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Oxyfluorfen -
Human Health and Ecological Risk Assessment – Final Report

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ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
a.e.	acid equivalents
AEL	adverse-effect level
a.i.	active ingredient
ALS	acetolactate synthase
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
bw	body weight
CBI	confidential business information
CI	confidence interval
cm	centimeter
CNS	central nervous system
DAA	days after application
DAT	days after treatment
d.f.	degrees of freedom
EC_x	concentration causing X% inhibition of a process
EC_{25}	concentration causing 25% inhibition of a process
EC_{50}	concentration causing 50% inhibition of a process
ExToxNet	Extension Toxicology Network
F	female
FH	Forest Health
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FQPA	Food Quality Protection Act
g	gram
ha	hectare
HQ	hazard quotient
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
k_a	absorption coefficient
k_e	elimination coefficient
kg	kilogram
$K_{o/c}$	organic carbon partition coefficient
$K_{o/w}$	octanol-water partition coefficient
K_p	skin permeability coefficient
L	liter
lb	pound
LC_{50}	lethal concentration, 50% kill
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
m	meter
M	male

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

COMMON UNIT CONVERSIONS AND ABBREVIATIONS

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

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

CONVERSION OF SCIENTIFIC NOTATION

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

EXECUTIVE SUMMARY

OVERVIEW

Oxyfluorfen is used by the USDA Forest Service for the control of weeds around conifers and some deciduous trees. Based on the available scientific studies and methods employed by the Forest Service in the assessment of risk, it is plausible that oxyfluorfen exposure resulting from typical and maximum application rates and methods could result in adverse health effects among workers who handle the herbicide without extensive use of personal protective equipment, and among members of the general public who might consume vegetation contaminated with the herbicide primarily through spray drift. The potential adverse effects include an increased risk of liver cancer, and toxicity associated with disruption of heme biosynthesis. Individuals in the population who have a genetically inherited disease known as variegate porphyria could be uniquely sensitive to oxyfluorfen exposure due to an inherent deficit in an enzyme (protoporphyrinogen oxidase) which oxyfluorfen disrupts as it primary mechanism of action.

Adverse effects on populations of nontarget terrestrial plants, mammals and birds are plausible following use of oxyfluorfen at the typical and maximum application rates and methods. Adverse effects on aquatic life, especially plants and aquatic invertebrates, are virtually certain if steps are not taken to prevent contamination of nearby aquatic habitats.

PROGRAM DESCRIPTION

Oxyfluorfen is a diphenyl-ether herbicide that is used to control a large number of broadleaf and grassy weeds in both forestry and agriculture. In Forest Service programs, oxyfluorfen is used almost exclusively in tree nursery applications.

Oxyfluorfen is not very soluble in water. All commercial formulations of oxyfluorfen that are labeled for forestry applications are liquid, in which oxyfluorfen is dissolved in petroleum solvents or propylene glycol. Although oxyfluorfen is registered for aerial applications in some crop uses, the Forest Service does not use oxyfluorfen in aerial applications. Most nursery applications in Forest Service programs are conducted using mechanized equipment such as boom sprays. The highest labeled application rate for oxyfluorfen is 2 lbs a.i./acre and this is also the maximum amount of oxyfluorfen that may be applied in a given year and is the highest application rate reported in any Forest Service program. For this risk assessment, the typical application rate is taken as 1 lb a.i./acre with a range of 0.25 lb a.i./acre to 2 lbs a.i./acre. Based on national data from USGS and the U.S. EPA as well as data from California, it appears that the use of oxyfluorfen in Forest Service programs is extremely small relative to the total amount of the herbicide used in agriculture and in other non-Forest Service applications.

HUMAN HEALTH RISK ASSESSMENT

Hazard Identification **–** The database for oxyfluorfen toxicity in mammals is fairly complete as a result of compliance by registrants with U.S. EPA requirements for testing as part of the pesticide registration process. The studies on the toxicity of oxyfluorfen generally fall into two classes: older studies conducted with lower purity technical grade herbicide (71 - 85% active ingredient); and newer studies conducted with higher purity technical grade herbicide (>95% active

ingredient). The higher purity herbicide is the basis for current formulations and registration. It contains similar impurities to the lower purity, older herbicide, but in lower concentrations. As seen in developmental and sub-chronic toxicity studies with rodents, the toxicity of the lower purity herbicide is greater than that of the higher purity herbicide. This observation suggests that some of the observed toxicity in the older studies is due to impurities rather than oxyfluorfen itself. Consequently, studies conducted with the higher purity technical grade herbicide are given precedence over those conducted with the lower purity material. This conclusion is consistent with prior U.S. EPA evaluations and decision-making policies for oxyfluorfen.

Oxyfluorfen is rapidly absorbed and excreted, primarily as unchanged compound in the feces and urine following oral exposure. Very little remains in the tissues. Oxyfluorfen is not appreciably absorbed following dermal exposure, and what is absorbed, is rapidly excreted.

The mammalian toxicity database for oxyfluorfen is fairly complete. Oxyfluorfen is known to inhibit protoporphyrinogen oxidase (also known as "protoporphyrinogen IX oxidase" or "protox"), resulting in inhibition of heme biosynthesis, and induction of symptoms in rodents consistent with the expression of human variegate porphyria (i.e. effects on the liver, blood, blood-forming tissue). Oxyfluorfen is of a low order of acute oral toxicity, is a mild eye and skin irritant, and only causes reproductive/developmental effects in rodents and rabbits at doses/concentrations which cause toxicity in pregnant dams or does. High-purity technical grade oxyfluorfen is not mutagenic in standard bioassays. An increased incidence of combined liver adenoma/carcinoma in a cancer bioassay with mice results in oxyfluorfen being classified as a Group C, possible human carcinogen by the U.S. EPA. One of the inert ingredients found in oxyfluorfen formulations, N-methyl-pyrrolidone, also has been shown to cause liver adenoma/carcinomas in a cancer bioassay with mice, and to cause teratogenic effects in rats.

Exposure Assessment – All exposure assessments are conducted at the typical application rate for oxyfluorfen of 1 lb/acre. The consequences of using lower or higher application rates are discussed in the risk characterization. For workers applying oxyfluorfen, three types of application methods are modeled: directed ground spray, broadcast ground spray, and aerial spray. Of these, broadcast ground spray is the method of application that is most likely to be used in Forest Service applications. Aerial applications are not anticipated in Forest Service programs but are included as part of the standard set of exposure assessments used in Forest Service risk assessments in the event that aerial applications might be considered at some point in the future.

Central estimates of exposure for workers are approximately 0.014 mg/kg/day for aerial and backpack workers and about 0.022 mg/kg/day for broadcast ground spray workers. Upper ranges of exposures are approximately 0.15 mg/kg/day for broadcast ground spray workers and 0.08 mg/kg/day for backpack and aerial workers. All of the accidental exposure scenarios for workers involve dermal exposures. Most of these accidental exposures lead to estimates of dose that are in the range of the general exposure estimates for workers. The one exception involves wearing contaminated gloves for one-hour. The upper range of exposure for this scenario is about 2.5 mg/kg bw.

