8% surfactant **tallow amine exthoxylate (CAS No. 61791-26-2)** 51% water MSDS also states that this product is hazardous according to the OSHA Hazard Communication Standard
	HIGH-VOLUME BROADCAST APPLICATION: 1 to 1 ½ qt/acre **LOW-VOLUME BROADCAST APPLICATION**: 1 to 1 ½ qt/acre	
	PERENNIAL WEEDS: 1 qt/acre (Alfalfa) to 5 qt/acre (Bermudagrass)	
	WOODY BRUSH AND TREES: 2 qt/acre (Birch) to 5 qt/acre (Poison Ivy or Oak)	
	CUT STUMP APPLICATION: 50-100% solution to freshly cut surface	

Appendix 1: Glyphosate Formulations with Forestry Applications (C&P Press Database)		
Brand Name Company/Composition	**Application Rate (Specified by Label)**	**Inerts (Specified)**
Roundup PRO **MONSANTO** 41% glyphosate (**isopropylamine salt**) 59% inert ingredients 4 lbs a.i./gallon 3 lbs a.e./gallons liquid formulation **Label indicates that product is formulated as a water soluble liquid containing surfactant and no additional surfactant is needed** ***labeled for aerial application (NOS)***	**ANNUAL WEEDS**: 1 qt/acre (<6" tall) and 1.5 to 4 qt/acre (>6" tall)	**44.5% water** **14.5% surfactant (NOS)** (SARA Title III)
	HIGH-VOLUME BROADCAST APPLICATION: 1 to 1 ½ qt/acre **LOW-VOLUME BROADCAST APPLICATION**: 1 to 1 ½ qt/acre	
	PERENNIAL WEEDS: 1 qt/acre (Alfalfa) to 5 qt/acre (Bermudagrass)	
	CUT STUMP APPLICATION: 50-100% solution to freshly cut surface	
	WOODY BRUSH AND TREES: 2 qt/acre (Birch) to 5 qt/acre (Poison Ivy or Oak)	
	CHEMICAL MOWING-PERENNIALS: 6 fl oz/acre (Kentucky bluegrass) to 8 fl oz/acre (tall fescue, fine fescue, orchardgrass, or quackgrass covers)	
	CHEMICAL MOWING-ANNUALS: 4 to 5 fl oz/acre	
Roundup PRO Concentrate **MONSANTO** 50.2% glyphosate (**isopropylamine salt**) 49.8% inert ingredients 5 lbs a.i./gallon liquid formulation **Label indicates that product is formulated as a water soluble liquid containing surfactant** ***labeled for aerial application (NOS)***	**ANNUAL WEEDS**: 26 fl oz/acre (<6" tall) and 1.2 to 3.2 qt/acre (>6" tall)	specific identity withheld because it is a trade secret MSDS indicates that the product is hazardous according to the OSHA Hazard Communication Standard
	PERENNIAL WEEDS: 0.8 qt/acre (Alfalfa) to 4 qt/acre (Bermudagrass)	
	CUT STUMP APPLICATION: 50-100% solution to freshly cut surface	
	WOODY BRUSH AND TREES: **BROADCAST APPLICATION**: 1.6 qt/acre (Birch) to 4 qt/acre (Poison Ivy or Oak) **HAND-HELD SPRAY-TO-WET**: 0.8% (Birch) to 1.6% (Poison Ivy or Poison Oak)	
	INJECT ION AND FRILL APPLICATION: 50-100% concentration of product either to continuous frill around the tree or as cuts evenly spaced around the tree below all branches	
	CHEMICAL MOWING-PERENNIALS: 5 fl oz/acre (Kentucky bluegrass) to 6.4 fl oz/acre (tall fescue, fine fescue, orchardgrass, or quackgrass covers)	
	CHEMICAL MOWING-ANNUALS: 3 to 4 fl oz/acre	

Appendix 1: Glyphosate Formulations with Forestry Applications (C&P Press Database)		
Brand Name Company/Composition	**Application Rate (Specified by Label)**	**Inerts (Specified)**
Roundup ProDry **MONSANTO** 71.4% glyphosate (**monoammoniumsalt**) 28.6% inert ingredients 71.4% of glyphosate in the form of its ammonium salt is eequal to 64.9% of the acid glyphosate 1.56 lbs of Roundup ProDry contains 0.75 lbs of glyphosate acid and is equivalent to 1 quart of Roundup Pro Herbicide granular formulation **Label indicates that product is formulated as water soluble granules containing surfactant and no additional surfactant is needed** ***labeled for aerial application (NOS)***	**ANNUAL WEEDS**: 1.2 lbs/acre (<6" tall) and 1.8 to 4.8 lbs/acre (>6" tall)	<0.5% sodium sulphite 28.6% trade secret MSDS indicates that the product is hazardous according to the OSHA Hazard Communication Standard
	PERENNIAL WEEDS: 1.25 lbs/acre (Alfalfa) to 6.25 lbs/acre (Bermudagrass)	
	WOODY BRUSH AND TREES: **BROADCAST APPLICATION**: 2.5 lbs/acre (Birch) to 6.25 lbs/acre (Poison Ivy or Oak) **HAND-HELD SPRAY-TO-WET**: 0.64% (Birch) to 1.3% (Poison Ivy or Poison Oak)	
	CHEMICAL MOWING-PERENNIALS: 3.6 oz/acre (Kentucky bluegrass) to 4.8 oz/acre (tall fescue, fine fescue, orchardgrass, or quackgrass covers)	
	CHEMICAL MOWING-ANNUALS: 2.4 oz/acre	

Appendix 1: Glyphosate Formulations with Forestry Applications (C&P Press Database)		
Brand Name Company/Composition	**Application Rate (Specified by Label)**	**Inerts (Specified)**
Roundup UltraDry **MONSANTO** 71.4% glyphosate (**monoammoniumsalt**) 28.6% inert ingredients 71.4% of glyphosate in the form of its ammonium salt is equal to 64.9% of the acid glyphosate 1.2 lbs of Roundup ProDry contains 0.75 lbs of glyphosate acid and is equivalent to 1 quart of Roundup Pro Herbicide granular formulation **Label indicates that product is formulated as water soluble granules containing surfactant and no additional surfactant is needed** ***labeled for aerial application by fixed wing and helicopter***	**ANNUAL WEEDS**: 1.2 lbs/acre (<6" tall) and 1.8 lbs/acre (>6" tall)	25% surfactant/antifoam 4% trade secret MSDS indicates that both inert ingredients are hazardous according to the OSHA Hazard Communication Standard
	PERENNIAL WEEDS: 1.2 lbs/acre (Alfalfa) to 5.9 lbs/acre (Bermudagrass)	
	WOODY BRUSH AND TREES: **BROADCAST APPLICATION**: 2.4 lbs/acre (Birch) to 5.9 lbs/acre (Poison Ivy or Oak) **HAND-HELD SPRAY-TO-WET**: 0.6% (Birch) to 1.1% (Poison Ivy or Poison Oak)	
Roundup ULTRA MAX **MONSANTO** 50.2% glyphosate (**isopropylamine salt**) 49.8% inert ingredients 5 lbs a.i./gallon liquid formulation **No additional surfactant needed or recommended** ***labeled for aerial application by fixed wing and helicopter***	**ANNUAL WEEDS**: 26 fl oz/acre (<6" tall) and 40 fl oz/acre (>6" tall)	specific identity withheld because it is a trade secret MSDS indicates that the product is hazardous according to the OSHA Hazard Communication Standard
	PERENNIAL WEEDS: 1 qt/acre (Alfalfa) to 4 qt/acre (Bermudagrass)	
	CUT STUMP APPLICATION: 50-100% solution to freshly cut surface	
	WOODY BRUSH AND TREES: **BROADCAST APPLICATION**: 1.75 qt/acre (Birch) to 4 qt/acre (Poison Ivy or Oak) **HAND-HELD SPRAY-TO-WET**: 1% (Birch) to 2% (Poison Ivy or Poison Oak)	
	INJECT ION AND FRILL APPLICATION: 50-100% concentration of product either to continuous frill around the tree or as cuts evenly spaced around the tree below all branches	
	CHEMICAL MOWING-PERENNIALS: 5 fl oz/acre (Kentucky bluegrass) to 6.5 fl oz/acre (tall fescue, fine fescue, orchardgrass, or quackgrass covers)	

Appendix 2: Forest Service Use of Glyphosate in 2001 (sorted by region and use) (USDA/FS 2002).

Region	Forest	Use Classification	Acres	Pounds	lbs/acre
1	10	Agricultural Weed Control	0.25	0.3	1.20
1	11	Noxious Weed Control	6.5	6.5	1.00
1	14	Noxious Weed Control	2	5.4	2.70
1	16	Noxious Weed Control	32.5	43.9	1.35
1	17	Noxious Weed Control	3	1.211	0.40
1	18	Noxious Weed Control	25	9.5	0.38
1	2	Noxious Weed Control	10	7	0.70
1	4	Noxious Weed Control	2.25	1.14	0.51
1	4	Nursery Weed Control	34	183	5.38
1	4	ROW Veg Management	1.5	4	2.67
1	4	Site Preparation	16	2.06	0.13
1 Total	Northern		133	264	1.99
2	3	Noxious Weed Control	2	0	0.02
2	4	Noxious Weed Control	12	9	0.75
2	7	Noxious Weed Control	11	37	3.35
2	10	Noxious Weed Control	7	14	2.00
2	13	Noxious Weed Control	163	48	0.29
2	14	Noxious Weed Control	15	30	2.00
2	7	Nursery Weed Control	54	44	0.82
2 Total	Rocky Mountain		264	182	0.69
3	3	Noxious Weed Control	3	3	1.00
3 Total	Southwestern		3	3	1.00
4	1	Noxious Weed Control	15	22	1.47
4	2	Noxious Weed Control	68	16	0.23
4	3	Noxious Weed Control	0	1	3.01
4	7	Noxious Weed Control	30	3	0.10
4	10A	Noxious Weed Control	123	166	1.35
4	13	Noxious Weed Control	0	1	1.67
4	14	Noxious Weed Control	3	6	2.07
4	15A	Noxious Weed Control	80	16	0.20
4	17	Noxious Weed Control	75	15	0.20
4	18	Noxious Weed Control	9	12	1.33
4	19	Noxious Weed Control	2	4	2.00
4 Total	Intermountain		405	261	0.64
5	8	Agricultural Weed Control	172	628	3.64
5	15	Conifer and Hardwood Release	361	1,161	3.22
5	3	Conifer Release	803	2,918	3.63
5	13	Conifer Release	1,400	2,695	1.93
5	16	Conifer Release	3,990	19,999	5.01
5	17	Conifer Release	45	83	1.85
5	1	Facilities Maintenance	5	2	0.40
5	3	Facilities Maintenance	6	11	1.87
5	13	Facilities Maintenance	2	4	2.05
5	15	Facilities Maintenance	10	4	0.44
5	1	Noxious Weed Control	93	29	0.31
5	7	Noxious Weed Control	9	90	9.96

	5	15 Noxious Weed Control	42	34	0.82
	5	16 Noxious Weed Control	0	0	0.32
	5	3 Nursery Weed Control	9	30	3.48
	5	10 Nursery Weed Control	83	192	2.30
	5	13 Recreation Improvement	8	23	2.88
	5	1 Right-of-Way	10	20	2.00
	5	16 Site Preparation	1,346	6,815	5.06
5 Total	Pacific Southwest		8,395	34,740	4.14
	6	16 Conifer Release	14	11	0.80
	6	15 Facilities Maintenance	1	1	1.25
	6	1 Noxious Weed Control	6	6	1.00
	6	2 Noxious Weed Control	3	3	1.00
	6	3 Noxious Weed Control	280	93	0.33
	6	4 Noxious Weed Control	0	0	2.13
	6	5 Noxious Weed Control	18	13	0.69
	6	7 Noxious Weed Control	11	25	2.33
	6	8 Noxious Weed Control	3	3	1.10
	6	10 Noxious Weed Control	1	1	0.83
	6	12 Noxious Weed Control	113	62	0.55
	6	14 Noxious Weed Control	0	2	6.67
	6	16 Noxious Weed Control	241	1,033	4.29
	6	17 Noxious Weed Control	62	121	1.96
	6	18 Noxious Weed Control	20	30	1.49
	6	20 Noxious Weed Control	129	21	0.16
	6	21 Noxious Weed Control	16	1	0.03
	6	10 Nursery Weed Control	67	268	4.00
	6	15 Nursery Weed Control	0	1	3.75
	6	1 Right-of-Way	1	1	1.00
	6	6 Seed Orchard Protection	16	10	0.63
6 Total	Pacific Northwest		1,003	1,706	1.70
	8	10 Aquatic Weed Control	3	2	0.67
	8	13 Aquatic Weed Control	2	3	1.80
	8	9 Conifer and Hardwood Release	288	284	0.99
	8	10 Conifer and Hardwood Release	305	56	0.18
	8	7 Conifer Release	1,089	324	0.30
	8	10 Conifer Release	514	2	0.00
	8	8 Facilities Maintenance	1	1	1.00
	8	4 Noxious Weed Control	93	150	1.61
	8	5 Noxious Weed Control	47	16	0.34
	8	7 Noxious Weed Control	30	292	9.75
	8	8 Noxious Weed Control	1	2	2.00
	8	9 Noxious Weed Control	2	6	2.82
	8	10 Noxious Weed Control	210	1,050	5.00
	8	12 Noxious Weed Control	9	48	5.33
	8	1 Recreation Improvement	35	1	0.03
	8	3 Recreation Improvement	2	2	1.00
	8	7 Recreation Improvement	30	8	0.27
	8	8 Recreation Improvement	3	5	1.80
	8	3 Right-of-Way	1	1	1.00

8	4	Right-of-Way	9	26	2.97
8	7	Right-of-Way	2	2	1.00
8	7	Site preparation	161	296	1.84
8	9	Site Preparation	40	35	0.88
8	10	Site preparation	474	13	0.03
8	12	Site Preparation	30	40	1.33
8	7	Wildlife Habitat Improvement	211	298	1.41
8	10	Wildlife Habitat Improvement	92	406	4.41
8	12	Wildlife Habitat Improvement	205	50	0.24
8 Total	Southern		3,888	3,419	0.88
9	5	Facilities Maintenance	25	25	1.00
9	5	Noxious Weed Control	30	12	0.40
9	15	Noxious Weed Control	4,199	3,149	0.75
9	3	Recreation Improvement	1	0	0.20
9	5	Right-of-Way	474	787	1.66
9	19	Right-of-Way	79	54	0.69
9	19	Site Preparation	122	118	0.97
9 Total	Eastern		4,930	4,146	0.84
Grand Total			19,021	44,721	2.35

Appendix 3a: Summary of standard toxicity values for glyphosate, AMPA, POEA surfactant and various formulations of glyphosate [a]						
Formulation	**Rat Oral LD_{50}**	**Rabbit Dermal LD_{50}**	**4-Hour Rat Inhalation LC_{50}**	**Skin Irritation**	**Eye Irritation**	**Allergic Sensitization**
Glyphosate, AMPA, and POEA						
GLYPHOSATE ACID	>5000 mg/kg	>5000 mg/kg		Mild irritation [b]	Severe [b]	Negative [b]
GLYPHOSATE IPA				Non-irritating [b]	Non-irritating [b]	
AMPA	8300 mg/kg					
POEA SURFACTANT	1200 mg/kg [b]	>1260 mg/kg [b]		Corrosive [b]	Severe [b]	
Formulations						
ACCORD SP	>5000 mg/kg	>5000 mg/kg	>5 mg/L	Non-irritating	Slight	Negative
AQUA NEAT	>5000 mg/kg	>5000 mg/kg	>1.3 mg/L	Non-irritating	Non-irritating	Negative
AQUAMASTER	>5000 mg/kg	>5000 mg/kg	>1.3 mg/L	Non-irritating	Category IV	Negative
CORNERSTONE	>5000 mg/kg	>5000 mg/kg (rat acute LD_{50})	>7.03 mg/L	Category IV	Irritating (Category III)	Negative
CREDIT SYSTEMIC	>5000 mg/kg	>5000 mg/kG	>2.05 mg/L	Slightly irritating (Category IV)	Moderately irritating to unrinsed eyes; mildly irritating to rinsed eyes (Category III)	Negative
CREDIT	>5000 mg/kg	>5000 mg/kg	2.6 mg/L (Category III)	Slight erythema (Category IV)	Slight to moderate irritation (Category II)	Negative
DEBIT TMF	>5000 mg/kg	>5000 mg/kg (rat acute LD_{50})	>2.07 mg/L (slightly toxic)	Non-irritating	Minimally irritating	Negative
EAGRE	>5000 mg/kg	>5000 mg/kg	>1.3 mg/L (slightly toxic)	Slightly irritating	Slightly irritating	Negative
FORESTERS' NON-SELECTIVE HERBICIDE	>5000 mg/kg	>5000 mg/kg	>1.3 mg/L (slightly toxic)	Practically non-irritating	Non-irritating	Negative
GLYFOS	>5000 mg/kg	>5000 mg/kg	>2.6 mg/L (slightly toxic) (Category III)	Slight erythema clearing within 24 hours (Category IV)	Slight to moderate irritation (Category II)	Negative

Appendix 3a: Summary of standard toxicity values for glyphosate, AMPA, POEA surfactant and various formulations of glyphosate [a]						
Formulation	**Rat Oral LD_{50}**	**Rabbit Dermal LD_{50}**	**4-Hour Rat Inhalation LC_{50}**	**Skin Irritation**	**Eye Irritation**	**Allergic Sensitization**
GLYFOS X-TRA	>5000 mg/kg	>2000 mg/kg	>4.86 mg/L	Non-irritating	May cause substantial but temporary eye injury	Negative
GLYFOS PRO	>5000 mg/kg	>2000 mg/kg	4.24 mg/L	Non-irritating	Minimal	Negative
GLYFOS AQUATIC	>5000 mg/kg	>2000 mg/kg	>4.86 mg/L	Very slightly irritating	Slightly irritating	Negative
GLYPHOMAX	>5000 mg/kg	>5000 mg/kg	>5.00 mg/L	Non-irritating	Slightly irritating	Negative
GLYPHOMAX PLUS	>5000 mg/kg	>5000 mg/kg	>5.00 mg/L	Non-irritating	Slightly irritating	Negative
GLYPHOSATE	>5000 mg/kg	>5000 mg/kg	2.6 mg/L (slightly toxic)	Non-irritating	Slight to moderate	Negative
GLYPHOSATE ORIGINAL	5000 mg/kg (slightly toxic)	>5000 mg/kg	3.18 mg/L (slightly toxic)	Slightly irritating	Moderately irritating	Negative
GLYPHOSATE VMF	>5000 mg/kg	>5000 mg/kg	1.3 mg/L (Slightly toxic)	Non-irritating	Non-irritating	Negative
GLYPRO	>5000 mg/kg	>5000 mg/kg	>6.37	Non-irritating	Slight irritation	Negative
GLYPRO PLUS	>5000 mg/kg	>5000 mg/kg	>5.00 mg/L	Non-irritating	Slight irritation	Negative
HONCHO	>5000 mg/kg	>5000 mg/kg (rat LD_{50})	2.6 mg/L (Category IV)	Non-irritating	Moderate irritation (Category II)	Negative
MIRAGE	>5000 mg/kg	>5000 mg/kg	2.6 mg/L	Non-irritating	Slight to moderate irritation (Category II)	Negative
PROSECUTOR PLUS TRACKER	>5000 mg/kg	>5000 mg/kg	>2.05 mg/L	Slightly irritating	Moderately irritating	Negative
PROSECUTOR	>5000 mg/kg	>5000 mg/kg	>2.05 mg/L	Slightly irritating	Moderately irritating	Negative
RATTLER	>5000 mg/kg (mouse LD_{50})	>5000 mg/kg	>3.18 mg/L	Slightly irritating	Non-irritating	NS

Appendix 3a: Summary of standard toxicity values for glyphosate, AMPA, POEA surfactant and various formulations of glyphosate [a]						
Formulation	**Rat Oral LD_{50}**	**Rabbit Dermal LD_{50}**	**4-Hour Rat Inhalation LC_{50}**	**Skin Irritation**	**Eye Irritation**	**Allergic Sensitization**
RAZOR	>5000 mg/kg	>5000 mg/kg	>2.05 mg/L	Slightly irritating	Moderately irritating to unrinsed eyes; mildly irritating to rinsed eyes (Category III)	Negative
RAZOR SPI	>5000 mg/kg	>5000 mg/kg	>2.05 mg/L	Slightly irritating	Moderately irritating to unrinsed eyes; mildly irritating to rinsed eyes (Category III)	Negative
RODEO	>5000 mg/kg	>5000 mg/kg	>6.37 mg/L	Non-irritating	Slight irritation	Negative
ROUNDUP ULTRAMAX	>5000 mg/kg	>5000 mg/kg (rat LD_{50})	>2.01 mg/L (Category IV)	Slight irritation (Category IV)	Moderate irritation (Category III)	Negative
ROUNDUP PRO	5108 mg/kg	>5000 mg/kg (rat LD_{50})	2.9 mg/L	Non-irritating	Slight irritation (Category III)	Negative
ROUNDUP CUSTOM	>5000 mg/kg	>5000 mg/kg	>1.3 mg/L (Category III)	Non-irritating	Category IV	Negative
ROUNDUP ORIGINAL	>5000 mg/kg	>5000 mg/kg (rat LD_{50})	2.6 mg/L	Non-irritating	Moderate irritation (Category II)	Negative
ROUNDUP PRODRY	3794 mg/kg (female rat) (Category III)	>5000 mg/kg (rat LD_{50})	2.6 mg/L	Slight irritation	Slight irritation (Category III)	Negative
ROUNDUP ULTRADRY	5827 mg/kg (slightly toxic) (Category III) (***Female rat LD_{50} = 3700 mg/kg***)	>5000 mg/kg (rat LD_{50})	granular formulation	Slightly irritating (Category IV)	Moderately irritating (Category III)	Negative
ROUNDUP PRO CONCENTRATE	>5000 mg/kg	>5000 mg/kg (rat LD_{50})	>2.01 mg/L (Category IV)	Slight irritation (Category IV)	Moderate irritation (Category III)	Negative

[a] Taken from Material Safety Data Sheets in C&P Press (2002) unless otherwise specified.
[b] Williams et al. 2000

Appendix 3b: Nontarget toxicity values for various formulations of glyphosate [a]						
Formulation	**Bobwhite quail (*Colinus virginianus*)**	**Mallard duck (*Anas platyrhynchos*)**	**Dog**	**Goat**	**Earthworm (*Eisenia foetida*)**	**Honeybee (*Apis mellifera*)**
ACCORD SP	LD_{50}>2000 mg/kg				LC_{50}>1000 mg/kg	
AQUA NEAT				LD_{50} = 5700 mg/kg		
AQUAMASTER	LD_{50}>3851 mg/kg LC_{50}>4640 mg/kg (5 days, dietary) NOEC>1000 mg/kg (17 weeks, diet)	LC_{50}>4640 mg/kg (5 days, dietary) NOEC>1000 mg/kg (16 weeks, diet)			LC_{50}>5000 mg/kg (14 days, dry soil)	LD_{50}>100 µg/bee (48 hours, oral/contact)
CORNERSTONE	NS	NS	NS	NS	NS	NS
CREDIT SYSTEMIC	LC_{50}>6300 mg/kg (8 days)	LC_{50}>6300 mg/kg (8 days)				
CREDIT	LC_{50}>6300 mg/kg (8 days)	LC_{50}>6300 mg/kg (8 days)				
DEBIT TMF				LD_{50} = 5700 mg/kg		
EAGRE				LD_{50} = 5700 mg/kg		
FORESTERS' NON-SELECTIVE HERBICIDE				LD_{50} = 5700 mg/kg		
GLYFOS	LC_{50}>6300 mg/kg (8 days)	LC_{50}>6300 mg/kg (8 days)				
GLYFOS PRO	LD_{50}>2000 mg/kg	LD_{50}>2000 mg/kg				
GLYFOS X-TRA	LD_{50}>2000 mg/kg[b]	LD_{50}>2000 mg/kg[b]				
GLYFOS AQUATIC	NS	NS	NS	NS	NS	NS
GLYPHOMAX PLUS	LD_{50}>2000 mg/kg				LC_{50}>1000 mg/kg	LD_{50}>100 µg/bee (acute contact) LD_{50}>100 µg/bee (acute oral)

Appendix 3b: Nontarget toxicity values for various formulations of glyphosate [a]						
Formulation	**Bobwhite quail (*Colinus virginianus*)**	**Mallard duck (*Anas platyrhynchos*)**	**Dog**	**Goat**	**Earthworm (*Eisenia foetida*)**	**Honeybee (*Apis mellifera*)**
GLYPHOMAX	LD_{50} = 2000 mg/kg				LC_{50} = 1000 mg/kg	LD_{50}>100 µg/bee (acute contact) LD_{50}>100 µg/bee (acute oral)
GLYPHOSATE	LC_{50}>6300 mg/kg (8 days)	LC_{50}>6300 mg/kg (8 days)v				
GLYPHOSATE ORIGINAL			LD_{50}>5.0 mg/kg	LD_{50} = 4660 mg/kg		LD_{50}>100 µg/bee (48-hour oral) LD_{50}>100 µg/bee (48-hour dermal)
GLYPHOSATE VMF				LD_{50} = 5700 mg/kg		
GLYPRO PLUS	LD_{50}>2000 mg/kg				LC_{50}>1000 mg/kg	LD_{50}>100 µg/bee (acute contact) LD_{50}>100 µg/bee (acute oral)
GLYPRO	LD_{50}>2000 mg/kg				LC_{50}>1000 mg/kg	
HONCHO	LC_{50}>5620 mg/kg (5 days, dietary)	LC_{50}>5620 mg/kg (5 days, dietary)			LC_{50}>5000 mg/kg (14 days, dry soil)	LD_{50}>100 µg/bee (48 hours, oral/contact)
MIRAGE	LC_{50}>6300 mg/kg (8 days)	LC_{50}>6300 mg/kg (8 days)				
PROSECUTOR PLUS TRACKER	LC_{50}>6300 mg/kg (8 days)	LC_{50}>6300 mg/kg (8 days)				
PROSECUTOR	LC_{50}>6300 mg/kg (8 days)	LC_{50}>6300 mg/kg (8 days)				
RATTLER	NS	NS	NS	NS	NS	NS
RAZOR	LC_{50}>6300 mg/kg (8 days)	LC_{50}>6300 mg/kg (8 days)				

Appendix 3b: Nontarget toxicity values for various formulations of glyphosate [a]						
Formulation	**Bobwhite quail (*Colinus virginianus*)**	**Mallard duck (*Anas platyrhynchos*)**	**Dog**	**Goat**	**Earthworm (*Eisenia foetida*)**	**Honeybee (*Apis mellifera*)**
RAZOR SPI						
RODEO	LD_{50}>2000 mg/kg				LC_{50}>1000 mg/kg	
ROUNDUP PRO CONCENTRATE	LC_{50}>5620 mg/kg (5 days, dietary)	LC_{50}>5620 mg/kg (5 days, dietary)			LC_{50}>1250 mg/kg (14 days, soil)	LD_{50}>100 µg/bee (48 hours, oral/contact)
ROUNDUP PRODRY	LD_{50} = 1651 mg/kg body weight				LC_{50}>1250 mg/kg (14 days, dry soil)	LD_{50}>100 µg/bee (48 hours, oral/contact)
ROUNDUP ULTRADRY	Not tested		Not tested	Not tested	Not tested	Not tested
ROUNDUP CUSTOM	LD_{50}>3851 mg/kg LC_{50}>4640 mg/kg (5 days, dietary) NOEC>1000 mg/kg (17 weeks, diet)	LC_{50}>4640 mg/kg (5 days, dietary) NOEC>1000 mg/kg (16 weeks, diet)			LC_{50}>5000 mg/kg (14 days, dry soil)	LD_{50}>100 µg/bee (48 hours, oral/contact)
ROUNDUP PRO BIACTIVE					LC_{50}>1250 mg/kg (14 days, soil)	LD_{50}>1000 µg/bee (48-hour oral)
ROUNDUP PRO	LC_{50}>5620 mg/kg (5 days, dietary)	LC_{50}>5620 mg/kg (5 days, dietary)			LC_{50}>1250 mg/kg (14 days, soil)	LD_{50}>100 µg/bee (48 hours, oral/contact)
ROUNDUP ORIGINAL	LC_{50}>5620 mg/kg (5 days, dietary)	LC_{50}>5620 mg/kg (5 days, dietary)			LC_{50}>5000 mg/kg (14 days, dry soil)	LD_{50}>100 µg/bee (48 hours, oral/contact)
ROUNDUP ULTRAMAX	LC_{50}>5620 mg/kg (5 days, dietary)	LC_{50}>5620 mg/kg (5 days, dietary)			LC_{50}>1250 mg/kg (14 days, soil)	LD_{50}>100 µg/bee (48 hours, oral/contact)

[a] Taken from Material Safety Data Sheets in C&P Press (2002) unless otherwise specified.
[b] MSDS specifies glyphosate acid
NS = Not specified