For the general public, the range for acute exposures is about 0.00001 mg/kg bw to about 1.35 mg/kg bw. The upper bound of exposure is associated with the consumption of contaminated vegetation. For chronic or longer term exposures, the modeled exposures are lower than corresponding acute exposures by about a factor of 10. As in acute exposures, the highest longer term exposure is associated with the consumption of contaminated vegetation and the upper range of the estimated dose is about 0.17 mg/kg/day. Because oxyfluorfen will typically be used in tree nurseries that are generally not located in populated or recreational areas, the plausibility of exposures associated with consumption of contaminated vegetation may be low and this supposition does have a substantial impact on the risk characterization. Exposures associated with the longer term consumption of water are very low, with an upper range of about 0.0007 mg/kg/day. Because oxyfluorfen may substantially bioconcentrate in fish, these exposures are much higher – i.e., an upper range of about 0.014 mg/kg/day – than those associated with contaminated water.

Dose-Response Assessment – Following standard practices for Forest Service risk assessments, the RfD values and estimates of carcinogenic potency derived by U.S. EPA are used in this risk assessment. U.S. EPA currently has two different chronic RfD values for oxyfluorfen. One value is presented in the Integrated Risk Information System and the other is presented in the re-registration document prepared by the U.S. EPA's Office of Pesticides (U.S. EPA/OPP).

U.S. EPA/OPP has derived a chronic RfD for oxyfluorfen of 0.03 mg/kg/day to assess risks associated with chronic systemic toxicity. This RfD is well-documented and is used directly for all longer term exposures to oxyfluorfen. This value is based on a NOAEL of 3 mg/kg/day in dogs and mice and an uncertainty factor of 100 – two factors of 10 for interspecies and intraspecies variability. The studies from which the NOAEL is derived used lower purity technical grade oxyfluorfen.

U.S. EPA/OPP did not to derive an acute RfD for oxyfluorfen because no adverse effects reflecting a single dose were identified at the highest dose tested in the studies available at the time the acute RfD was considered. However, a study from the published literature in which mice were shown to develop signs similar to human variegate porphyria following short-term dietary exposure to oxyfluorfen can be used as the basis for a surrogate acute RfD. Dividing the NOAEL of 19.8 mg/kg by an uncertainty factor of 100 (Factors of 10 each for intra- and inter-species variability) yields an acute RfD of 0.20 mg/kg.

U.S. EPA/OPP has derived a carcinogenic potency factor (Q1*) of 0.0732 $(mg/kg/day)^{-1}$ for oxyfluorfen. This value is based on combined hepatocellular adenomas and carcinomas observed in male mice in a chronic toxicity/carcinogenicity study. This value is used to assess risks associated with a one-in-one-million chance of developing cancer over a period of longer-term exposure.

Risk Characterization – In this assessment, risks associated with systemic toxicity and potential one-in-one million cancer risk are estimated for workers and members of the general public. Central and upper bound estimates of risks due to systemic toxicity indicate that workers with

contaminated gloves (i.e. leaky or loose gloves which allow the hand to be immersed in herbicide) or not wearing appropriate protective equipment may be at greatest risk due to acute exposure to oxyfluorfen, regardless of application rate.

For members of the general public, the acute exposure scenarios resulting in hazard quotients for systemic toxicity that exceed a level of concern (HQ>1), involve an accidental spill into a small pond, direct spray of a small child, and consumption of contaminated fruit and vegetation by an adult female. Of these scenarios, the only non-accidental acute scenarios which result in hazard quotients that substantially exceed the level of concern are those associated with longer-term exposure to contaminated vegetation after the application of oxyfluorfen at either the typical (1 lb/acre) or maximum (2 lbs/acre) application rates. For members of the general public, the only exposure scenarios resulting in greater than one-in-one-million cancer risk are for adult females consuming contaminated vegetation. While these scenarios yield risks which exceed a level of concern, they are not likely to occur in remote areas where residences are distant from Forest Service land.

Given that oxyfluorfen inhibits protoporphyrinogen oxidase, individuals who are innately deficient in protoporphyrinogen oxidase (i.e. have variegate porphyria) might be uniquely sensitive to oxyfluorfen exposure.

ECOLOGICAL RISK ASSESSMENT

Hazard Identification – Oxyfluorfen is an herbicide which disrupts photosynthesis through interference with chlorophyll production, and inhibition of photosystem II and electron transport. In mammals, oxyfluorfen interferes with heme biosynthesis, which ultimately impacts the blood, liver, and blood-forming tissues such as bone marrow.

The toxicity of oxyfluorfen is fairly well characterized in plants and animals. A comparison of older studies, conducted with less pure technical grade oxyfluorfen, with newer studies conducted with higher purity technical grade oxyfluorfen, demonstrates that impurities are responsible for some of the observed toxicity in the older studies. Similarly, a comparison of studies conducted with oxyfluorfen formulations, with those conducted with highly pure technical grade herbicide (>95% a.i.), demonstrate that inerts in the formulations are responsible for much of the observed toxicity. This latter observation is true for dermal and ocular irritation in mammals, acute toxicity in mammals, acute toxicity in aquatic invertebrates, and acute toxicity in aquatic algae.

Based on classification schemes developed by U.S. EPA on the basis of acute toxicity, oxyfluorfen is practically non-toxic to mammals, birds, and honey bees; highly toxic to fish; and very highly toxic to aquatic invertebrates. Oxyfluorfen does not cause effects on reproduction or fetal development in birds, or mammals at doses/concentrations which do not cause toxic effects in maternal animals. The only available study which addresses the potential for oxyfluorfen to adversely affect early growth and development in fish, was conducted with low-purity technical grade herbicide, and demonstrated adverse effects on growth and survival. Oxyfluorfen causes phytotoxicity in non-target plants at concentrations which are likely used under field conditions,

but these effects are often transient and reversible, depending on the species, cultivar and application rates used. A limited number of studies suggest that the effects of oxyfluorfen on soil microorganisms are also likely to be transient, with measured variables in exposed populations ultimately rebounding above those of control levels.

Exposure Assessment – A number of different exposure scenarios are developed mammals, birds, terrestrial invertebrates, terrestrial plants and aquatic species. The specific levels of exposure for each group of organisms are summarized in the G-Series worksheets in the EXCEL workbook that accompanies this risk assessment. In many respects, these exposures parallel the exposure scenarios used in the human health risk assessment and the scenarios fall into two general groups: exposures that may be anticipated in the normal use of oxyfluorfen and atypical exposures that could occur as a result of mischance or misapplication. In some cases, the atypical exposures have somewhat different interpretations. The direct spray of a human is regarded as accidental. The direct spray of a small mammal or insect during any broadcast application, however, is more plausible. Nonetheless, it is highly unlikely that a substantial proportion of small mammals or insects would be directly sprayed. Exposures would likely be reduced both by animal behavior as well as foliar interception.

For terrestrial animals, exposure assessments are developed for direct spray, the ingestion of contaminated media (vegetation, prey species, or water), grooming activities, or indirect contact with contaminated vegetation. Not all exposure scenarios are developed for all groups of animals because toxicity data are not available in all groups to support the use of such exposure assessments in the risk characterization. For terrestrial plants, exposure assessments are developed for direct spray, spray drift, and off-site movement of the compound by percolation, runoff, wind erosion of soil. For aquatic species, the concentrations in water are identical to those used in the human health risk assessment.

Also as in the human health risk assessment, the major route of exposure for most terrestrial species involves the consumption of contaminated vegetation rather than the consumption of contaminated water.

Dose-Response Assessment – The available toxicity data on oxyfluorfen support separate dose-response assessments in eight classes of organisms: terrestrial mammals, birds, terrestrial invertebrates, terrestrial plants, fish, aquatic invertebrates, aquatic algae, and aquatic macrophytes. Different units of exposure are used for different groups of organisms depending on how exposures are likely to occur and how the available toxicity data are expressed.