Appendix 3c: Standard aquatic toxicity values for various formulations of glyphosate [a]										
Formulation	**Rainbow trout LC_{50}**	**Bluegill sunfish LC_{50}**	**Fathead minnow LC_{50}**	**Channel catfish LC_{50}**	**Chinook salmon LC_{50}**	**Coho salmon LC_{50}**	**Carp LC_{50}**	**Crustacea LC_{50}/EC_{50}**	***Daphnia* LC_{50}/EC_{50}**	**Algae EC_{50}**
ACCORD SP	60 mg/L (acute)									
AQUA NEAT	>1000 mg/L (96-hr)	>1000 mg/L (96-hr)							930 mg/L (48-hr)	
AQUAMASTER	>1000 mg/L [b] (96-hr)	>1000 mg/L [b] (96-hr)							930 mg/L[b] (48-hr)	72.9 mg/L [b] (72-hr) (*Scenedesmus subspicatus*)
CORNERSTONE	NS	NS							NS	NS
CREDIT SYSTEMIC	22 mg/L (96-hr) (static) 8.2 mg/L (96-hr) (dynamic)	5.8 mg/L (96-hr) (dynamic) 14 mg/L (96-hr) (static)	9.4 mg/L (96-hr)	16 mg/L (96-hr)	20 mg/L (96-hr)	2.1 mg/L (96-hr)		42 mg/L (48-hr)	37 mg/L (48-hr) (aeration) 24 mg/L (48-hr) (without aeration)	2.1 mg/L (72-hr) (*S. Capricornutum)*
CREDIT	22 mg/L (96-hr) (static) 8.2 mg/L (96-hr) (dynamic)	5.8 mg/L (96-hr) (dynamic) 14 mg/L (96-hr) (static)	9.4 mg/L (96-hr)	16 mg/L (96-hr)	20 mg/L (96-hr)	2.1 mg/L (96-hr)		42 mg/L (48-hr)	37 mg/L (48-hr) (aeration) 24 mg/L (48-hr) (without aeration)	2.1 mg/L (72-hr) (*S. Capricornutum)*
DEBIT TMF	>1000 mg/L (96-hr)	>1000 mg/L (96-hr)							930 mg/L (48-hr)	
EAGRE	>1000 mg/L (96-hr)	>1000 mg/L (96-hr)							930 mg/L (48-hr)	
FORESTER'S	>1000 mg/L (96-hr)	>1000 mg/L (96-hr)							930 mg/L (48-hr)	

Appendix 3c: Standard aquatic toxicity values for various formulations of glyphosate [a]										
Formulation	**Rainbow trout LC_{50}**	**Bluegill sunfish LC_{50}**	**Fathead minnow LC_{50}**	**Channel catfish LC_{50}**	**Chinook salmon LC_{50}**	**Coho salmon LC_{50}**	**Carp LC_{50}**	**Crustacea LC_{50}/EC_{50}**	***Daphnia* LC_{50}/EC_{50}**	**Algae EC_{50}**
GLYFOS PRO	95-171 mg/L[e] (96-hr)								87 mg/L (48-hr)	118 mg/L (96-hr) (*Scenedesmus subspicatus*)
GLYFOS X-TRA	18.6 mg/L (96-hr) (static)	11.9 mg/L (96-hr) (static)							21.6 mg/L (48-hr)	17.4 mg/L (72-hr)
GLYFOS AQUATIC	95-171mg/L[d] (96-hr)								87 mg/L[d] (48-hr)	118 mg/L[d] (96-hr) (*Scenedesmus subspicatus*)
GLYFOS	22 mg/L (96-hr) (static) 8.2 mg/L (96-hr) (dynamic)	5.8 mg/L (96-hr) (dynamic) 14 mg/L (96-hr) (static)	9.4 mg/L (96-hr)	16 mg/L (96-hr)	20 mg/L (96-hr)	22 mg/L (96-hr)		42 mg/L (48-hr)	37 mg/L (48-hr) (aeration) 24 mg/L (48-hr) (without aeration)	2.1 mg/L (72-hr) (*S. Capricornutum)*
GLYPHOMAX PLUS	109 mg/L (acute)								105 mg/L (acute immobiliza -tion)	2.50 mg/L[c] (*Scenedesmus subspicatus*) 48.4 mg/L[c] (duckweed)
GLYPHOMAX	109 mg/L (acute)								105 mg/L (acute immobiliza -tion)	2.50 mg/L (*Scenedesmus subspicatus*) 48.4 (duckweed)

Appendix 3c: Standard aquatic toxicity values for various formulations of glyphosate [a]										
Formulation	**Rainbow trout LC_{50}**	**Bluegill sunfish LC_{50}**	**Fathead minnow LC_{50}**	**Channel catfish LC_{50}**	**Chinook salmon LC_{50}**	**Coho salmon LC_{50}**	**Carp LC_{50}**	**Crustacea LC_{50}/EC_{50}**	***Daphnia* LC_{50}/EC_{50}**	**Algae EC_{50}**
GLYPHOSATE	22 mg/L (96-hr) (static) 8.2 mg/L (96-hr) (dynamic)	5.8 mg/L (96-hr) (dynamic) 14 mg/L (96-hr) (static)	9.4 mg/L (96-hr)	16 mg/L (96-hr)	20 mg/L (96-hr)	22 mg/L (96-hr)		42 mg/L (48-hr)	37 mg/L (48-hr) (aeration) 24 mg/L (48-hr) (without aeration)	2.1 mg/L (72-hr) (*S. Capricornutum)*
GLYPHOSATE VMF	>1000 mg/L (96-hr)	>1000 mg/L (96-hr)							930 mg/L (48-hr)	
GLYPHOSATE ORIGINAL	15.26 mg/L (96-hr) (static) 8.2 mg/L (96-hr) (flow-through)	14 mg/L (96-hr) (static) 5.8 mg/L (96-hr) (flow-through)	9.4 mg/L (96-hr)	16 mg/L (96-hr)	20 mg/L (96-hr)	22 mg/L (96-hr)	19.7 ppm (96-hr TL_{50})	42 mg/L (48-hr) (*Gammarus pseudolimnaeus*) >1000 ppm (96-hr) (crawfish)	37 mg/L (48-hr) (aeration) 24 mg/L (48-hr) (without aeration)	
GLYPRO	60 mg/L (acute)									
GLYPRO PLUS	109 mg/L (acute)								105 mg/L (acute immobiliza-tion)	2.50 mg/L[c] (*Scenedesmus subspicatus*) 48.4 mg/L[c] (duckweed)
HONCHO	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

Appendix 3c: Standard aquatic toxicity values for various formulations of glyphosate [a]										
Formulation	**Rainbow trout LC_{50}**	**Bluegill sunfish LC_{50}**	**Fathead minnow LC_{50}**	**Channel catfish LC_{50}**	**Chinook salmon LC_{50}**	**Coho salmon LC_{50}**	**Carp LC_{50}**	**Crustacea LC_{50}/EC_{50}**	***Daphnia* LC_{50}/EC_{50}**	**Algae EC_{50}**
MIRAGE	22 mg/L (96-hr) (static) 8.2 mg/L (96-hr) (dynamic)	14 mg/L (96-hr) (static)	9.4 mg/L (96-hr)	16 mg/L (96-hr)	20 mg/L (96-hr)	22 mg/L (96-hr)		42 mg/L (48-hr)	37 mg/L (48-hr) (aeration) 24 mg/L (48-hr) (without aeration)	2.1 mg/L (72-hr) (*S. Capricornutum)*
PROSECUTOR PLUS TRACKER	22 mg/L (96-hr) (static) 8.2 mg/L (96-hr) (dynamic)								37 mg/L (48-hr) (aeration) 24 mg/L (48-hr) (without aeration)	
PROSECUTOR	22 mg/L (96-hr) (static) 8.2 mg/L (96-hr) (dynamic)								37 mg/L (48-hr) (aeration) 24 mg/L (48-hr) (without aeration)	
RATTLER	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
RAZOR SPI	22 mg/L (96-hr) (static) 8.2 mg/L (96-hr) (dynamic)	5.8 mg/L (96-hr) (dynamic) 14 mg/L (96-hr) (static)	9.4 mg/L (96-hr)	16 mg/L (96-hr)	20 mg/L (96-hr)	2.1 mg/L (96-hr)		42 mg/L (48-hr	37 mg/L (48-hr) (aeration) 24 mg/L (48-hr) (without aeration)	

Appendix 3c: Standard aquatic toxicity values for various formulations of glyphosate [a]										
Formulation	**Rainbow trout LC_{50}**	**Bluegill sunfish LC_{50}**	**Fathead minnow LC_{50}**	**Channel catfish LC_{50}**	**Chinook salmon LC_{50}**	**Coho salmon LC_{50}**	**Carp LC_{50}**	**Crustacea LC_{50}/EC_{50}**	***Daphnia* LC_{50}/EC_{50}**	**Algae EC_{50}**
RAZOR	22 mg/L (96-hr) (static) 8.2 mg/L (96-hr) (dynamic)	5.8 mg/L (96-hr) (dynamic) 14 mg/L (96-hr) (static)	9.4 mg/L (96-hr)	16 mg/L (96-hr)	20 mg/L (96-hr)	2.1 mg/L (96-hr)		42 mg/L (48-hr)	37 mg/L (48-hr) (aeration) 24 mg/L (48-hr) (without aeration)	2.1 mg/L (72-hr) (*S. Capricornutum)*
RODEO	60 mg/L (acute)									
ROUNDUP PRODRY	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
ROUNDUP ULTRADRY	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested
ROUNDUP PRO	5.4 mg/L (96-hr) (static)	7.3 mg/L (96-hr) (static)							11 mg/L (48-hr) (static)	
ROUNDUP ORIGINAL	8.2 mg/L (96-hr) (flow-through)	5.8 mg/L (96-hr) (flow-through)							12.9 mg/L (48-hr) (static)	2.6 mg/L (96-hr) (static) (*S. Capricornutum)*
ROUNDUP PRO CONCENTRATE	5.4 mg/L (96-hr) (static)	7.3 mg/L (96-hr) (static)							11 mg/L (48-hr) (static)	
ROUNDUP CUSTOM	>1000 mg/L (96-hr) (static)	>1000 mg/L (96-hr) (static)							930 mg/L (48-hr) (static)	72.9 mg/L (72-hr) (*Scenedesmus subspicatus*)

Appendix 3c: Standard aquatic toxicity values for various formulations of glyphosate [a]

Formulation	Rainbow trout LC_{50}	Bluegill sunfish LC_{50}	Fathead minnow LC_{50}	Channel catfish LC_{50}	Chinook salmon LC_{50}	Coho salmon LC_{50}	Carp LC_{50}	Crustacea LC_{50}/EC_{50}	*Daphnia* LC_{50}/EC_{50}	Algae EC_{50}
ROUNDUP PRO BIACTIVE	>989 mg/L (96-hr)						>895 mg/L (96-hr)		676 mg/L[c] (48-hr)	150 mg/L (EbC_{50}) (growth total) 393 mg/L (ErC_{50}) (growth rate) (*Selenastrum capricornutum)*
ROUNDUP ULTRAMAX	5.4 mg/L (96-hr) (static)	7.3 mg/L (96-hr) (static)							11 mg/L (48-hr) (static)	72.9 mg/L[b] (72-hr) (*Scenedesmus subspicatus*)

[a] Taken from Material Safety Data Sheets in C&P Press (2002) unless otherwise specified.
[b] Isopropylamine salt of glyphosate (62%)
[c]Growth inhibition
[d] MSDS specifies that value represents the acute toxicity of glyphosate free acid
[e] MSDS specifies that value represents the acute toxicity of the active ingredient glyphosate

Appendix 4. Case reports of poisoning by glyphosate formulations

Number of individuals, formulation, [Location]	Average Dose	Symptoms, Outcome, and post mortem pathology	Reference
50, Roundup [Japan]	181±201 mL	Esophageal injury observed in 68% of patients; gastric injury in 72%; and duodenal injury in 16%. One patient died on the second hospital day due to refractory shock and aspiration pneumonia.	Chang et al. 1999
2, Roundup [New Zealand]	200-250 ml [fatal]	Vomiting and acidosis. Both individuals died. Ulcerated oropharynx, congested lungs and airway mucosa, petechial submucosal hemorrhages and gastric funduc, acute pulmonary edema, and acute tubular necrosis of the lungs in on individual. Edema of the bronchi and lungs in the other individual.	Dickson et al. 1988
2, glyphosate [Spain]	NS [fatal]	Concentrations in blood (1.64-892.27 ppm) and gastric content (0.08-11.06 ppm)	Garcia-Repetto et al. 1998
53, Roundup [Taiwan]	258±347 mL (range 15-2000 mL)	Blood WBC counts significantly higher and hospital stays significantly longer in patients with laryngeal injury ($p<0.005$); laryngeal injury stronly correlated with aspiration pneumonitis ($X^2=4.449$, $p<0.05$)	Hung et al. 1997
1, Roundup [U.S.]	N.S.	A self report of "*nervous system and immune system problems*" that "*no doctor has been able to accurately diagnose and treat...* "	Jensen 1989
1, Roundup [Japan]	N.S.	Foam and fluid in the trachea and bronchi. Death attributed to infalation of vomitus into the lungs	Kageura et al. 1988
N.S., Roundup and others, [France]	N.S.	Estimated lethal dose of about 1 g/kg.	Kammerer 1995
131, GlySH (glyphosate-surfactant herbicide), [Taiwan]	330±42 mL [fatal]	11 fatalities (mortality rate of 8.4%); most common presentations included sore throat, nausea (with or without vomiting) and ferver; most common laboratory abnormalities included leukocytosis (68%), decreased bicarbonate (48.1%); acidosis (35.8%), elevated AST (33.6%), hypoxemia (28.4%), and elevated BUN (17.1%).	Lee et al. 2000
1, Chun-Dou-Dou (41% isopropylamine salt of glyphosate, 15% polyoxy-ethylene-amine) [China]	~150 mL	Cardiogenic shock with accelerated idio-ventricular rhythm	Lin et al. 1999
4, Roundup [New Zealand]	50 -1,000 ml [non-fatal] 200-250 ml [fatal]	Abdominal pain, diarrhea and vomitting. Decreased urinary output. Estimates of non-fatal doses: 85 g for 27 year old male, 18-36 g for 15 year old female, "*up to 1 liter*" for a 38 year old male. About 72-91 g for a 43 year old woman.	Menkes et al. 1991

Appendix 4. Case reports of poisoning by glyphosate formulations

Number of individuals, formulation, [Location]	Average Dose	Symptoms, Outcome, and post mortem pathology	Reference
1, Roundup, [Israel]	NS [non fatal]	Shortness of breath, irritative cough, dizziness, throat discomfort, episodes of hemoptysis, temperature of 38.40 °C (101.12 °F), mild to moderate respiratory distress, diffuse rales and crackles heard over the lungs. 42-year-old, male mechanic.	Pushnoy et al. 1998
56, Roundup [Japan]	104 ml [non-fatal] 206 ml [fatal]	Hypovolemic shock. Sore throat, abdominal pain, and vomiting. Pulmonary edema (3 cases) and severe pneumonia (2 cases). Oliguria, anuria, and hypotension in all fatal cases. Increases serum amylase and WBC count, some with increased bilirubin and LDH activity, probably attributable to hemolysis.	Sawada et al. 1988
93, Roundup [Taiwan]	184±70 mL (range 85-200 mL) [fatal]; however, ingestion of much higher amounts (500 mL) only resulted in mild to moderate signs and symptoms	Mild: mainly GIT symptoms (nausea, vomiting, diarrhea, abdominal pain, mouth and throat pain) that resolved in 24 hours Moderate: GII symptoms lasting longer than 24 hours, GIT hemorrhage, endoscopically verified oesophagitis or gastritis, oral ulceration, hypotension responsive to IV fluids, pulmonary dysfunction not requiring intubation, acid-base disturbance, evidence of transient hepatic or neal damage, or temporary oliguira. Severe: pulmonary dysfunction requiring intubation, renal failure requiring dialysis, hypotension requiring treatment with pressor amines, cardiac arrest, coma, repeated seizures, or death.	Talbot et al. 1991
1, Roundup [New Zealand]	200-250 ml [fatal]	Hypotension, metabolic acidosis, and vomiting, and hyperkalemia. Death due to respiratory and cardiac arrest. Pulmonary edema and acute renal tubular necrosis.	Temple and Smith 1992
92, Roundup [Taiwan]	120 ml (range of 5-500 ml) [non-fatal] 263 ml (range of 150-500 ml) [fatal]	Irritation and pain in the throat and mouth, some with oral mucosal ulceration. Gastritis, esophagitis, and mucosal edema. Vomiting and diarrhea. Abdominal or epigastric pain. Diffuse pulmonary damage, non-cardiogenic pulmonary edema. Intensive therapy failed to reverse hypoxemia in fatal cases. Oliguria or anuria in 10 patients, perhaps related to hypotension. Metabolic acidosis. Mild temperature elevations in 7 patients.	Tominack et al. 1991
74, Glyphosate (NOS) [Taiwan]	NS	Glyphosate was among the 28 substances (1.27%) most frequently involved in pediatric poisoning exposures reported to NPC Taiwan 1985-1993. Details regarding the signs and symptoms of poisoning are not provided.	Yang et al. 1997
83 [France]	NS	34 cases were associated with Roundup. 40 individuals evidenced no signs of toxicity. 3 individuals died. The most frequent clinical signs involved gastrointestinal irritation.	Weppelman 1994

Appendix 5. Effects on mammals of long-term exposure to glyphosate[a]

Species/ Strain/ Sex/No.	Route/ Exposure Level (Estimated Dose) and Duration	Effects	Reference
Rats/ F344/N 10/sex/ dose	3125, 6250, 12500, 25000, 50000 ppm in diet for 13 weeks. (205, 410, 811, 1678, 3393 mg/kg/day for males) (213, 421, 844, 1690, 3393 mg/kg/day for females)	Decrease in body weight in males (20%) and females (5%) at the highest dose level. In males, small increases in relative liver, kidney, and testicle weights and a decrease in relative thymus weight. No significant organ weight changes in females. Hematologic changes (increased hematocrit, RBC) at the three higher dose levels and increased hemoglobin at the two higher dose levels in males. The hematologic effects are unremarkable and attributed to mild dehydration. Treatment related increases in alkaline phosphatase in both sexes at all time points suggestive of mild liver toxicity. In males at the two higher dose levels, a 20% decrease in sperm counts. In females, a longer estrous cycle at the highest dose. Salivary gland lesions in both sexes at all dose levels with increasing incidence and severity with increasing dose. The effect could be blocked by isoproterenal, indicating an adrenergic mechanism.	NCI 1992
Rat/ Sprague Dawley6 0/sex/ group	2000, 8000, or 20,000 ppm in diet for 24 months (89, 362, or 940 mg/kg/day for males) (113, 45, or 1183 mg/kg/day for females)	Significant decrease in body weight gain in high-dose females (day 51-month 20); significant increases in cataracts and lens abnormalities in high-dose males; significant decrease in urinary tract pH in high-dose males; increased relative liver weights; significantly in-creased incidence of inflammation of the gastric mucosa in mid-dose females. This study reports a NOAEL of 8000 ppm based on decreased body weight data. Increased incidence of pancreatic islet cell adenomas (low-dose males) and C-cell adenomas in the thyroid of mid- and high-dose males and females; slight increase in hepatocellular adenomas in males. Due to the high incidence of pancreatic cell adenomas, the EPA recommended that the carcinogenic potential of glyphosate be evaluated by the Peer Review Committee.	Stout and Ruecker 1990
Rat/ Sprague Dawley5 0/sex/ group	0, 30, 100, or 300 ppm in diet for 26 months (3.1, 10.3, or 31.5 mg/kg/day for males) (3.4, 11.3, or 34.0 mg/kg/day for females)	No significant changes in body weight gain, organ weights, organ/body weight ratios, or hematological and clinical chemistry parameters. Increased rate of interstitial cell tumors of the testes in high-dose males. Systemic NOAEL for nonneoplastic effects = 31 mg/kg/day. Authors concluded that HDT not carcinogenic to rats. EPA concluded that since the HTD was not an MTD, study was not a valid carcinogenicity study under EPA guidelines.	Lankas and Hogan 1981; Bio/ dynamics, Inc. 1981a

Appendix 5. Effects on mammals of long-term exposure to glyphosate[a]

Species/ Strain/ Sex/No.	Route/ Exposure Level (Estimated Dose) and Duration	Effects	Reference
Mouse/CD/50/sex/group	1000, 5000, or 30,000 ppm in diet for 24 months (111–250, 519–1264, or 3465–7220 mg/kg/day for males) (129–288, 690–1322, or 4232–9859 mg/kg/day for females)	Lower mean body weights (as much as 11% at week 102) among high-dose males; elevated mean absolute and relative weights of testes in high-dose males. Histopathological changes included hepatic centrilobular hypertrophy and necrosis of hepatocytes in high-dose males and chronic interstitial necrosis and proximal tubule epithelial cell basophilia and hypertrophy of the kidneys in high-dose females. Sporadic occurrence (not dose related) of lymphoreticular tumors in treated females and renal tubular adenomas in males. The NOAEL for non-neoplastic chronic effects from this study is 5000 ppm, which corresponds to a dose of 750 mg/kg/day. The oncogenic response in this study (occurrence of renal adenomas in male mice) is considered equivocal. **NOTE: U.S. EPA 1995 [Federal Register July 7, Vol 60, No. 130 indicates that the exposure duration was 18 months, not 24 (*cf* #5, pg. 35366)].**	U.S. EPA 1986
Dog/ NS/ 6/sex/ group[b]	20, 100, or 500 mg/kg/day in gelatin capsules for 1 year	At 3 months, slight but toxicologically important decrease in serum sodium and potassium concentrations in males at mid- and high-dose levels and in females at high-dose level. Apparent decreases in absolute and relative weights of pituitaries in mid- and high-dose males not correlated with histopathological effects. Systemic NOAEL >500 mg/kg/day.	Reyna, 1985 Monsanto Co. 1985
Mice/ $B6C3F_1$/ 10/sex/ dose	3125, 6250, 12500, 25000, 50000 ppm in diet for 13 weeks. (507, 1065, 2273, 4776, 10780 mg/kg/day for males) (753, 1411, 2707, 5846, 11977 mg/kg/day for females)	Body weight depression at the two highest dose levels for both sexes. Increases in relative heart, kidney, liver, lung, thymus, and testis for male mice. No differences in food consumption between the dosed and control groups. No effects on sperm motility or estrous cycle length. Salivary gland lesions.	NCI 1992

[a] Adapted from U.S. EPA 1992, except for NCI 1992.

[b] Although U.S. EPA 1992 indicates that the strain of dogs is not specified, the title of the study title indicates that Beagle dogs were used.

NS = Not specified; M = male; F = female; NOAEL = no-observed-adverse-effect level; MTD = maximum tolerated dose

Appendix 6. Assays for reproductive/teratogenic effects in mammals after exposure to glyphosate, POEA, or neutralized POEA.

Species/ Strain/Sex/ No	Exposure	Effects	Reference
		TERATOLOGY STUDIES	
Rats/CD/females/ 25/dose group	0, 300, 1000, or 3500 mg/kg/day glyphosate (98.7% pure) by gavage on days 6-19 of gestation	At 3500 mg/kg/day, severe maternal toxicity, including decreased weight gain and mortality in 6/25 animals was accompanied by decreases in fetal weights, viability, and ossification of sternebrae. NOEL = 1000 mg/kg/day for maternal and developmental toxicity	Farmer et al. 2000b
Rats/CD/ females/ 25/dose group	0, 15, 100, or 300 mg/kg/day POEA by gavage on days 6-15 of gestation	No developmental toxicity at any doses. At 100 mg/kg/day, slight maternal toxicity – i.e., decreased food consumption and mild clinical signs. At 300 mg/kg/day, mortality as well as decreases in food consumption and body weight gain. NOEL = 15 mg/kg/day for maternal toxicity	Farmer et al. 2000b
Rats/CD/ females/ 25/dose group	0, 15, 50, or 150 mg/kg/day phosphate ester neutralized POEA by gavage on days 6-15 of gestation	No developmental toxicity. At 150 mg/kg/day, mortality as well as decreases in food consumption and body weight gain. NOEL = 50 mg/kg/day for maternal toxicity Note: Farmer et al. 2000b state that the NOEL for maternal toxicity was 150 mg/kg/day. This is not consistent with the reported data and appears to be a typographical error.	Farmer et al. 2000b
Rats/Wistar/F/24	0, 250, 500 or 1000 mg/kg/day by gavage on Days 7-16 of gestation	No signs of maternal or developmental toxicity.	Moxon 1996a
Rat/CD/F/NS	0, 300, 1000, or 3500 mg/kg/day by gavage	Breathing difficulty, reduced activity, diarrhea, stomach hemorrhages, weight gain deficits, altered physical appearance, and mortality during treatment in high-dose dams; unossified sternebrae in fetuses from high-dose dams. The NOAELs for fetotoxicity and maternal toxicity are each 1000 mg/kg/day and the NOAEL for teratogenicity is 3500 mg/kg/day (HDT).	Rodwell et al. 1980a; Cited as Monsanto Co. 1980 in U.S. EPA 1986
Rabbits/New Zealand White/F/20	0, 100, 175, and 300 mg/kg/day by gavage on Days 8-20 of gestation	Maternal toxicity – observed at 175 and 300 mg/kg/day – diarrhea, reduced fecal output, reduced food intake and body weight. Fetal toxicity – observed at 300 mg/kg/day – reduced body weight and delayed ossification. No effects on survival and no signs of teratogenicity.	Moxon 1996b

Appendix 6. Assays for reproductive/teratogenic effects in mammals after exposure to glyphosate, POEA, or neutralized POEA.

Species/ Strain/Sex/ No	Exposure	Effects	Reference
Rabbits/Dutch Belted/F/16	0, 75, 175, or 350 mg/kg/day by gavage on Days 6-27 of gestation	Maternal toxicity – 175 mg/kg/day – diarrhea. 350 mg/kg/day – diarrhea and nasal discharge. Some animals in both controls and dosed groups died from causes unrelated to glyphosate treatment. No developmental effects.	Rodwell et al. 1980b
		REPRODUCTION STUDIES	
CD Rats/12 M, 24F	0, 3, 10, or 30 mg/kg bw/day in diet for 3 generations	No effects on any reproductive parameters. Increase in unilateral renal tubule dilation at 30 mg/kg/day in F3b pups. Note: This appears to be a synopsis of Schroeder and Hogan (1981), summarized below.	Farmer et al. 2000a
CD Rats/30 per sex per group	0, 2000, 10000, 30000 ppm (97.7%) in the diet.	Decreased body weight in parents and pups and equivocal decrease in average litter size at 30000 ppm. No effects at lower doses. NOAEL for systemic and reproductive effects: 10000 ppm (equivalent to 740 mg/kg/day). LOAEL for reproductive effects: 30000 ppm (equivalent to 2268 mg/kg/day).	Farmer et al. 2000a
Charles River CD Rats/12 M, 24F	0, 3, 10, or 30 mg/kg bw/day in diet for 60 days	An increase in unilateral focal tubular dilation of the kidney in the male F_{3b} pups (7/10 in treated animals compared with 2/10 in concurrent controls) of dams treated with 30 mg/kg/day. No compound-related effects were observed on fetal, pup, and adult survival; mean parental and pup body weight and food consumption; and mating, pregnancy, fertility, and gestation length. The authors of this study noted that the historical control indices of tubular lesions varied markedly in male weanling rat, and on the basis of the data from this 3-generation study concluded that the highest dose tested (30 mg/kg/day) had no adverse reproductive effects. Nonetheless, in view of the observed kidney lesions in the male F_{3b} pups of dams treated with the highest dose, U.S. EPA 1992 concludes that a more appropriate systemic NOAEL for this study is 10 mg/kg/day, and that the LOAEL is 30 mg/kg/day based on renal effects observed in male F_{3b} weanlings.	Schroeder and Hogan 1981
		OTHER	
Rabbits/ New Zealand white/ male/ 4/dose	$1/10^{th}$ and $1/100^{th}$ of the LD_{50} orally in geletin capsul for 6 weeks with an additional 6 week recovery period.	Decreased body weight, libido, ejaculate volume, sperm concentrations, semen initial fructose and semen osmolality. Increases in abnormal and dead sperm.	Yousef et al. 1995

Appendix 7. Studies assessing the mutagenicity of glyphosate

Formulation	Organism	Exposure Level	Nature of Exposure	Effects	Reference
Glyphosate	bovine	17-70 µM	in vitro lymphocyte cultures	statistically significant increase of structural aberrations, sister chromatid exchanges, and G6PD activity	Lioi et al. 1998a
Glyphosate	human	5.0, 8.5, 17.0, or 51.0 µM	in vitro lymphocyte cultures	dose-related incrase in the percent of abberant cells and an increse of SCE/cell	Lioi et al. 1998b
Glyphosate	*Vicia faba*	35, 70, 105, 140, 350, 700, 1050, 1400 µg/g soil[c]	frequency of micronucleated cells	no genotoxicity	De Marco et al. 1992
Glyphosate	Allium	1440, 2880 µg/L	Allium anaphase-telophase assay	no effect	Rank et al. 1993
Roundup	*Salmonella typhimurium*	360, 720, 1081, 1440 µg/plate	plate incorporation assay in the absence or presence of Aroclor induced S9 mix	slight but significant number of revertants at 360 µg/plate for TA98 (without S9) and at 720 µg/plate for TA100 (with S9)	Rank et al. 1993
Roundup	Allium	1440, 2880 µg/L	Allium anaphase-telophase assay	statistically significant increase in chromosome aberrations	Rank et al. 1993
Roundup	Tadpole (*Rana catesbeiana)*	1.69, 6.75, or 27 mg/L	Alkaline SCG assay (24-hour exposure).	No significant increase ($p>0.05$) in DNA damage, compared with control at 1.69 mg/L; significant increases in DNA damage at 6.75 mg/L ($p<0.05$) and 27 mg/L ($p<0.001$), compared with controls	Clements et al. 1997
Roundup	Drosophila larvae	1 ppm	sex-linked recessive lethal (SLRL)	high frequency of lethals in laraval spermatocytes and in spermatogonia	Kale et al. 1995
Pondmaster	Drosophila larvae	0.1 ppm	sex-linked recessive lethal (SLRL)	high frequency of lethals in laraval spermatocytes and in spermatogonia	Kale et al. 1995
Roundup	mouse	133, 200 mg/kg bw	mice bone marrow micronucleus assay	no clastogenicity	Rank et al. 1993