As with the human health dose-response assessment, priority is given to studies which used highly pure technical grade oxyfluorfen, as this is the basis for currently registered end-use products. Special consideration is given to studies conducted with end-use products for certain species (e.g. aquatic invertebrates and algae) in which oxyfluorfen formulations appear to be more toxic than the highly pure technical grade herbicide.

Based on both acute and chronic dietary toxicity values, mammals appear to be more sensitive to oxyfluorfen than birds. On the basis of acute toxicity, mammals are approximately 10 times more sensitive than birds. On the basis of chronic toxicity, mammals are approximately 3 times more sensitive than birds. For mammals, the dose-response assessment for chronic toxicity is based on the same data as the human health risk assessment (i.e., a chronic NOAEL of 3 mg/kg/day). As discussed in the human health risk assessment, U.S. EPA has not derived an acute RfD for oxyfluorfen. However, a study from the open literature yields a NOAEL value of 19.8 mg/kg/day which is used to derive a surrogate acute RfD. An acute NOAEL of 200 mg/kg is selected for birds on the basis of a dietary study with Mallard ducks. No lifetime toxicity studies on birds have been encountered. Based on the reproduction study, the chronic NOAEL for birds is set at 64.7 mg/kg/day. Relatively little information is available on terrestrial insects. A contact toxicity value of 1075 mg/kg bw (for honey bees) is taken as a NOAEC for terrestrial invertebrates.

The toxicity of oxyfluorfen to terrestrial plants can be characterized relatively well and with little ambiguity. Oxyfluorfen is relatively ineffective in inhibiting seed germination but is toxic after either direct spray or soil application. Based on toxicity studies in which exposure can be characterized as an application rate, oxyfluorfen is more toxic in pre-emergent soil applications than direct spray. In pre-emergent soil applications, the NOAEC values for the most sensitive and tolerant species are 0.0024 lb/acre and 0.31 lb/acre, respectively. The corresponding values for direct spray (post-emergent bioassays) are 0.00066 lb/acre and 0.034 lb/acre.

Oxyfluorfen is highly toxic to aquatic animals. The acute NOAEC values for sensitive and tolerant species of fish vary three-fold, with a range of 0.056 mg/L to 0.180 mg/L. For longer term exposures, the data are not sufficient to identify tolerant and sensitive species and a single NOAEC value of 0.038 mg/L is used. A much greater variability is apparent in aquatic invertebrates, with acute NOAEC values ranging from 0.0001 mg/L to 2 mg/L. This is not an artifact of comparisons between freshwater and saltwater species, because the large range of sensitivities is apparent upon examination of either freshwater or saltwater data sets. The NOAEC of 0.013 mg/L from the sole reproduction study (in *Daphnia*) is used to assess the effects of longer-term exposures in tolerant aquatic invertebrates, while an estimated value of 0.0022 mg/L is used to assess longer term exposure in sensitive species. The latter value is based on the daphnid NOAEC that is adjusted for relative sensitivity between *Daphnia* and Eastern oyster from acute toxicity studies.

Aquatic algae are more sensitive than fish but are equal in sensitivity with aquatic invertebrates. Oxyfluorfen formulations appear to be more toxic than technical grade herbicide, regardless of purity, although the lower purity material is more toxic than higher purity herbicide. NOAEC values of 0.001 mg/L and 2 mg/L are used to assess sensitive (green algae) and tolerant species (blue-green algae) and to account for the more toxic end-use product.

Aquatic macrophytes are equally sensitive to oxyfluorfen with respect to algae, as demonstrated by the only available study, which was conducted with duckweed. Since only one study was available, the LOAEC of 0.00055 for both sensitive and tolerant macrophytes is derived from

this standard 5-day growth bioassay. This value is used for the assessment of both acute and chronic exposures. A NOAEC was not identified in the study due to adverse effects on growth at the lowest concentration tested.

Risk Characterization – Oxyfluorfen has been tested in a variety of organisms. However, by necessity, the available tests represent a limited number of species, and the conditions of the tests may not represent actual conditions of exposure in the wild. These are limitations inherent to any risk characterization, and may result in underestimates or overestimates of actual risk. The methods used in both the exposure and dose-response assessments are intended to consider these uncertainties by using protective assumptions in developing both the exposure and dose-response assessments which form the basis of the risk characterization.

Because oxyfluorfen is an effective herbicide, unintended effects on nontarget vegetation are plausible. The effective use of oxyfluorfen is achieved by applying it to target vegetation at a time and in a manner which will minimize effects on nontarget plant species. If this is done properly and with care, effects on nontarget vegetation could be minor. Nonetheless, in the normal course of applications of formulations at rates that are effective in weed control, adverse effects on terrestrial plants are plausible due to either drift or runoff. Depending on local conditions and the proximity of streams or ponds to oxyfluorfen applications, damage to aquatic vegetation is also plausible and could be substantial.

Over the range of application rates used in Forest Service programs (0.25 to 2 lbs/acre), adverse effects on aquatic vegetation and invertebrates are highly likely if steps are not taken to prevent oxyfluorfen from entering nearby ponds or streams. Adverse effects in fish are likely only in association with the maximum application rate of 2 lbs/acre.

Over the range of application rates used in Forest Service programs, adverse effects are plausible in mammals consuming contaminated vegetation and insects following application at the typical and maximum application rates, but not likely at the lower application rate. There is no indication that substantial numbers of mammals would be subject to lethal exposure to oxyfluorfen. Consequently, adverse effects such as weight loss and reproductive impairment could occur but might not be readily apparent or easy to detect. Birds appear to be much more tolerant to oxyfluorfen than mammals and adverse effects on birds do not seem plausible.

In addition to the direct effects mentioned above, both terrestrial and aquatic animals could be impacted secondarily by the adverse effects of oxyfluorfen on vegetation. These secondary effects associated with the depletion of vegetation would likely be variable over time and among different species of animals. Some effects could be detrimental for some species – i.e., a reduction in the supply of preferred food or a degradation of habitat – but beneficial to other species – i.e., an increase in food or prey availability or an enhancement of habitat.

1. INTRODUCTION

Oxyfluorfen is used by the USDA Forest Service for the control of weeds around conifers and some deciduous trees. This document provides risk assessments for human health effects and ecological effects to support an assessment of the environmental consequences of this use.

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

Although this is a technical support document and addresses some specialized technical areas, an effort was made to ensure that the document can be understood by individuals who do not have specialized training in the chemical and biological sciences. Certain technical concepts, methods, and terms common to all parts of the risk assessment are described in plain language in a separate document (SERA 2001). Technical terms that are common to this and many other risk assessments conducted for the Forest Service is available on the internet at www.sera-inc.com.

The human health and ecological risk assessments presented in this document are not, and are not intended to be, comprehensive summaries of all of the available information. No substantial reviews or risk assessments of oxyfluorfen have been located in the open literature. A brief overview of oxyfluorfen is available for EXTOXNET (1996) and the WHO (2002) has classified oxyfluorfen as a pesticide that is *unlikely to present acute hazard in normal use*. Documentation for this classification is not given by WHO (2002). As part of the current risk assessment, primary literature on oxyfluorfen was identified by queries of Toxline (http://toxnet.nlm.nih.gov/) and Medline (http://www.ncbi.nlm.nih.gov/entrez) and supplemental literatures searches were conducted using Agricola (http://agricola.cos.com/). A total of 109 studies were ordered from the open literature. Additional sources of information were identified through standard Internet search engines.