Appendix 7. Studies assessing the mutagenicity of glyphosate

Formulation	Organism	Exposure Level	Nature of Exposure	Effects	Reference
Roundup	*Tilapia rendalli*	50.0, 100.0, or 200.0 mg/kg	erythrocyte micronuclei (MN) assay	statistically significant induction of MN frequencies at all doses	Grisolia 2002
Roundup	mouse	two injections of 0.5 mL within 24-hour interval	erythrocyte micronuclei (MN) assay	no MN induction	Grisolia 2002
Roundup	human	0.25, 2.5, 25 mg/mL	SCE in human lymphocytes *in vitro*	statistically significant increase ($p<0.001$) in SCE at 0.25 and 2.5 mg/mL; no lymphocyte growth at highest dose	Vyse and Vigfusson 1979, Vigfusson and Vyse 1980

[a]This study not considered adequate for assessing endpoint of concern.
[b]Highest nontoxic concentration.
[c]Used as an emulsifiable liquid in Solado trading formulation (SIAPA) containing 21% active ingredient
CHO = Chinese hamster ovary; SCE = sister-chromatid exchange, NOS = not otherwise specified

Appendix 8: Summary of field or field simulation studies on glyphosate formulations

Application	Observations	Reference
Glyphosate (NOS), 0.75 lbs/acre, aerial application. Less than 7 year post cutting clear cut. Comparable are uses as control.	**Vegetation:** Mortality in only about 5% of shrubs (primarily salmonberry and thimpleberry). Defoliation in about 50% of shrubs one year post-spray with increase in herbaceous (grass) cover. **Small Mammals:** No marked changes in diversity and evenness of small-mammal communities over two year post-application observation period. Transient increase in *Microtus oregoni* associated with increase in grasses.	Anthony and Morrison 1985
Roundup at 2.5 to 5 kg a.e./ha, two sites in British Columbia	Either no significant differences in plant community or an increase in diversity and species richness after 10 to 12 years.	Baoteng et al. 2000
Roundup, 1 ml applied in drilled holes around root collar of treated pine trees. Untreated trees served as controls.	Increased attack success as well as egg and larval development of mountain pine beetle (MPB). Corresponding increases observed in MPB predators and parasites.	Bergvinson and Borden 1991
Roundup, applied in drilled holes around root collar at doses ranging from about 0.006 to 0.6 g/tree.	Increased predation by woodpeckers on mountain pine beetles (MPB) over a 1 year observation period.	Bergvinson and Borden 1992
Roundup, 1.7 kg a.e./ha, in summer of 1985 using a spray system mounted on a crawler-tractor. Site Description: Central Georgia, herbaceous and woody species. 0.6-0.8 ha. Woody plants removed prior to treatment. Loblolly pine seedlings planted in 1982.	Observations made in 1992-1993. No significant differences in species richness for any plant groups [Arborescents, nonarborescents, legume and nonlegume forbs, grasses, and woody vines]. No effect on plant species diversity. The only effect compared to controls was a reduction in nonarborescent species *Vaccinium stamineum* and all *Vaccinium* species combined.	Boyd et al. 1995
Roundup	ED50 of 0.7-93 µg/plant for 14 non-target plant species. Dispersion model indicated that glyphosate could damage non-target plant species when aerially applied at concentrations of 6.4 g/L.	Breeze et al. 1992
Roundup	Applications of 3 kg a.i./ha to ponderosa pine plantations over a period of 7 to 13 years. No substantial effect on soil microorganisms based on basal respiration, metabolic quotient, total bacteria, or mineralizable nitrogen.	Busse et al., 2001

Appendix 8: Summary of field or field simulation studies on glyphosate formulations

Application	Observations	Reference
Herbicidal glyphosate spray formulated as the isopropylamine salt applied at the rate of 1.4 kg a.i./ha by tractor mounted sprayer to silty clay loam soil from 1980 to 1983.	No pesticide residues detected in the soil 17 months after the last experimental treatment; no deleterious effects on crop productivity; and no differences noted in microbial processes in soils sampled in April 1992	Bromilow et al. 1996
Glyphosate (NOS)	In laboratory toxicity tests using adult carabids, no signs of toxicity at exposures equivalent to an application rate of 1.57 kg/ha. No repellant effects under laboratory conditions. In field studies, no toxic or repellent effects. Decreased numbers of carabids in field plots were secondary to effects on vegetation.	Brust 1990
Glyphosate (NOS), 3.4 kg a.i/ha.	Effects on soil invertebrates were secondary to effects on alfalfa density.	Byers and Bierlein 1984
Roundup, 2 lbs/acre by tractor mounted pump and hand-held sprayer in pine release.	Significant increase (38%) in mortality of pine seedlings after 1 year. Increased mortality also apparent after 5 years. There was, however, an increase in the number of free-to-grow survivors after 5 years.	Cain 1991
Roundup, 1.4 kg a.i./ha by hand held controlled drop band applicators in a six year old spruce plantation (North Wales)	An initial decrease in Calluna and increased amount of bare ground. After 2 years, no difference in the abundance of *Vaccinium* and *Empetrum* species. Black grouse evidenced a preference for treated areas, probably because of increased accessibility or fruiting quality.	Cayford 1988
Roundup, 0.54-3.23 kg a.i./ha	At 0.54 kg/ha, a decrease in soil fungi and bacterial populations after 2 months. No effect after 6 months. At 3.23 kg/ha, no effect on soil fungi and bacteria after 10-14 months.	Chakravarty and Chatarpaul 1990
Glyphosate applied at 2.2.kg a.i./ha via spray application to 0.75x40 m strips of crested wheatgrass (height: 20-30 cm) in June 1989 and same application repeated in May 1991(height of wheatgrass 10-15 cm) in Swift Current Saskatchewan.	Glyphosate residues in treated foliage decreased to <50 mg/kg (international MRL for fodder of grasses) within 2 weeks of application. The major route of dissipation appeared to be washoff by rainfall. AMPA residues were generally about one order of magnitude less than the corresponding glyphosate residues.	Cessna and Waddington 1995

Appendix 8: Summary of field or field simulation studies on glyphosate formulations

Application	Observations	Reference
Roundup, 2.25 kg/ha applied aerially to field to suppress angiosperms competing with conifer regeneration.	Herbicide treatment had no effect on captures of most small mammal species over a one year observation period [Masked shrew, deer mouse, pygmy shrew, short-tailed shrew, southern bog lemming, or meadow jumping mouse]. Southern Red-backed voles were more numerous in control than in treated sites. This effect was attributed to defoliation of overhead cover.	D'Anieri et al. 1987
Roundup, 6 L/ha (about 2.1 kg/ha)	Assays for the degradation of leaf litter by isopods. There was an increased decomposition of birch and a decreased decomposition of black cherry. Possible signs of toxicity but not statistically significant.	Eijsackers 1992
Roundup	Inhibition of growth in three species of ectomycorrhizal fungi in laboratory cultures at concentrations of over 10 mg/L.	Estok et al. 1989
Roundup applied in September 1984 at a rate of 2.0 kg a.e./ha via helicopter equipped with boom to 45 ha of coastal British Columbia watershed.	Maximum glyphosate residues in two intentionally oversprayed tributaries were: **stream water**: 162 µg/L; **sediments**: 6.80 µg/g dry mass **suspended sediments**: <0.03 µg/L these levels dissipated to <1 µg/L within 96 hours Residue levels of glyphosate in buffered streams were very low (2.4-3.2 µg/L). In the off-target assessment, <0.1% of applied glyphosate was detected at 8 m from the spray boundary.	Feng et al. 1990
Glyphosate applied aerially at rate of 1.3 kg/ha in 92 L/ha water to 40- to 60-year-old hardwood stands in Oregon during the slate summer	No direct effect on the six sampled species of amphibians	Cole et al. 1997
Glyphosate (NOS), 2.2-3 kg/ha aerial over pine forest.	Glyphosate applications had a greater impact on stream water quality than clearcutting. Effects were evident over a 5-year period. Changes in water quality would not impact the suitability of the water for human consumption.	Feller 1989
Glyphosate (NOS) applied to litter.	Concentrations of 5,000 to 10,000 ppm in litter caused a significant decrease in decomposition.	Fletcher and Freedman 1986
Glyphosate, 2 lb/acre, broadcast ground application		Haywood 1994

Appendix 8: Summary of field or field simulation studies on glyphosate formulations

Application	Observations	Reference
Glyphosate (NOS), 1 kg/ha in clearcut area.	Substantial decrease utilization by mountain hare one year after spraying. A lesser decrease, not statistically significant, after 2 years.	Hjeljord et al. 1988
Roundup, 4 L/ha (1.4 kg/ha), pre-harvest treatment of pasture.	No significant effects on the consumption of treated hay by sheep.	Jones and Forbes 1984
Rodeo repeated applications via hand sprayer to control smooth cordgrass in July 1997 and July 1998. Application rates on mudflat plots during 1997 ranged from 59.5 to 67.4 L/ha, while rates during 1998 ranged from 31.5 to 34.3 L/ha. Application rates for *Spartina* plots ranged from 34.1 to 39.3 L/ha in 1997 and from 39.5 to 43.0 L/ha in 1998	Glyphosate concentrations in sediment from mudflat plots decreased 88-96% by day 1 after treatment in 1997 to 1 year after the second Rodeo application. Glyphosate concentrations in *Spartina* plots increased 231-591% from 1997 to 1999 because *Spartina* rhizomes did not readily metabolize or exude the compound. Comparison between the results of the study and toxicity values for marine biota suggests that under worst-case conditions, detrimental effects to aquatic biota are highly unlikely to result from repeated application of Rodeo to control *Spartina*	Kilbride and Paveglio 2001
Roundup, 2.52 kg/ha on pasture	Cattle preferred grazing on treated pasture over first 5-7 days post-treatment. There was an aversion to the treated area 15-21 days post treatment. Reasons for the preference and aversion were not apparent.	Kisseberth et al. 1986
Roundup, 2.0 kg a.i./ha by Microfil boom w/1.5 mm hayrack nozzles mounted on Bell helicopter. Applied to 11 spray blocks at various times over 4 days to watershed on west coast of Vancouver Island in September 1984	No undue disturbance of stream invertebrates; no increase in drift densities of most aquatic invertebrates; no significant increase in total invertebrate catches.	Kreutzweiser et al. 1989
Rodeo, 5.8 kg a.i./ha with a surfactant and drift retardant over a wetland areas.	An increase or no significant change in the usage of treated wetlands by black terns over a two year observation period. The increased usage was associated with an increase in open water and newly formed mats of dead emergent vegetation.	Linz et al. 1994

Appendix 8: Summary of field or field simulation studies on glyphosate formulations

Application	Observations	Reference
Rodeo, aerially applied to a designated pool of 23 cattail-dominated wetlands in N. Dakota at 50, 70, or 90% coverages in 1990 and 1991 to assess the effects of herbicide treatments on the densities of territorial male Red-wing Blackbirds, Yellow-headed Blackbirds, and Marsh Wrens.	Two years after treatment, the densities of all three species of birds were greater in the control plots than in the treated plots. There was a positive correlation between the percent coverage of live emergent vegetation (mostly cattails) and the numbers of blackbirds and wrens. The results suggest that the numbers of the wetland dwelling birds were limited by the alteration of the cattail density, due to herbicide treatment. The investigators recommend staggering vegetation management treatments on large wetland complexes in order to help diversify the stages of cattail regeneration.	Linz et al. 1996
Rodeo, aerially applied to a designated pool of 17 cattail-dominated wetlands in N. Dakota at 50, 70, or 90% coverages in 1990 and 1991 to assess the effects of herbicide treatments on the densities of American Coots and Soras.	American Coot densities were lower in the control wetlands than in the glyphosate treated wetlands 1 year ($p=0.04$) and 2 years ($p=0.09$) after treatment. There was a positive correlation between the numbers of American Coots and the coverages of water and dead vegetation; however, there was a negative correlation between the numbers of American Coots and live vegetation ($p<0.1$). One year after treatment, Soras were more numerous in the control wetlands ($p=0.08$) than in the treated wetlands, but by 2 years after treatment, the numbers of Soras were similar among treatments. There was a positive correlation between the numbers of Soras and the coverage of live vegetation.	Linz et al. 1997
Rodeo, aerially applied to a designated pool of 24 cattail-dominated wetlands in N. Dakota at 50, 70, or 90% coverages in 1990 and 1991to assess the influence of habitat changes on birds.	Positive correlation between the Black Terns and selected duck species and open water and dead cattails; positive correlation between blackbird numbers and live cattails; positive correlation between the numbers of Black Terns and the numbers of Mallards, Blue-winged Teals, Redheads, and Yellow-headed Blackbird, which suggests some common habitat requirements among these species. Investigators conclude that cattail management programs designed to specifically enhance duck use and decrease Red-winged Blackbird numbers may be benefit Black Terns.	Linz and Blixt 1997
Glyphosate (NOS), 0.75-1.0 kg/ha.	Reduction of plant coverage by brush species by about 60%. Vegetation recovered after 3 years. No effect on plant species diversity. A substantial increase in the number of Norway spruce over 50 cm in height on treated vs untreated plots.	Lund-Hoie and Gronvold 1987

Appendix 8: Summary of field or field simulation studies on glyphosate formulations

Application	Observations	Reference
Glyphosate (NOS), 1 kg/ha by portable mist blower.	Glyphosate used for comparison to imazapyr.	Lund-Hoie and Rognstad 1990
Glyphosate (NOS), 2.3 kg/ha aerial over clearcut.	Heavy defoliation of ferns, birch, raspberry, maple, and other taxa. No difference in abundance of breeding birds in first-post spray season. A decrease in abundance of breeding birds was noted in the second post-spray season. Changes in bird density were associated with changes in vegetation.	MacKinnon and Freedman 1993
Glyphosate (NOS), 2.2 kg/ha. Tractor-mounted team sprayer.	Bioassay of drift using five species of plants in pots. Plants were placed in greenhouse after spraying. Most species evidenced no effect when placed 4 meters downwind and no plants exposed to glyphosate drift evidenced a decrease in yield at the end of the season.	Marrs et al. 1991
Glyhosate applied at simulated drift rates (4, 14, 43, or 143 g/ha) via CO_2 pressurized backpack sprayer to grapevines (*Vitis vinifera*)	Leaf area was reduced only by the highest application rate.	Bhatti et al. 1997
see Powers 1995	No effect on soil arthropods.	Moldenke 1992
Glyphosate (NOS), 2.6 kg/ha.	Initial glyphosate residues of 17 ppm in loam and 3.8 ppm in silt. No effect on soil nitrification or denitrification.	Mueller et al. 1981
Glyphosate (NOS), 0.8-3.0 kg/ha,	Three dose levels assayed at five different application times during the year to 13 species of wood ornamentals. The most sensitive species, damaged at all times and exposure levels, were ajuga, azalea, and variegated liriope. Other species, such as juniper, evidenced only minor and transient damage.	Neal and Skroch 1985
Glyphosate (NOS), 3.3 kg/ha.	Levels in wildlife monitored over a 55 day period. No residues exceeded 2 mg/kg in viscera and 0.5 mg/kg in whole body [shrews, deermice, woodrats, squirrel, voles, and chipmunks]. Body residues were consistently less than residues on vegetation.	Newton et al. 1984
Roundup, 1.7 and 3.3 kg/ha.	Vegetative hardwood and shrub cover over 1.5 meters in height virtually eliminated. Differences in height and cover were apparent at 9 years after application.	Newton et al. 1992a [NJAF 9:126]
Roundup, 1.7 and 3.3 kg/ha.	Conifers dominated over hardwoods. Some injury to conifers at the higher application rate.	Newton et al. 1992b [NJAF, 9:130]

Appendix 8: Summary of field or field simulation studies on glyphosate formulations

Application	Observations	Reference
Glyphosate (NOS), 0.1 g/m^2 in lysimeters (30 cm x 45 cm). [1 kg/ha]	Death of vegetation in lysimeters associated with increased leaching of nitrates and cations from soil. Reestablishment of vegetation over 28 month observation period retarded leaching.	Ogner 1987a,b
Glyphosate (NOS), 0.72 kg/ha, mechanical ground application in forest	Increase in nitrogen levels in streams, consistent with lysimeter studies. Increases were small and did not significantly affect water quality. Similar effects were observed after manual clearing and were judged to be secondary to changes in vegetation.	Ogner 1987c,d
Roundup, 2.88 kg a.e./ha, ground application made by 5 men in dogout canoes using knapsack sprayers in Abiala creek, Nigeria to control hyacinth infestation.	Significant ($p<0.5$) increase in fish population after treatment.	Olaleye and Akinyemiju 1996
Glyphosate (NOS), 2.2 kg/ha applied to 20 randomly selected larkspur plants. Direct application by single cone nozzle on CO_2-pressurized backpack. Each plant was sprayed to wetness and analyzed for alkaloid concentration.	No effect on the absolute amount of toxic alkaloids, compared with controls. Nonetheless, gyphosate treatment did not decrease the larkspur toxicity. Consequently, the risk of poisoning (to cattle) remains until the plants dessicate. The investigators did not examine how the herbicide used in the study affect larkspur palatability.	Ralphs et al. 1998
Roundup, simulated direct spraying of pond at application rate of 0.43 kg/ha or about 0.4 lbs/acre	No effects on plankton productivity, zooplankton populations, or water quality.	Perschbacher et al. 1997
Glyphosate (NOS), 1.2 kg/ha aerial or 1.1 kg/ha manual, 54 ha clearcut and surrounding old growth forest.	No effect on body size and apparent reproductive capacity [assayed as number of placental scars and foeti] of deer mice. Deer mice were more abundant in untreated clearcut probably due to changes in food abundance and quality secondary to changes in vegetation.	Ritchie et al. 1987
Roundup, aerial application at 4.7 L a.i./42.1 L water/ha. [≃1.7 kg/ha?] on 4-5 year old clearcuts in North Maine.	Decrease in available browse plants on 2-year post-treatment clearcuts. Moose used treated areas less than untreated areas.	Santillo 1994
Roundup, aerial application at 4.7 L a.i./42.1 L water/ha. [≃1.7 kg/ha?] on 4-5 year old clearcuts in North Maine.	Total shrub, forb, and grass cover was diminished 1-3 years post treatment. Decrease in species richness of shrubs and forbs on treated clearcuts. Decrease in numbers of invertebrates. Fewer small herbivorous mammals at 1-3 years post-treatment. No effect on carnivorous mammals. Effects attributable to changes in cover, food resources, and microclimate.	Santillo et al. 1989a,b

Appendix 8: Summary of field or field simulation studies on glyphosate formulations

Application	Observations	Reference
Rodeo (4.7 L/ha) and X-77 Speader (1 L/ha) aerially applied to three mudflat sites in Willapa Bay, WA with invasive *Spartina alterniflora* in August 1992.	No direct or indirect short term (28 days post treatment) or long term (119 days post treatment) effects on mudflat biota.	Simenstad et al. 1996
Rodeo, 2.8 L/ha [1.3 kg/ha] in wetlands to control cattails.	Effective control of cattails. Breeding ducks and over-water duck nest densities greater on treated areas because of increase wetland opening. Decrease in aquatic invertebrates in treated areas. Could not determine if this was due to toxicity or habitat changes.	Solberg and Higgins 1993
Glyphosate (NOS), 0.7, 1.4, and 2.8 g/ha, sprayed twice weekly on to culture dishes.	Earthworms evidenced decreased growth over 100 day exposure period with an uneven dose-effect relationship. Mortality observed in some worms after about 80 days. Co-exposure to Captan appeared to reduce the response. Co-exposure to azinphos-methyl and Captan had no more effect than exposure to glyphosate alone.	Springett and Gray 1992
Roundup, aerial application to conifer forest at 1.7 kg a.i./ha.	No significant impact on numbers of bacteria, fungi, and actinomycetes in litter or soil. In laboratory bioassays, no effects are rates up to 100 times field application rates.	Stratton and Stewart 1992.
Roundup, aerial application to 2-year clearcut at 3.0 kg/ha.	Little difference in recruitment of voles between control and treated areas. Decline in deer mice during first post-spray summer and winter only. Population of deer mice increased in subsequent years. Significantly ($p<0.05$) better survival of female voles on treated sites.	Sullivan 1990
Roundup aerially applied at a rate of 3.0 kg/ha of active ingredient on June 18, 1982 or Roundup aerially applied at a rate of 2.2 kg/ha of active ingredient on September 12, 1979. Purpose of study is to investigate the effects of forest herbicide use on demography and diversity of small mammal communities extending to a decade.	No adverse affect on reproduction, survival. or growth of deer mice and Oregon voles in a coastal forest one decade after application. Little change noted in species richness or diversity of small mammal communities.	Sullivan et al. 1997

Appendix 8: Summary of field or field simulation studies on glyphosate formulations

Application	Observations	Reference
Vision, aerial application of 2.14 kg a.i./ha during August 17-28, 1987; one treated site was retreated in 1988 due to poor application. Study area included 8 sites in the sub-boreal spruce forest in British Columbia.	Decrease in species richness of shrubs in year 1 after treatment and remained lower on treated sites throughout the 5-year period; initial decrease in crown volume index of herbaceous vegetation with quick recovery to untreated levels by year 2; no adverse effect on herbaceous species diversity or on small mammal communities.	Sullivan et al. 1998a
Roundup, 1.5 kg/ha a.i. to total orchard floor on two contiguous treatment blocks in British Columbia in July and September 1983, May, July, and September 1984 and 1985.	Vole populations consistently reduced in response to treatment, with average abundance ranging from 2.8 to 28.0 times higher on control plots, compared with treated plots. Voles declined to or near extirpation in all orchards during the winer of 1985-1986. No differences in the abundance of deer mice or northwestern chipmunks after treatment. The average abundance of deer mice ranged from 1.3 to 11.1 times higher and that of chipmunks ranged from 1.8 to 13.3 time higher on treated blocks, compared with control blocks. The large numbers of deer mice and chipmunks on treated blocks were composed mainly of resident animals.	Sullivan et al. 1998b
Roundup, 5 and 8 L/ha randomly applied to tree rows in an umbric Regosol located in northwest Spain in spring of 1996. Residues of glyphosate and AMPA were monitored in the solid and liquid phases for 8 weeks after treatment	Treated soil peaked at 6.9 µg/g glyphosate; soil water samples peaked at 0.74 µg/mL glyphosate. Glyphosate and AMPA concentrations in soil and water samples were almost negligible 1 month after treatment. AMPA peaked at 0.77 µg/mL in soil water samples. Both Glyphosate and AMPA exhibited high vertical mobility in the treated soil, quickly reaching high concentrations in subsurface horizons where degradation is slower.	Veiga et al. 2001
Roundup, applied aerially in August 1991 to six clearcuts harvested between 1983 and 1985. Deciduous tree cover dominated the clearcuts and was approximately 1-2 m high.	Abundance of leaves of deciduous trees was greater on untreated sites (38 vs 11%) 1 year after treatment, but the difference was less (18 vs 12%) 7-10 years after treatment. A similar pattern was observed for deciduous shrubs. The abundance of forbs was similar (13-14%) 1 year after treatment but great on tread sties (29 vs 15%) 7-10 year after treatment. Grasses and ferns were less abundant than other forage classes. Overall, glyphosate application initially decreased the abundance of leaves of deciduous trees and shrubs used as food in summer by white-tailed deer.	Vreeland et al. 1998
Roundup, aerial application at 4 kg/ha on farmland planted for hay in previous 5 years.	No effect on any microbial soil variables tested: biomass, substrate-induced respiration, basal respiration, bacterial:fungal ratio.	Wardle and Parkinson 1991

Appendix 8: Summary of field or field simulation studies on glyphosate formulations

Application	Observations	Reference
Glyphosate (NOS), 5 kg/ha directly incorporated into soil of barley or weed plots.	No direct effect on basal soil respiration, microbial activity, or microbial biomass. Transient decrease in biomass on some plots secondary to toxic effects on weeds.	Wardle and Parkinson 1992
Glyphosate (NOS), 1.1 and 6.7 kg/ha, on cotton leaves.	Bioassay using Western bigeyed bug, *Geocoris pallens*. Females exposed to glyphosate laid slightly more viable eggs than matched controls. A slight dose/response related improvement in survival is also apparent over a 192 day observation period.	Yokoyama and Pritchard 1984

Appendix 9: Toxicity of glyphosate and glyphosate formulations to fish

Formula-tion	Species	Nature of Exposure	Exposure Time	Effects	Comments[a]	Reference
Roundup Pro	rainbow trout	NS	96 hours	LC_{50} = 8.3 ppm		Matura 1996a
Roundup Pro	bluegill sunfish	NS	96 hours	LC_{50} = 6.5 ppm		Matura 1996a
Roundup	rainbow trout	static bioassay	24 hours 96 hours	LC_{50} = 8.3 ppm LC_{50} = 8.3 ppm	(7.0-9.9 ppm) 12°C (54°F) (7.0-9.9 ppm) 12°C (54°F)	Folmar et al. 1979
Roundup	fathead minnow	static bioassay	24 hours 96 hours	LC_{50} = 2.4 ppm LC_{50} = 2.3 ppm	(2.0-2.9 ppm) 22°C (72°F) (1.9-2.8 ppm) 22°C (72°F)	Folmar et al. 1979
Roundup	channel catfish	static bioassay	24 hours 96 hours	LC_{50} = 13 ppm LC_{50} = 13 ppm	(11-16 ppm) 22°C (72°F) (11-16 ppm) 22°C (72°F)	Folmar et al. 1979
Roundup	bluegill	static bioassay	24 hours 96 hours	LC_{50} = 6.4 ppm LC_{50} = 5.0 ppm	(4.8-8.6 ppm) 22°C (72°F) (3.8-6.6 ppm) 22°C (72°F)	Folmar et al. 1979
Roundup	rainbow trout eyed eggs	static bioassay	24 hours 96 hours	LC_{50} = 46 ppm LC_{50} = 16 ppm	(35-61 ppm) (13-19 ppm)	Folmar et al. 1979
Roundup	rainbow trout sac fry	static bioassay	24 hours 96 hours	LC_{50} = 11 ppm LC_{50} = 3.4 ppm	(8.8-13 ppm) (2.2-5.3 ppm)	Folmar et al. 1979
Roundup	rainbow trout swim-up fry	static bioassay	24 hours 96 hours	LC_{50} = 2.4 ppm LC_{50} = 2.4 ppm	(2.0-2.9 ppm) (2.0-2.9 ppm)	Folmar et al. 1979

Appendix 9: Toxicity of glyphosate and glyphosate formulations to fish

Formula-tion	Species	Nature of Exposure	Exposure Time	Effects	Comments[a]	Reference
Roundup	rainbow trout fingerling (1.0 g)	static bioassay	24 hours 96 hours	LC_{50} = 2.2 ppm LC_{50} = 1.3 ppm	(0.93-5.2 ppm) (1.1-1.6 ppm)	Folmar et al. 1979
Roundup	rainbow trout fingerling (2.0 g)	static bioassay	24 hours 96 hours	LC_{50} = 8.3 ppm LC_{50} = 8.3 ppm	(7.0-9.9 ppm) (7.0-9.9 ppm)	Folmar et al. 1979
Roundup	channel catfish eyed eggs	static bioassay	24 hours 96 hours	LC_{50} = 43 ppm LC_{50} = ND	(36-51 ppm) ND	Folmar et al. 1979
Roundup	channel catfish sac fry	static bioassay	24 hours 96 hours	LC_{50} = 4.3 ppm LC_{50} = 4.3 ppm	(3.6-5.1 ppm) (3.6-5.1 ppm)	Folmar et al. 1979
Roundup	channel catfish swim-up fry	static bioassay	24 hours 96 hours	LC_{50} = 3.7 ppm LC_{50} = 3.3 ppm	(3.4-4.1 ppm) (2.8-3.9 ppm)	Folmar et al. 1979
Roundup	channel catfish fingerling (2.2 g)	static bioassay	24 hours 96 hours	LC_{50} = 13 ppm LC_{50} = 13 ppm	(11-16 ppm) (11-16 ppm)	Folmar et al. 1979
Roundup	rainbow trout fingerling (1.4 g)	static bioassay	96 hours	LC_{50} = 54.8 ppm	(50-60 ppm)	Hildebrand et al. 1982
Roundup	rainbow trout fingerling (1.6 g)	static bioassay (field)	96 hours	LC_{50} = 52 ppm	not reported	Hildebrand et al. 1982
Roundup	rainbow trout fingerling (2.1 g)	manual application	1 hour	100% survival; short period (15 minutes) of increased swimming activity during and shortly after application; no acute manifestations of physical discomfort such as coughing or loss of equilibrium	indigenous cutthroat trout and caddis fly larae in pools along the stream course did not show signs of stress during the period of spraying	Hildebrand et al. 1982