A complete search of the U.S. EPA FIFRA/CBI files was conducted. These are studies that are required by the U.S. EPA to support the registration of pesticides. These studies are typically conducted either by the company seeking registration of the pesticide or by commercial testing facilities under funding by the company seeking registration of the pesticide. These studies are preferred by the U.S. EPA for pesticide registration because they follow guidelines established by the U.S. EPA (e.g., http://www.epa.gov/OPPTS_Harmonized/).

A total of 846 FIFRA submissions were identified. Of these, 133 studies were identified as potentially relevant to this risk assessment. This proportion, about 16% of submissions, is atypically low. In most Forest Service risk assessments, about 30 to 70% of the submitted

studies are considered relevant and are requested. As noted in Section 2, however, oxyfluorfen is commonly used in agriculture. In addition, oxyfluorfen used in many formulations of herbicide mixtures. As also noted in Section 2, this risk assessment does not address agricultural uses or formulations that contain oxyfluorfen with other herbicides. These two factors account for the relatively low proportion of studies identified as potentially relevant to this risk assessment.

Under the Freedom of Information Act (FOIA), SERA requested and received a total of 95 studies. The difference between the 133 potentially relevant studies and the 95 studies received through FOIA relate to limitations on FOIA requests. Only studies conducted after 1986 and studies relating to toxicity or environmental fate are eligible for FOIA. Studies on the identity of impurities, inerts, adjuvants, and manufacturing processes are considered proprietary (CBI) and are not eligible for release under FOIA. Full text copies of the studies that could be released under FOIA were kindly provided by the U.S. EPA Office of Pesticide Programs. These studies were reviewed, are discussed in Sections 3 and 4 as necessary, and synopses of the most relevant studies are provided in the appendices to this document. Citations to studies that were not eligible for release under FOIA are cited in this risk assessment as appropriate – i.e., in the discussion of studies submitted on inerts, adjuvants, and manufacturing processes. Limitations on the release of CBI studies under FOIA have a relatively minor impact on this risk assessment. The U.S. EPA has recently completed reregistration and pesticide tolerance analyses for oxyfluorfen (U.S. EPA U.S. EPA/OPP 2001a-g, 2002a-d, 2004). These analyses as well as analyses and assessments submitted by the registrant (Dow AgroSciences 2001a,b) were consulted as part of the current risk assessment for the U.S. Forest Service.

All identified studies (n=275) are listed in Section 5. The studies most relevant to this risk assessment are summarized in the appendices included with this risk assessment. The discussions in Section 3 (Human Health Risk Assessment) and Section 4 (Ecological Risk Assessment) focus on those studies that have a direct impact on the risk assessment for oxyfluorfen.

The Forest Service will update this and other similar risk assessments on a periodic basis and the Forest Service welcomes input from the general public on the selection of studies included in the risk assessment. This input is helpful, however, only if recommendations for including additional studies specify why and/or how the new or not previously included information would be likely to alter the conclusions reached in the risk assessments.

Almost no risk estimates presented in this document are given as single numbers. Usually, risk is expressed as a central estimate and a range, which is sometimes very large. Because of the need to encompass many different types of exposure as well as the need to express the uncertainties in the assessment, this risk assessment involves numerous calculations. Some of the calculations are relatively simple and these are included in the body of the document. Other calculations are more complicated. For these calculations, worksheets are 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 contained in an Excel workbook and are included as

Attachment 1 to this risk assessment. Documentation for the use of these worksheets is presented in SERA (2005). The worksheets are an integral part of the risk assessment. The worksheets are designed to isolate the large number of calculations from the risk assessment narrative. In general, all calculations of exposure scenarios and quantitative risk characterizations (i.e., hazard quotients) are derived and contained in the worksheets. The rationale for the calculations as well as the interpretation of the hazard quotients are contained in this risk assessment document.

2. PROGRAM DESCRIPTION

2.1. Overview

Oxyfluorfen is a diphenyl-ether herbicide that is used to control a large number of broadleaf and grassy weeds in both forestry and agriculture. In Forest Service programs, oxyfluorfen is used almost exclusively in tree nursery applications. Oxyfluorfen is not very soluble in water. All commercial formulations of oxyfluorfen that are labeled for forestry applications are liquid, in which oxyfluorfen is dissolved in petroleum solvents or propylene glycol. Although oxyfluorfen is registered for aerial applications in some crop uses, the Forest Service does not use oxyfluorfen in aerial applications. Most nursery applications in Forest Service programs are conducted using mechanized equipment such as boom sprays. The highest labeled application rate for oxyfluorfen is 2 lbs a.i./acre and this is also the maximum amount of oxyfluorfen that may be applied in a given year and is the highest application rate reported in any Forest Service program. For this risk assessment, the typical application rate is taken as 1 lb a.i./acre with a range of 0.25 lb a.i./acre to 2 lbs a.i./acre. Based on national data from USGS and the U.S. EPA as well as data from California, it appears that the use of oxyfluorfen in Forest Service programs is extremely small relative to the total amount of the herbicide used in agriculture and in other non-Forest Service applications.

2.2. Chemical Description and Commercial Formulations

Oxyfluorfen is a herbicide (postemergence and preemergence) that is used to control a large number of weeds in both agriculture and forestry. As detailed in Section 4.1.2.4, oxyfluorfen is readily absorbed by the leaves of plants and is used as a contact herbicide. This herbicide acts by inhibiting protoporphyrinogen oxidase, an enzyme that is important in the synthesis of porphyrin in plant chloroplasts. Inhibition of this enzyme causes a build up of chlorophyll precursors. In the presence of light, these precursors are converted to reactive molecules that disrupt plant cell membranes, leading to cell death (necrosis). This in turn leads to abnormal growth that is characterized by discoloration of leaves (chlorosis) followed by the death of the plant (e.g., U.S. EPA/OPP 2002a, p. 4).

The structure and basic chemical and physical properties of oxyfluorfen are summarized in Table 2-1. The specific values for the various properties of oxyfluorfen that are used quantitatively in this risk assessment are summarized in Worksheet B01. As illustrated in Table 2-1, oxyfluorfen is a biphenyl ether. Unlike many herbicides used by the Forest Service, oxyfluorfen is not a weak acid – i.e., it does not contain a carboxylic acid (-COOH) moiety. Thus, in this risk assessment, amounts of oxyfluorfen are expressed as active ingredient (a.i.) rather than acid equivalents (a.e.). Technical grade oxyfluorfen itself is an orange crystalline solid. Commercial formulations of oxyfluorfen that have active labels (i.e., products that appear to be marketed commercially) are liquids in which the oxyfluorfen is dissolved in a carrier.

As summarized in Table 2-2, four commercial formulations of oxyfluorfen are available. Three of the commercial formulations (Galigan 2E, Goal 2XL, and Goal Tender) have forestry applications. The other liquid formulation, Delta Goal, is labeled only for crops. Goal 2XL and Delta Goal appear to be essentially the same or at least very similar formulations. While several

standard studies have been submitted to the U.S. EPA for the registration of Goal 2XL (e.g., Lutz and Parno 1993a,b,c,d; Lutz et al. 1995; Ulrich 1993; Weisel 1994), no such studies have been identified for Delta Goal. This suggests that the U.S. EPA has allowed studies on Goal 2XL to be bridged to Delta Goal – i.e., studies on Goal 2XL can be used to satisfy testing requirements for Delta Goal. In addition, as summarized in Table 3-2, the MSDS (material safety data sheet) for Delta Goal reports toxicity values for the formulation that are identical to those of Goal 2XL, further suggesting the data bridging was allowed by U.S. EPA because the two products are identical or very similar.

The Goal formulations are supplied by Dow AgroSciences and the Galigan formulation is provided by Makhteshim-Agan. A conditional label has been identified for one granular formulation, Weedfree 63. As summarized in Table 2-2, this is a 2% granular formulation with a provisional label for preemergent weed control. Other commercial formulations of oxyfluorfen in combination with other herbicides are available (e.g., FirePower from Monsanto which is a mixture of oxyfluorfen and glyphosate and Showcase from Dow AgroSciences which is a mixture of trifluralin, isoxaben, and oxyfluorfen). These and other herbicide mixtures (see U.S. EPA/OPP 2002a, Table 1, p. 4) are not considered in the current risk assessment.

Oxyfluorfen is highly lipophilic; it has a relatively low water solubility and a relatively high $K_{o/w}$. Thus, all commercial formulations contain non-polar liquids as a carrier, either petroleum distillates or propylene glycol. The identity and quantity of all inerts and impurities in each formulation has been disclosed to the U.S. EPA as part of the registration process (Berrier 1990a,b; Bischoff 2003a,b; Bowers-Daines 1995; Carpenter 1990a,b,c; Crawford 1999a,b; Guzikevich 1997, 1998; Kelly and Regetta 1988; Mierkowski 1999; Nelson 2003; Rhodes 2003; Rohm and Haas 1984; Rohm and Haas 1995; Weisel 1994,2000,2001,2003a,b; Wells 1997). As indicated in Section 1, these studies are considered proprietary, are not eligible for release under FOIA, and have not been reviewed as part of the current risk assessment.

As summarized in Table 2-2, some information is available publically on the inerts contained in the formations of oxyfluorfen that are covered in this risk assessment. This information comes primarily from the Material Safety Data Sheets for the formulations. The potential effects of the inerts on the toxicity of oxyfluorfen formulations is discussed in Section 3.1.14.

2.3. Application Methods

The product labels for oxyfluorfen formulations do not detail the types of equipment that would be used to apply the liquid formulations. In general, the most common methods of ground application for liquid herbicide formulations involve backpack and boom spray operations. The Forest Service will typically use oxyfluorfen in nursery applications which commonly employ mechanized equipment such as boom sprays. Backpack applications are less likely but are possible. In backpack applications, the herbicide sprayer or container is carried by backpack. Usually, a worker treats approximately 0.5 acres/hour with a plausible range of 0.25-1.0 acre/hour. Oxyfluorfen is applied directly to soil for preemergent weed control or to very young weeds in postemergent weed control.

Boom spray applications involve spray equipment mounted on tractors or trucks. A standard assumption used in most Forest Service risk assessments is that 8 acres are treated in a 45-minute period (approximately 11 acres/hour). Some special truck mounted spray systems may be used to treat up to 12 acres in a 35-minute period with approximately 300 gallons of herbicide mixture (approximately 21 acres/hour and 510 gallons/hour) (USDA 1989b, p 2-9 to 2-10).

Although oxyfluorfen is registered for aerial applications in some crop uses (C&P Press 2005), the Forest Service does not and does not intend to use oxyfluorfen in aerial applications.

2.4. MIXING AND APPLICATION RATES

The specific application rates used in a ground application vary according to local conditions and the nature of the target vegetation. Application rates may be expressed in various units such as volume of formulation per acre (used in most product labels) and lbs a.i. per acre (designating the amount of oxyfluorfen). Many herbicides used by the Forest Service are weak acids that are formulated as salts or esters. For these herbicides, units of acid equivalents per acre (lbs a.e./acre) are commonly used. As noted above, oxyfluorfen is not a weak acid and thus units of acid equivalents per acre do not apply. Unless otherwise specified in this risk assessment, all application rates and other expressions of the amounts of oxyfluorfen are based on active ingredient, the amount of oxyfluorfen itself.

The recommended application rates for oxyfluorfen are reasonably consistent among the various formulations and range from 0.25 lbs a.i./acre to 2 lbs a.i./acre. Although oxyfluorfen can be used either as a preemergence herbicide or postemergence herbicide, the data of South and Zwolinski (1996) suggest that preemergence applications may be most efficient. Somewhat lower application rates are generally recommended for preemergence applications, in a range of 0.25 to 1 lb a.i./acre. Post-emergence applications generally involve rates of 0.5 to 2 lb a.i./acre. For all applications, the maximum amount that may be applied in a given year is 2 lb a.i./acre. This is also the highest application rate reported in any Forest Service program (i.e., Forest 10 in Region 5, Pacific Southwest).

The use of oxyfluorfen by management objectives in Forest Service Programs for fiscal years 2000 through 2003 is summarized in Table 2-3. Oxyfluorfen is used currently in Forest Service Programs in nursery weed control and noxious weed control (about 93% of total Forest Service use). The reported application for insect suppression involves a single forest (Forest 7) in Region 2 (Rocky Mountains). This appears to be a reporting error. Based on the total amount used and total number of acres treated, the average application rate for all regions combined is about 0.85 lb a.i./acre (Table 2-3).

For this risk assessment, the typical application rate will be taken as 1 lb a.i./acre. This application rate is in the range of rates that may be used in either preemergence or postemergence applications. The range of application rates will be taken as 0.25 lbs a.i./acre to 2 lbs a.i./acre, the range of application rates recommended on the product labels (Table 2-2). The lower bound of this range would be typical in preemergence applications in soils with little organic matter (<1% organic matter). The upper bound of this range is the maximum labeled application rate

specified on all labels. While multiple application rates are allowed, the use of the maximum labeled rate for a single application will lead to higher peak concentrations of oxyfluorfen in all media than any combination of multiple lower application rates.

In addition to application rates, spray volumes have a direct impact on risk assessment values. Spray volumes refer to the gallons of water or other materials that are applied per acre with the herbicide. These spray volumes, sometimes referred to as dilution volumes, are used to calculate the concentration of the herbicide in field solutions. For exposure scenarios involving spills onto the skin or accidental spills into a small pond, higher spray volumes lead to decreased concentrations and decreased risk.

As noted in Table 2-2, application volumes for oxyfluorfen range from 5 gallons of water per acre (the minimum volume for any ground application of Galigan 2E) to 110 gallons of water per acre (the spray volume for spot applications of Galigan 2E). The application volume of 5 gallons per acre is recommended for applications to eucalyptus, cotton, and soybeans. This low volume application is not used in Forest Service programs. For plausible Forest Service applications, the lowest dilution volume will be taken as 20 gallons of water per acre. This is the minimum application volume recommended for forestry applications. The maximum dilution volume will be taken as 110 gallons of water per acre. The central estimate of spray volume will be taken as 50 gallons per acre, the approximate geometric mean of the range [$(20 \times 110)^{0.5} = 46.9$] and the spray volume recommended on the labels for Goal 2XL, Galigan 2E, and Goal Tender in preemergent or early postemergent control of weeds around deciduous trees.

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

2.5. USE STATISTICS

Use statistics for oxyfluorfen are available from the Forest Service (pesticide use on national forests). In addition, estimates of national use have been complied by the U.S. EPA (2001g) and the USGS (1998). Lastly, reports of oxyfluorfen applications in California are also available (California Department of Pesticide Regulation 2001 to 2004). These reports suggest that the use of oxyfluorfen by the Forest Service is very small compared to the use of oxyfluorfen in agriculture.