Appendix 9: Toxicity of glyphosate and glyphosate formulations to fish

Formula-tion	Species	Nature of Exposure	Exposure Time	Effects	Comments[a]	Reference
Roundup	rainbow trout fingerling (2.3 g)	aerial application	NS	100% survival; no obvious signs of physical stress or discomfort from the time of spraying to conclusion of study (17 days)	no indication of stressful behavior by fish after first rainfall	Hildebrand et al. 1982
Roundup	rainbow trout	static bioassay	96 hours	LC_{50} = 26 ppm	(12-38 ppm) 11°C	Mitchell et al. 1987a
Roundup	chinook salmon	static bioassay	96 hours	LC_{50} = 20 ppm	(17-27 ppm) 11°C	Mitchell et al. 1987a
Roundup	coho salmon	static bioassay	96 hours	LC_{50} = 22 ppm	(12-38 ppm) 11°C	Mitchell et al. 1987a
Roundup	bluegill	not reported	96 hours	TL_{50} = 14 ppm	none	Monsanto Co. 1982b
Roundup	carp	not reported	96 hours	TL_{50} = 3.9 ppm	none	Monsanto Co. 1982b
Roundup	trout	not reported	96 hours	TL_{50} = 11 ppm	none	Monsanto Co. 1982b
Roundup	catfish	not reported	96 hours	LC_{50} = 16 ppm	none	Monsanto Co. 1982b
Roundup	fathead minnow	not reported	96 hours	LC_{50} = 9.4 ppm	none	Monsanto Co. 1982b
Roundup	rainbow trout	not reported	96 hours	TL_{50} = 48 ppm	none	USDA 1981
Roundup	bluegill	not reported	96 hours	TL_{50} = 24 ppm	none	USDA 1981
Roundup	rainbow trout	static bioassay	24 hours 96 hours	LC_{50} = 8.3 mg/L LC_{50} = 8.3 mg/L	none	Folmar et al. 1979
Roundup	channel catfish	static bioassay	24 hours 96 hours	LC_{50} = 13 mg/L LC_{50} = 13 mg/L	none	Folmar et al. 1979
Roundup	bluegill	static bioassay	24 hours 96 hours	LC_{50} = 6.4 mg/L LC_{50} = 5.0 mg/L	none	Folmar et al. 1979
Roundup	bleak	static bioassay	96 hours	LC_{50} = 16 ppm	(15-18 ppm)	Linden et al. 1979
Roundup	harpacticoid	static bioassay	96 hours	LC_{50} = 22 ppm	(17-29 ppm)	Linden et al. 1979

Appendix 9: Toxicity of glyphosate and glyphosate formulations to fish

Formula-tion	Species	Nature of Exposure	Exposure Time	Effects	Comments[a]	Reference
Roundup	coho salmon smolts	sublethal exposure	10 days	no affect on seawater adaptation: plasma sodium values not significantly different from control	there was no effect on growth and several sublethal parameters at exposure concentrations up to 2.78 ppm	Mitchell et al. 1987b
Roundup	carp (*Cyprinus caripio*)	ermersion in 205 mg/L glyphosate f or 410 mg/L glyphosate rs	1 hour or 0.5 hours	significant mortality (p=0.01); treated caused the appearanc eof myelin-like structures in carp hepatocytes, swelling of mitochondria,a nd disappearance of internal membrane of mitochondria at both exposure concentrations	none	Szarek et al. 2000
Roundup	grass carp	intermittent dosing	24 hours 48 hours 96 hours	LC_{50} = 26 ppm LC_{50} = 24 ppm LC_{50} = 15 ppm	(22-30 ppm) 18-21°C; pH 8.1; hardness 270 mg/L (21-28 ppm) 18-21°C; pH 8.1; hardness 270 mg/L (13-18 ppm) 18-21°C; pH 8.1; hardness 270 mg/L	Tooby et al. 1980
Roundup	sockeye (fingerling)	static bioassay	96 hours	LC_{50} = 26.7 ppm	4.2°C; pH 7.95; average weight 3.8 g	Servizi et al. 1987
Roundup	sockeye (fingerling)	static bioassay	96 hours	LC_{50} = 27.7 ppm	4.2°C; pH 8.0; average weight 3.7 g	Servizi et al. 1987
Roundup	sockeye (fry)	static bioassay	96 hours	LC_{50} = 28.8 ppm	4.5°C; pH 7.7; average weight 0.25 g	Servizi et al. 1987
Roundup	rainbow trout (fry)	static bioassay	96 hours	LC_{50} = 28.0 ppm	15°C; pH <6.3; average weight 0.33 g	Servizi et al. 1987
Roundup	rainbow trout (fry)	static bioassay	96 hours	LC_{50} = 25.5 ppm	14.5°C; pH <6.3; average weight 0.60 g	Servizi et al. 1987

Appendix 9: Toxicity of glyphosate and glyphosate formulations to fish

Formula-tion	Species	Nature of Exposure	Exposure Time	Effects	Comments[a]	Reference
Roundup	coho salmon (fry)	static bioassay	96 hours	LC_{50} = 42.0 ppm	15°C; pH <6.3; average weight 0.30 g	Servizi et al. 1987
Roundup	coho salmon (juvenile)	static bioassay	96 hours	LC_{50} = 31 ppm	14°C; intermediate pH	Wan et al. 1991
Roundup	pink salmon (juvenile)	static bioassay	96 hours	LC_{50} = 10 ppm	14°C; intermediate pH	Wan et al. 1991
Roundup	rainbow trout (juvenile)	static bioassay	96 hours	LC_{50} = 31 ppm	14°C; intermediate pH	Wan et al. 1991
Roundup	Channel catfish	static bioassay	48 hours 96 hours	LC_{50} = 16.2 ppm LC_{50} = 14.5 ppm		Abdelghani et al. 1997
Roundup	Bluegill sunfish	static bioassay	48 hours 96 hours	LC_{50} = 13.2 ppm LC_{50} = 13.0 ppm		Abdelghani et al. 1997
Rodeo	carp	not reported	96 hours	TL_{50} >10,000	none	Monsanto Co. 1982d
Rodeo	trout	not reported	96 hours	TL_{50} >1000	none	Monsanto Co. 1982d
Rodeo	bluegill	not reported	96 hours	TL_{50} >1000	none	Monsanto Co. 1982d
Rodeo	plains minnow	renewal	96 hours	NOAEC = 1000 mg/L	none	Beyers 1995
Rodeo	fathead minnow	renewal	96 hours	NOAEC = 1000 mg/L	none	Beyers 1995
Rodeo	rainbow trout (0.52 g)	static bioassay	96 hours	LC_{50} = 1100	(850-1300 ppm) 11°C; pH 6.0; hardness 5.0 mg/L	Mitchell et al. 1987a
Rodeo/X-77[b])	rainbow trout (0.52 g)	static bioassay	96 hours	LC_{50} = 680 ppm	(600-820 ppm) 11°C; pH 6.0; hardness 5.0 mg/L	Mitchell et al. 1987a
Rodeo/X-77[b])	rainbow trout (0.21 g)	static bioassay	96 hours	LC_{50} = 1070 ppm	(600-1920 ppm) 11°C; pH 7.8; hardness 75 mg/L	Mitchell et al. 1987a
Rodeo/X-77[b])	chinook salmon (4.2 g)	static bioassay	96 hours	LC_{50} = 750 ppm	(600-1100 ppm) 11°C; pH 5.8; hardness 5.0 mg/L	Mitchell et al. 1987a

Appendix 9: Toxicity of glyphosate and glyphosate formulations to fish

Formula-tion	Species	Nature of Exposure	Exposure Time	Effects	Comments[a]	Reference
Rodeo/X-77[b])	chinook salmon (5.9 g)	static bioassay	96 hours	LC_{50} = 1440 ppm	(1070-1920 ppm) 11°C; pH 7.4; hardness 77 mg/L	Mitchell et al. 1987a
Rodeo/X-77[b])	coho salmon (17.9 g)	static bioassay	96 hours	LC_{50} = 1000 ppm	(600-1900 ppm) 11°C; pH 5.8; hardness 5.0 mg/L	Mitchell et al. 1987a
Rodeo/X-77[b])	coho salmon (11.8 g)	static bioassay	96 hours	LC_{50} = 600 ppm	(340-1100 ppm) 11°C; pH 6.2; hardness 4.5 mg/L	Mitchell et al. 1987a
Glyphosate (IPA salt in Rodeo)	rainbow trout (0.52 g)	static bioassay	96 hours	LC_{50} = 580	(460-730 ppm) 11°C; pH 6.0; hardness 5.0 mg/L	Mitchell et al. 1987a
Glyphosate (IPA salt in Roundup)	rainbow trout (0.37 g)	static bioassay	96 hours	LC_{50} = 12 ppm	(5.7-18 ppm) 11°C; pH 6.1; hardness 4.5 mg/L	Mitchell et al. 1987a
Glyphosate (IPA salt in Roundup)	rainbow trout (0.37 g)	static bioassay	96 hours	LC_{50} = 11 ppm	(5.7-18 ppm) 11°C; pH 7.6; hardness 85 mg/L	Mitchell et al. 1987a
Glyphosate (IPA salt in Roundup)	rainbow trout (0.37 g)	static bioassay	96 hours	LC_{50} = 7.4 ppm	(5.7-10 ppm) 11°C; pH 7.7; hardness 81 mg/L	Mitchell et al. 1987a
Glyphosate (IPA salt in Roundup)	chinook salmon (4.6 g)	static bioassay	96 hours	LC_{50} = 9.6 ppm	(7.9-13 ppm) 11°C; pH 6.1; hardness 4.5 mg/L	Mitchell et al. 1987a
Glyphosate (IPA salt in Roundup)	coho salmon (11.8 g)	static bioassay	96 hours	LC_{50} = 11 ppm	(5.7-18 ppm) 11°C; pH 6.2; hardness 4.5 mg/L	Mitchell et al. 1987a
Glyphosate (IPA salt in Rodeo/X-77[b])	rainbow trout (0.52 g)	static bioassay	96 hours	LC_{50} = 130 ppm	(120-160 ppm) 11°C; pH 6.0; hardness 5.0 mg/L	Mitchell et al. 1987a
Glyphosate (IPA salt in Rodeo/X-77[b])	rainbow trout (0.21 g)	static bioassay	96 hours	LC_{50} = 210 ppm	(120-380 ppm) 11°C; pH 7.8; hardness 75 mg/L	Mitchell et al. 1987a
Glyphosate (IPA salt in Rodeo/X-77[b])	chinook salmon (4.2 g)	static bioassay	96 hours	LC_{50} = 140 ppm	(120-220 ppm) 11°C; pH 5.8; hardness 5.0 mg/L	Mitchell et al. 1987a
Glyphosate (IPA salt in Rodeo/X-77[b])	chinook salmon (5.9 g)	static bioassay	96 hours	LC_{50} = 290 ppm	(210-380 ppm) 11°C; pH 7.4; hardness 77 mg/L	Mitchell et al. 1987a

Appendix 9: Toxicity of glyphosate and glyphosate formulations to fish

Formula-tion	Species	Nature of Exposure	Exposure Time	Effects	Comments[a]	Reference
Glyphosate (IPA salt in Rodeo/X-77[b])	coho salmon (17.9 g)	static bioassay	96 hours	LC_{50} = 200 ppm	(120-370 ppm) 11°C; pH 5.8; hardness 5.0 mg/L	Mitchell et al. 1987a
Glyphosate (IPA salt in Rodeo/X-77[b])	coho salmon (11.8 g)	static bioassay	96 hours	LC_{50} = 120 ppm	(68-220 ppm) 11°C; pH 6.2; hardness 4.5 mg/L	Mitchell et al. 1987a
Glyphosate	sockeye (fingerling)	static bioassay	96 hours	LC_{50} = 8.1 ppm	4.2°C; pH 7.95; average weight 3.8 g	Servizi et al. 1987
Glyphosate	sockeye (fingerling)	static bioassay	96 hours	LC_{50} = 8.4 ppm	4.2°C; pH 8.0; average weight 3.7 g	Servizi et al. 1987
Glyphosate	sockeye (fry)	static bioassay	96 hours	LC_{50} = 8.7 ppm	4.5°C; pH 7.7; average weight 0.25 g	Servizi et al. 1987
Glyphosate	rainbow trout (fry)	static bioassay	96 hours	LC_{50} = 8.5 ppm	15°C; pH <6.3; average weight 0.33 g	Servizi et al. 1987
Glyphosate	rainbow trout (fry)	static bioassay	96 hours	LC_{50} = 7.8 ppm	14.5°C; pH <6.3; average weight 0.60 g	Servizi et al. 1987
Glyphosate	coho salmon (fry)	static bioassay	96 hours	LC_{50} = 12.8 ppm	15°C; pH <6.3; average weight 0.30 g	Servizi et al. 1987
Glyphosate	rainbow trout	static bioassay	96 hours	LC_{50} = 10.42 ppm	(9.37-11.67) 12°C; pH 6.01; hardness 9.6 mg/L	Morgan and Kiceniuk 1992
Glyphosate	rainbow trout	static bioassay	24 hours 96 hours	LC_{50} = 140 ppm LC_{50} = 140 ppm	(120-170 ppm) 12°C (54°F) (120-170 ppm) 12°C (54°F)	Folmar et al. 1979
Glyphosate	fathead minnow	static bioassay	24 hours 96 hours	LC_{50} = 97 ppm LC_{50} = 97 ppm	(79-120 ppm) 22°C (72°F) (79-120 ppm) 22°C (72°F)	Folmar et al. 1979
Glyphosate	channel catfish	static bioassay	24 hours 96 hours	LC_{50} = 130 ppm LC_{50} = 130 ppm	(110-160 ppm) 22°C (72°F) (110-160 ppm) 22°C (72°F)	Folmar et al. 1979
Glyphosate	bluegill	static bioassay	24 hours 96 hours	LC_{50} = 150 ppm LC_{50} = 140 ppm	(120-190 ppm) 22°C (72°F) (120-190 ppm) 22°C (72°F)	Folmar et al. 1979
Glyphosate	rainbow trout fry	not reported	96 hours	LC_{50} = 50 ppm	3 lbs a.e./gallon	Folmar 1976

Appendix 9: Toxicity of glyphosate and glyphosate formulations to fish

Formula-tion	Species	Nature of Exposure	Exposure Time	Effects	Comments[a]	Reference
Glyphosate	bleak	not reported	96 hours	LC_{50} = 16 ppm	(15-18 ppm) 10°C (50°F)	Linden et al. 1979
Glyphosate (95% pure)	flagfish	pulse exposure	96 hours	LC_{20} = 29.6 ppm	fed 8-day-old flagfish	Holdway and Dixon 1988
Glyphosate, technical	rainbow trout	not reported	96 hours	TL_{50} = 38 ppm	none	USDA 1981
Glyphosate, technical	bluegill	not reported	96 hours	TL_{50} = 78 ppm	none	USDA 1981
Glyphosate, technical	bluegill	dynamic test	96 hours	TL_{50} = 24 ppm	none	USDA 1981
Glyphosate, technical	bluegill	not reported	96 hours	LC_{50} = 120 ppm	none	Monsanto Co. 1982a
Glyphosate, technical	trout	not reported	96 hours	LC_{50} = 86 ppm	none	Monsanto Co. 1982a
Glyphosate, technical (62% pure)	carp	semi-static	48 hours	LC_{50} = 645 ppm	(400, 500, 600, 700, or 800 mg/L) 20.0±1.0°C	Neskovic et al. 1996b
Glyphosate, technical (62% pure)	carp	semi-static	96 hours	LC_{50} = 620 ppm	(400, 500, 600, 700, or 800 mg/L) 20.0±1.0°C	Neskovic et al. 1996b
Glyphosate, technical	carp	not reported	96 hours	LC_{50} = 115 ppm	none	Monsanto Co. 1982a
Glyphosate, technical	harlequin fish	not reported	96 hours	LC_{50} = 168 ppm	none	Monsanto Co. 1982a
Glyphosate, technical	carp	static bioassay	48 hours	TL_{50} =119 ppm TL_{1} =146 ppm TL_{99} =96.7 ppm	none	USDA 1981
Glyphosate, technical	carp	static bioassay	96 hours	TL_{50} =115 ppm TL_{1} =125 ppm TL_{99} =105 ppm	none	USDA 1981
Glyphosate, technical	rainbow trout	static bioassay	96 hours	LC_{50} = 25,605 mg/L NOEC = 8,000 mg/L	36% active ingredient	Anton et al. 1994
Glyphosate, technical	rainbow trout	static bioassay	96 hours	LC_{50} = 25,657 mg/L NOEC = NR	38% active ingredient	Anton et al. 1994