The USDA Forest Service tracks and reports use by geographical areas referred to as "*Regions*". As illustrated in Figure 2-1, the Forest Service classification divides the U.S. into nine regions designated from Region 1 (Northern) to Region 10 (Alaska). [Note: There is no *Region 7* in the Forest Service system.] As illustrated in Figure 2-1, the greatest proportion of oxyfluorfen use (approximately 83% of the total use by the Forest Service in national forests between 2000 and 2004) occurs along the west coast of the United States: Region 6 (Pacific Northwest) and Region

5 (Pacific Southwest). Each of these regions accounts for a little over 40% of all use by the Forest Service.

Oxyfluorfen is used on a large number of crops, particularly on grapes, almonds, and cotton. A summary of the agricultural uses of oxyfluorfen is presented in Figure 2-2 (USGS 1998). These use statistics are based on the 1992 Census of Agriculture and estimates of pesticide use rates for individual crops that were compiled for the years 1991 to 1993 and 1995. As indicated in this figure, over 428,000 lbs of oxyfluorfen were applied to crops, primarily to grapes (20.9% of total), almonds (19.6% of total), and cotton (15.9% of total). Other minor uses included apples, pistachios, field and grass seed, olives, onions, plums, and walnuts. The geographic distribution of the agricultural uses of oxyfluorfen is similar to but somewhat broader than those of the Forest Service. As with use by the Forest Service, oxyfluorfen is used extensively in agricultural applications on the west coast of the United States. Unlike the Forest Service, agricultural uses of oxyfluorfen are also relatively common in Region 8 (Southeast).

More recent use statistics presented by U.S. EPA/OPP (2001g) indicate that the national average annual use of oxyfluorfen was about 761,000 lbs a.i./year applied to 1,167,000 acres [0.65 lb a.i./acer] over the period from 1990 to 1999. As noted in Tables 2-3 and 2-4, the total use of oxyfluorfen by the Forest Service from 2000 to 2003 was 1082.45 lbs a.i. or about 270 lbs a.i./year, which is a factor of about 2,800 [761,000 lbs / 270 lbs a.i./year = 2818.52] below the average national use of this herbicide by the Forest Service.

More recent data are available on the total amounts of pesticides applied in California (California Department of Pesticide Regulation 2000 to 2003). These data as well as use data from the Forest Service are summarized in Table 2-5 and illustrated in Figure 2-3. In Figure 2-3, the solid line represents the U.S. EPA/OPP (2001g) estimate of the total average use of oxyfluorfen. While total use in all applications in California has remained relatively constant, the use of oxyfluorfen by the Forest Service has declined by about 63% (about 20% per year) over the period from 2000 to 2003. As of 2003, the total use of oxyfluorfen in California was a factor of about 3,600 greater than the total national use of oxyfluorfen by the Forest Service [469,166.73 lbs / 131.15 lbs = 3,577.33].

Thus, based both on the national data from USGS (1998) and the U.S. EPA (2001g) as well as the more recent data from California (California Department of Pesticide Regulation 2001 to 2004), it appears that the use of oxyfluorfen in Forest Service programs is extremely small relative to the total amount of the herbicide used in agriculture and in other non-Forest Service applications. Consequently, there is no basis for asserting that Forest Service programs will substantially contribute to general concentrations of oxyfluorfen nationally. Nonetheless, the potential for local contamination of environmental media by the use of oxyfluorfen in Forest Service programs is discussed in detail in the human health risk assessment (Section 3) and the ecological risk assessment (Section 4).

3. HUMAN HEALTH RISK ASSESSMENT

3.1. HAZARD IDENTIFICATION

3.1.1. Overview

The database for oxyfluorfen toxicity in mammals is fairly complete as a result of compliance by registrants with U.S. EPA requirements for testing as part of the pesticide registration process. The available mammalian studies from CBI sources and the open literature are summarized in Appendices 1 (acute toxicity), 2 (developmental and reproductive toxicity) and 3 (sub-chronic and chronic toxicity). The studies generally fall into two classes: 1) older studies conducted with lower purity technical grade herbicide (71 - 85% active ingredient); and 2) newer studies conducted with higher purity technical grade herbicide (>95% active ingredient). The higher purity herbicide is the basis for current formulations and registration. It contains similar impurities to the lower purity, older herbicide, but in lower concentrations. As seen in developmental and sub-chronic toxicity studies with rodents, the toxicity of the lower purity herbicide is greater than that of the higher purity herbicide. This observation suggests that some of the observed toxicity in the older studies is due to impurities rather than oxyfluorfen itself. Consequently, studies conducted with the higher purity technical grade herbicide are given precedence over those conducted with the lower purity material. This conclusion is consistent with prior U.S. EPA evaluations and decision-making policies for oxyfluorfen (USEPA/OPP, 2001a, b; 2002a).

Throughout this document, the distinction is made between lower purity and higher purity technical grade herbicide when the study authors report it. In the appendices, the percent active ingredient is given as reported, when reported. Sometimes, the study authors report technical grade oxyfluorfen or a metabolite with a manufacturer's coded designation, such as RH2195 or AG510. The known chemical manufacturers codes and their common names, when given, are shown along with the corresponding molecular structures in Table 3-1.

Oxyfluorfen is rapidly absorbed and excreted, primarily as unchanged compound in the feces and urine following oral exposure. Very little remains in the tissues. Oxyfluorfen is not appreciably absorbed following dermal exposure, and what is absorbed, is rapidly excreted.

The mammalian toxicity database for oxyfluorfen is fairly complete. Oxyfluorfen is known to inhibit protoporphyrinogen oxidase (also known as "protoporphyrinogen IX oxidase" or "protox"), resulting in inhibition of heme biosynthesis, and induction of symptoms in rodents consistent with the expression of human variegate porphyria (i.e. effects on the liver, blood, blood-forming tissue). Oxyfluorfen is of a low order of acute oral toxicity, is a mild eye and skin irritant, and only causes reproductive/developmental effects in rodents and rabbits at doses/concentrations which cause toxicity in pregnant dams or does. High-purity technical grade oxyfluorfen is not mutagenic in standard bioassays. An increased incidence of combined liver adenoma/carcinoma in a cancer bioassay with mice results in oxyfluorfen being classified as a Group C, possible human carcinogen (U.S. EPA/OPP 2001a). One of the inert ingredients found in oxyfluorfen formulations, N-methyl-pyrrolidone, also has been shown to cause liver adenoma/carcinomas in a cancer bioassay with mice, and to cause teratogenic effects in rats.

3.1.2. Mechanism of Action

Oxyfluorfen and other light-dependent peroxidizing herbicides have been shown to be relatively non-selective in their affinity for protoporphyrinogen oxidase (also known as "protox") in plants and animals (Birchfield and Casida 1997), resulting in inhibition of porphyrin synthesis in plant chloroplasts, and in heme biosynthesis in animals (Krijt et al. 1993; Camadro et al. 1995; Krijt et al. 1997). Heme biosynthesis is important because hemoglobin, myoglobin and various cytochromes all require heme groups to be functional.

The biochemical synthesis of the heme group is an eight-step process catalyzed by eight different enzymes. This occurs primarily in the liver and bone marrow. In humans, a class of diseases known as porphyrias result from interference in heme biosynthesis, and the type of porphyria manifest is dependent upon which enzyme in the synthetic pathway is affected. Protoporphyrinogen oxidase catalyzes the next-to-last step heme biosynthesis, which entails the conversion of protoporphyrin IX to heme. A hereditary deficiency in protoporphyrinogen oxidase in humans results in a disease known as variegate porphyria (Poh-Fitzpatrick 2005; Hawkins 2002). Inhibition of protoporphyrinogen oxidase results in an accumulation of protoporphyrin IX and other porphyrin precursors, which subsequently leads to dermatological and neurological problems, and has been associated with an increased incidence of liver cancer (Birchfield and Casida 1996).

Oxyfluorfen has been shown to bind with high affinity to protoporphyrinogen oxidase in mouse liver mitochondria, causing inhibition within 19 hours of intraperitoneal administration of a 4 mg/kg dose (Birchfield and Casida 1996). Krijt et al. (1997) demonstrated that biochemical changes consistent with those observed in variegate porphyria could be experimentally induced in mice by exposing them to oxyfluorfen in the diet for nine days at a concentration as low as 200 ppm.

3.1.3. Pharmacokinetics and Metabolism

The pharmacokinetics of oxyfluorfen have been studied in laboratory animals. ^{14}C-trifluoromethyl-labeled oxyfluorfen administered to rats orally (approximately 100 mg/kg body weight, vehicle not specified) for 7 days was rapidly absorbed and eliminated primarily as unchanged compound in the feces. Approximately 95% of the administered radioactivity was detected in the feces, with 75% identified as unchanged oxyfluorfen. Other compounds identified in the feces included: 5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrophenol, 4-[2-chloro-4-(trifluoromethyl)phenoxy]-2-ethoxybenzenamine, N-[4-[2-chloro-4-(trifluoromethyl)phenoxy]-2-ethoxyphenyl]-2-ethoxybenzenamine, N-[4-[2-chloro-4-(trifloromethyl)phenoxy]-2-ethoxypehnyl]acetamide, and N-[4-[2-chloro-4-(trifloromethyl)phenoxy] -2-hydorxyphenyl]acetamide. Approximately 2-4% of the administered radioactivity was recovered in the tissues and urine (Adler et al. 1997).

DiDonato and Hazelton (1992) dosed male and female rats orally, via gavage, with 14-C-ring-labeled oxyfluorfen at low (4 mg a.i./kg) and high (320 mg a.i./kg)doses, and at 4 mg a.i./kg following administration of 40 ppm oxyfluorfen (Technical grade oxyfluorfen herbicide) in the diet for two weeks (pulse-dosed rats). Recovery of radioactivity was 97-99% for low dose rats,

84-91% for high dose rats, and 85-86% for pulse-dosed rats. Regardless of the dosing protocol, most of the radioactivity was excreted (primarily in the feces) within the first 2 days following administration. At seven days following administration, only trace amounts of radioactivity were detected in the specific tissues examined. Residuals of 0.1 to 0.8% were found primarily in fat, liver, adrenals, thyroid and ovaries. The remaining carcass contained 0.5 to 1.4%. The highest concentration of radio-label was observed in the plasma at 6 hours in the low-dose rats (about 0.75 ppm) and at 6-24 hours in the high-dose rats (about 55 ppm). For both low and high dose rats, the half-life of elimination from plasma of radio-label was biphasic, with a rapid phase of 9-13 hours, and a slow phase of 26-32 hours.

Using the same protocols reported by DiDonato and Hazelton (1992) in the study discussed in the previous paragraph, Zhang (1993) studied the metabolism of oxyfluorfen in rats. The pattern of elimination was consistent with that observed by DiDonato and Hazelton (1992). Urine and fecal excretion patterns for radioactivity were similar for the three dosing protocols (low-, high- and pulse-dosed as described above) with no differences between males and females. The profiles of metabolites identified in the low-, high- and pulse-dosed rats were qualitatively similar, with most of the identified radioactivity recovered in the feces. Oxyfluorfen and seven to nine other metabolites, including a hydroxylated metabolite (RH-34670) and metabolites formed by reduction of the nitro- group to an amino group followed by acylation (RH-45469, RH-45451, RH-120832, RH-120450, RH-120162, and RH-45298), were found in the feces. The chemical structures of these and the other metabolites listed under the manufacturer's coded designation (e.g., "RH-45469") are given in Table 3-. High-dose groups eliminated a higher percentage of parent compound (30% of dose) in the feces than low- or pulse-dosed rats (10-13%). The percentages of fecal RH-45469 were higher in low- and pulse-dosed rats (9-22%) than in high-dose rats (6-7%). Two major O-substrate conjugated metabolites (RH-45298 and RH-34980) and some minor N-substrate conjugated compounds were identified in the urine. No oxyfluorfen was identified in urine.

3.1.3.1. Dermal Absorption – Cheng (1989; Appendix 1, page 1-6) studied the dermal absorption of oxyfluorfen by applying radio-labeled Goal Technical herbicide to the skin of rats. He found that the majority (80 - 97.5%) of the ^{14}C *was not absorbed*, and that 2.18 to 14.6% of ^{14}C adhered to the skin at the test site. The predominant route of elimination of the minimally absorbed radiation was feces.

3.1.3.2. Dermal Absorption Rates – For the current risk assessment, dermal exposures are considered quantitatively in a number of different exposure scenarios (Section 3.2.2.2). Two types of dermal exposure scenarios are considered: those involving direct contact with a solution of the herbicide (e.g., immersion) and those associated with accidental spills of the herbicide onto the surface of the skin. As detailed in SERA (2001), dermal exposure scenarios involving immersion or prolonged contact with chemical solutions use Fick's first law and require an estimate of the permeability coefficient, K_p, expressed in cm/hour (also known as a zero-order dermal permeability coefficient). Using the method recommended by U.S. EPA (1992), the estimated dermal permeability coefficient for oxyfluorfen is 0.016 cm/hour with a 95% confidence interval of 0.0078 to 0.034 cm/hour (Attachment 1, Worksheet B05). These

estimates are used in all exposure assessments that are based on Fick's first law. For exposure scenarios like direct sprays or accidental spills, which involve deposition of the compound on the skin's surface, dermal absorption rates (proportion of the deposited dose per unit time) rather than dermal permeability rates are used in the exposure assessment. The estimated first-order dermal absorption coefficient (k_a) is 0.0032 $hour^{-1}$ with 95% confidence intervals of 0.0012 to 0.0087 $hour^{-1}$ (Attachment 1, Worksheet B06).

In the dermal absorption study by Cheng (1999) mentioned briefly in the previous section (3.1.3.1), 8.1% of a dermally applied dose was absorbed after 24 hours of exposure. Similarly, 17.1% of the dose was absorbed at 168 hours post-application. Assuming first-order absorption kinetics, the proportion (P) absorbed is defined by the equation:

$$P = 1 - e^{-kt}$$

where: k = first-order dermal absorption coefficient; and t = time. Solving for k, we get:

$$k = -\ln(1-P)/t$$

Substituting P = 0.081 at t = 24 hours into the latter equation, yields k = 0.00351 $hour^{-1}$. Substituting P = 0.0171 at t = 168 hours, yields k = 0.00112 $hour^{-1}$. These experimental values for rats are in agreement with the first-order absorption values (k_a) derived in Attachment 1, Worksheet B06, and used in this assessment to evaluate dermal exposure in humans (k_a = 0.0032 $hour^{-1}$ with 95% confidence intervals of 0.0012 to 0.0087 $hour^{-1}$).