Appendix 9: Toxicity of glyphosate and glyphosate formulations to fish

Formula-tion	Species	Nature of Exposure	Exposure Time	Effects	Comments[a]	Reference
Glyphosate, technical	rainbow trout	static bioassay	96 hours	LC_{50} = 7,620 mg/L NOEC = 6,250 mg/L	54.9% active ingredient	Anton et al. 1994
Glyphosate, technical	goldfish	static bioassay	96 hours	LC_{50} = 7,816 mg/L NOEC = 1,500 mg/L	54.9% active ingredient	Anton et al. 1994
Vision-10% surfactant	coho salmon	closed system respirometer	4 hours	hematocrit significantly increased over controls at lowest(3.75 and 60 ppm) concentrations ($p<0.05$) but expected to decrease as a result of stress; no significant increases in plasma lactate or plasma glucose	data suggest that a staress threshold was not reached for Vision-10% surfactant at concentrations up to 80% of the 96-hour LC_{50}	Janz et al. 1991
Vision	rainbow trout	sublethal exposure	1 month	fish in highest concentration (45.75 µg/L) had significantly higher frequency of wigwags	little overall effect of exposure to Vision on rainbow trout	Morgan and Kiceniuk 1992
Vision	rainbow trout	sublethal exposure	2 months	fish in lowest concentration (4.25 µg/L) performed significantly fewer wigwags	little overall effect of exposure to Vision on rainbow trout; it is not clear what the implications of a change in one agonistic activity in the repetoire of aggressive behavior would be in terms of fish's ability to hold a feeding station	Morgan and Kiceniuk 1992
MONO818	sockeye (fingerling)	static bioassay	96 hours	LC_{50} = 4.0 ppm	4.2°C; pH 7.95; average weight 3.8 g	Servizi et al. 1987
MONO818	sockeye (fingerling)	static bioassay	96 hours	LC_{50} = 4.2 ppm	4.2°C; pH 8.0; average weight 3.7 g	Servizi et al. 1987
MONO818	sockeye (fry)	static bioassay	96 hours	LC_{50} = 4.3 ppm	4.5°C; pH 7.7; average weight 0.25 g	Servizi et al. 1987

Appendix 9: Toxicity of glyphosate and glyphosate formulations to fish

Formula-tion	Species	Nature of Exposure	Exposure Time	Effects	Comments[a]	Reference
MONO818	rainbow trout (fry)	static bioassay	96 hours	LC_{50} = 4.2 ppm	15°C; pH <6.3; average weight 0.33 g	Servizi et al. 1987
MONO818	rainbow trout (fry)	static bioassay	96 hours	LC_{50} = 3.8 ppm	14.5°C; pH <6.3; average weight 0.60 g	Servizi et al. 1987
MONO818	coho salmon (fry)	static bioassay	96 hours	LC_{50} = 6.3 ppm	15°C; pH <6.3; average weight 0.30 g	Servizi et al. 1987
Glyphosate	rainbow trout	static bioassay	96 hours	LC_{50} = 10.42 ppm	(9.37-11.67) 12°C; pH 6.01; hardness 9.6 mg/L	Morgan and Kiceniuk 1992
Rodeo/X-77	rainbow trout	static bioassay	96 hours	LC_{50} = 880 ppm for Rodeo alone LC_{50} = 640 ppm with X-77	10±2°C	Mitchell and Chapman 1985a
Rodeo/X-77	coho salmon	static bioassay	96 hours	LC_{50} = 930 ppm	10±2°C	Mitchell and Chapman 1985b
Rodeo/X-77	chinook salmon	static bioassay	96 hours	LC_{50} = 700 ppm	10±2°C	Mitchell and Chapman 1985c
Rodeo/X-77	chinook salmon	static bioassay	96 hours	LC_{50} = 1440 ppm NOEC = 597 ppm	10±2°C	Mitchell and Chapman 1987a
Rodeo/X-77	rainbow trout	static bioassay	96 hours	LC_{50} = 1070 ppm NOEC = 340 ppm	10±2°C	Mitchell and Chapman 1987b
Rodeo/X-77	chinook salmon smolt	static bioassay	10 days	Concentrations of 0.71 to 60.4 ppm. No effect on adaptation from fresh to salt water	11±2°C fresh water for 10 days followed by transfer to salt water	Mitchell and Chapman 1987a
Surfactant used in Roundup	rainbow trout	static bioassay	24 hours 96 hours	LC_{50} = 2.1 ppm LC_{50} = 2.0 ppm	(1.6-2.7 ppm) 12°C (54°F) (1.5-2.7 ppm) 12°C (54°F)	Folmar et al. 1979
Surfactant used in Roundup	fathead minnow	static bioassay	24 hours 96 hours	LC_{50} = 1.4 ppm LC_{50} = 1.0 ppm	(1.2-1.7 ppm) 22°C (72°F) (1.2-1.7 ppm) 22°C (72°F)	Folmar et al. 1979

Appendix 9: Toxicity of glyphosate and glyphosate formulations to fish

Formula-tion	Species	Nature of Exposure	Exposure Time	Effects	Comments[a]	Reference
Surfactant used in Roundup	channel catfish	static bioassay	24 hours 96 hours	LC_{50} = 18 ppm LC_{50} = 13 ppm	(8.5-38 ppm) 22°C (72°F) (10-17 ppm) 22°C (72°F)	Folmar et al. 1979
Surfactant used in Roundup	bluegill	static bioassay	24 hours 96 hours	LC_{50} = 3.0 ppm LC_{50} = 3.0 ppm	(2.5-3.7 ppm) 22°C (72°F) (2.5-3.7 ppm) 22°C (72°F)	Folmar et al. 1979
Syndets surfactant	channel catfish	static bioassay	48 hours 96 hours	LC_{50} = 3.8 ppm LC_{50} = 3.6 ppm		Abdelghani et al. 1997
Syndets surfactant	bluegill sunfish	static bioassay	48 hours 96 hours	LC_{50} = 3.1 ppm LC_{50} = 3.1 ppm		Abdelghani et al. 1997

[a]Values in parentheses are the 95% confidence limits.
[b]Rodeo /X-77 consists of 312 mL Rodeo mixed with 699 mL water and 4 mL X-77 surfactant.
NOEC = No-observed-effect concentration; NOAEC = No-observed-acute-effect concentration; ND = not determined

Appendix 10: Acute toxicity of glyphosate to aquatic invertebrates

Formulation	Species	Exposure Time	Effects	Comments[a]	Reference
Roundup	Carwfish (*Proambarus*)	48 hours 96 hours	LC_{50} = 96597 ppm LC_{50} = 64002 ppm		Abdelghani et al. 1997
Syndets Surfactant	Carwfish (*Proambarus*)	48 hours 96 hours	LC_{50} = 27.9 ppm LC_{50} = 19.0 ppm		Abdelghani et al. 1997
Glyphosate	midge larvae (*Chironomus plumosus*; insecta)	48 hours	EC_{50} = 55 ppm	(31-97 ppm) 22°C (72°F)	Folmar et al. 1979
Roundup surfactant	midge larvae (*Chironomus plumosus*; insecta)	48 hours	EC_{50} = 13 ppm	(7.1-24 ppm) 22°C (72°F)	Folmar et al. 1979
Roundup	red swamp crawfish (*Procambarus clarkii*)	96	LC_{50} = 47.31 ppm	(41.06-51.69)	Holck and Meek 1987
Roundup	fourth instar *Anopheles quadrimaculatus* larvae	24	LC_{50} = 673.43 ppm	(572.57-770.17)	Holck and Meek 1987
Roundup	fourth instar *Psurophora columbiae* larvae	24	LC_{50} = 940.84 ppm	(823.08-1067.12)	Holck and Meek 1987
Roundup	fourth instar *Culex salinarius* larvae	24	LC_{50} = 1563.69 ppm	(1262.00-2214.54)	Holck and Meek 1987
Roundup	cladoceran (*Daphnia magna*; crustacea)	48 hours	EC_{50} = 3.0 ppm	(2.6-3.4 ppm) 22°C (72°F)	Folmar et al. 1979
Roundup	cladoceran (*Daphnia pulex*; crustacea)	48 hours	EC_{50} = 3.2 ppm	(3.0-3.4 ppm) 22°C (72°F)	Hartman and Martin 1984
Roundup	cladoceran (*Daphnia pulex*; crustacea)	48 hours	EC_{50} = 7.9 ppm	(7.2-8.6 ppm) 22°C (72°F)	Hartman and Martin 1984
Roundup	cladoceran (*Daphnia* sp.; crustacea)	48 hours	LC_{50} = 192 ppm	(181-205 ppm)	USDA 1981
Roundup	cladoceran (*Daphnia* sp.; crustacea)	48 hours	LC_{50} = 5.3 ppm	NS	Monsanto Co. 1982b
Roundup Pro	cladoceran (*Daphnia magna*; crustacea)	48 hours	LC_{50} = 8.9 ppm		Matura 1996a
Rodeo	cladoceran (*Daphnia* sp.; crustacea)	48 hours	LC_{50} = 930 ppm	NS	Monsanto Co. 1982d

Appendix 10: Acute toxicity of glyphosate to aquatic invertebrates

Formulation	Species	Exposure Time	Effects	Comments[a]	Reference
Rodeo	*Daphnia magna*	48 hours	LC_{50} = 218 ppm	(150-287 ppm)	Henry et al. 1994
Rodeo	*Hyalella azteca*	96 hours	LC_{50} = 720 ppm[b]	(399-1076 ppm)	Henry et al. 1994
Rodeo	*Chironomus riparius*	48 hours	LC_{50} = 1216 ppm[b]	(996-1566 ppm)	Henry et al. 1994
Rodeo	*Nephelopsis obscura*	96 hours	LC_{50} = 1177 ppm[b]	(941-1415 ppm)	Henry et al. 1994
Glyphosate	snails (*Pseudosuccinea columella*)	4 weeks	biochemical alteration	increased protein concentration of snails reared in 1.0 mg/L compared with those reared in 0.1 mg/L; exact mechanism for response not determined	Christian et al. 1993
Roundup	snails (*Pseudosuccinea columella*)	3 generations	delayed effect on growth and development, egg-laying capacity, and hatching	0.1-10 mg/L	Tate et al. 1997
Glyphosate (97%)	snails (*Pseudosuccinea columella*)	4 weeks	increased quantity of free amino acid pool	1-10 mg/L	Tate et al. 2000
Roundup	amphipod (*Gammarus pseudolimnaeus*; crustacea)	48 hours 96 hours	LC_{50} = 62 ppm LC_{50} = 43 ppm	(40-98 ppm) 12°C (54°F) (28-66 ppm) 12°C (54°F)	Folmar et al. 1979
Roundup	Harpacticoid (*Nitocra spinipes*; crustacea)	96 hours	LC_{50} = 22 ppm	(17-29 ppm) 21.1°C (70 ± 2°F)	Linden et al. 1979

[a] Values in parentheses are the 95% confidence limits.
[b] Only 50% of the test organisms were killed in the highest concentration tested.
NS = Not specified.

Appendix 11: Toxicity of glyphosate and glyphosate formulations to aquatic plants

Species	Endpoint	Reference
	Glyphosate	
Selenastrum capricornutum, green algae	4 day EC_{50} = 12.5 mg/L	U.S. EPA 1993b
Navicula pelliculosa, diatom	4 day EC_{50} = 39.9 mg/L	
Skeletonema costatum,	4 day EC_{50} = 0.85 mg/L	
Anabaena flosaquae, cyanobacter	4 day EC_{50} = 11.7 mg/L	
Lemna gibba, duckweed	7 day EC_{50} = 11.7 mg/L	
Chlorella fusca	1-generation cycle (24 hours) EC_{50} = 377 mg/L	Faust et al. 1994
Chlorella pyrenoidosa, green algae	4 day EC_{50} = 590 mg/L	Maule and Wright 1984
Chlorococcum hypnosporum, green algae	4 day EC_{50} = 68 mg/L	
Zygnema cllindricum, green algae	4 day EC_{50} = 88 mg/L	
Anabaena flosaquae, cyanobacter	4 day EC_{50} = 304 mg/L	
Cyclotella meneghiana, green algae	73% inhibition at 2.8 mg/L	Peterson et al. 1994
Nitzschia sp., green algae	77% inhibition at 2.8 mg/L	[Inhibition of carbon fixation after 24 hours. Negative values indicate stimulation.]
Scenedesmus quadricauda, green algae	3% inhibition at 2.8 mg/L	
Selenastrum capricornutum, green algae	18% inhibition at 2.8 mg/L	
Microcystis aeruginosa, cyanobacter	-41% inhibition at 2.8 mg/L	
Microcystis aeruginosa, cyanobacter	16% inhibition at 2.8 mg/L	
Oscillatoria sp., cyanobacter	-12% inhibition at 2.8 mg/L	
Pseudoanabaena sp, cyanobacter	12% inhibition at 2.8 mg/L	
Anabaena inaequalis, cyanobacter	11% inhibition at 2.8 mg/L	
Aphanizomenon flos-aquae, cyanobacter	74% inhibition at 2.8 mg/L	
Lemna minor, duckweed	no inhibition at 2.8 mg/L over 5 days	

Appendix 11: Toxicity of glyphosate and glyphosate formulations to aquatic plants

Species	Endpoint	Reference
Scenedesmus quadricauda, green algae	growth stimulation at 0.02 mg/L; stimulation of photosynthesis at 0.2 mg/L, and stimulation of chlorophyll-a synthesis at 0.02 mg/L glyphosate; at 2 mg/L glyphosate; at ≥20 mg/L glyphosate, algal growth, photosynthesis, and chlorophyll-a synthesis was completely inhibited.	Wong 2000
Scenedesmus acutus	NOEC = 2 mg/L LOEC = 4 mg/L 96-hr EC_{50} = 10.2 mg/L	Saenz et al. 1997
Scenedesmus quadricauda	NOEC = 3.2 mg/L LOEC = 4.08 mg/L 96-hr EC_{50} = 9.08 mg/L	Saenz et al. 1997
Scenedesmus acutus	NOEC = 3.2 mg/L LOEC = 4.08 mg/L 96-hr EC_{50} = 9.08 mg/L	Saenz et al. 1997
Scenedesmus acutus	NOEC = 1.25 mg/L LOEC = 2.5 mg/L 96-hr EC_{50} = 9.09 mg/L	Saenz et al. 1997
	ROUNDUP	
Mixed colonies of periphytic aglae	4 hour EC_{50}s = 35.4-44.4 mg/L for inhibition of photosynthesis. NOEC = 0.89 mg/L.	Goldsborough and Brown 1988