3.1.4. Acute Oral Toxicity

Oxyfluorfen is practically non-toxic (U.S. EPA/OPP Class IV) on the basis of standard acute oral toxicity tests, with NOAEL values at test limits of 5000 mg a.i./kg in tests on rats conducted with higher purity oxyfluorfen (>95%). U.S. EPA has not derived an acute oral RfD for oxyfluorfen due to a lack of observed toxicity (no mortality, no clinical signs, no pathology, etc.) at the highest doses tested (U.S. EPA/OPP 2001a, b; 2002a). Relevant acute oral toxicity studies are presented in detail in Appendix 1.

An important study reported in the open literature suggests that acute exposure to oxyfluorfen can cause acute toxic effects not normally measured in the standard tests. As discussed in the mechanism of action section (Section 3.1.2), oxyfluorfen inhibits protoporphyrinogen oxidase, which in turn, causes disruption of heme biosynthesis. Krijt et al. (1997; Appendix 1, page 1-3) demonstrated that administration of oxyfluorfen (99.4% a.i.; 200 and 1000 ppm) in the diet of mice for nine days caused an increase in relative liver weight and statistically significant increases in liver and kidney porphyrin concentrations, consistent with the inhibition of protoporphyrinogen oxidase and the development of variegate porphyria seen in humans. In an attempt to determine whether the neuropathy commonly observed in cases of human variegate porphyria could be attributed to the effects of increased concentrations of porphyrin precursors on nerve tissue, Krijt et al. (1997) measured protoporphyrinogen oxidase activity in brain tissue, and porphyrin content of the trigeminal nerve. They found no significant difference between

control and oxyfluorfen-treated mice for either variable, but did observe a significant increase in trigeminal nerve porphyrin content among mice treated with 1000 ppm of oxadiazon, an herbicide similar to oxyfluorfen. The overall NOAEC and LOAEC for the Krijt (1997) study are 125 and 200 ppm a.i. oxyfluorfen, respectively.

3.1.5. Subchronic or Chronic Systemic Toxic Effects

Systemic toxicity encompasses virtually any effects that a chemical has after the chemical has been absorbed. Certain types of effects are of particular concern and are assessed with a specific subset of toxicity tests. Such effects are considered in following subsections and include effects on the nervous system (Section 3.1.6), immune system (Section 3.1.7), endocrine function (Section 3.1.8), development or reproduction (Section 3.1.9), and carcinogenicity or mutagenicity (Section 3.1.10). This section summarizes the available information on other systemic effects and non-specific toxicity.

Studies which investigate the subchronic and chronic toxicity of oxyfluorfen are presented, in detail, in Appendix 3. In rats and mice, dietary exposure to lower purity technical grade oxyfluorfen (71.5 - 85.7% a.i.) at concentrations of 200 ppm a.i. or higher, resulted in decreased body weight gain, and adverse effects on the liver, kidneys, blood (anemia) and blood-forming tissues (bone marrow, spleen). A 52-week dietary study found no treatment-related changes in behavior, appearance, body weight, food consumption and hematological or biochemical variables in mice fed 85.7% pure technical grade oxyfluorfen at concentrations up to 200 ppm a.i. However, mice fed 200 ppm a.i. had cancerous and non-cancerous liver changes (Goldenthal and Wazeter 1977; Appendix 3, page 3-6). The NOAEC for the study, 20 ppm a.i., is equivalent to a NOAEL of 3 mg a.i./kg/day, and along with the NOAEL from the chronic dog study, discussed below, serves as the basis for the chronic RfD of 0.03 mg/kg/day for oxyfluorfen derived by U.S. EPA's Office of Pesticide Programs Health Effects and Environmental Fate and Effects Divisions (U.S. EPA/OPP 2001a, b; 2002a). Decreased body weight, and changes associated with liver damage (increased serum alkaline phosphatase, increased liver weight, and increased bile-pigmented hepatocytes) were seen in dogs fed oxyfluorfen (71.4 - 73.8% a.i.) in the diet for 52 weeks at concentrations of 600 ppm or higher (Piccirillo 1997; Rohm and Haas 1981, as cited in USEPA 2001a). The NOAEC for the dog study is 100 ppm, equivalent to a NOAEL of 3 mg a.i./kg/day. In a subchronic dietary study on rats conducted with 98% pure oxyfluorfen (Stewart 1997), the NOAEC for the study was 500 ppm (equivalent to a NOAEL of 46.7 mg a.i./kg/day for males and 50.4 mg a.i./kg/day for females), with anemia, liver and kidney effects seen at concentrations of 1500 ppm and higher.

3.1.6. Effects on Nervous System

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

No primary effects on the nervous system have been reported in the acute, subchronic or chronic studies conducted in mammals with oxyfluorfen. Some of the clinical signs reported at high doses in studies with lower- purity Technical grade oxyfluorfen (approximately 71-73% a.i.) summarized in Appendices 2 and 3 (e.g. hunched posture, ataxia in rats exposed orally to 750 mg/kg, Page 1, Appendix 2; or mice exposed via diet to 3200 ppm Page 1, Appendix 3) are associated with agonal death rather than primary neurotoxicity. On this basis, U.S. EPA has not required standard neurotoxicity testing for oxyfluorfen as part of the pesticide registration or re-registration processes (U.S. EPA/OPP 2002a).

While the available laboratory studies with mammals do not suggest that oxyfluorfen is neurotoxic, one should note that the mechanism by which variegate porphyria is assumed to cause the symptoms in humans is through the effects of an accumulation of porphyrin precursors on neurons (Poh-Fitzpatrick et al. 2005). As discussed in detail in Section 3.4.4, variegate porphyria is a genetic disorder resulting in a deficiency in protoporphyrinogen oxidase; the same enzyme inhibited by oxyfluorfen. Neither a decrease in brain protoporphyrinogen oxidase activity, nor an increase in trigeminal nerve porphyrin concentration were observed in the experimental system employed by Krijt et al. (1997) to induce experimental porphyria in mice through exposure to oxyfluorfen. However, an increase in trigeminal nerve porphyrin concentration was observed in response to treatment with oxadiazon, an herbicide similar to oxyfluorfen. As porphyrin concentrations are technically difficult to monitor, and given the short duration (nine day exposure) and limited sample size (4 mice per treatment group) employed by the Krijt et al. (1997) study, further investigation of this phenomenon seems warranted prior to ruling out the potential for oxyfluorfen exposure to result in effects on the nervous system.

A study conducted with fish from the Nile River in Egypt (Hassanein 2002; Appendix 8) suggests that oxyfluorfen formulations can adversely impact the nervous system. Hassanein (2002) exposed *Gambusia affinis* and *Oreochromis niloticus* to Goal herbicide (23.6 mg a.i./L), and monitored brain acetylcholinesterase levels on days 6, 15 and 30 of exposure. Statistically significant reductions in brain acetylcholinesterase activity with respect to pre-exposure control levels were observed at the lowest doses of exposure in both species, yielding 30-day LOAEC values of 0.3 mg a.i./L (*Oreochromis niloticus*) and 0.43 mg a.i./L (*Gambusia affinis*). In addition, one should note that formulations of oxyfluorfen contain N-methyl-2-pyrrolidone, aromatic solvent, petroleum solvents and naphthalene as "inerts" (see Section 3.1.14 for further discussion). The primary effect of naphthalene and petroleum solvents involves central nervous system depression and other signs of neurotoxicity.

3.1.7. Effects on Immune System

As discussed by Durkin and Diamond (2002), a variety of tests have been developed to assess the effects of chemical exposures on various types of immune responses, including assays of antibody-antigen reactions, changes in the activity of specific types of lymphoid cells, and assessments of changes in the susceptibility of exposed animals to resist infection from pathogens or proliferation of tumor cells. No such studies have been conducted on oxyfluorfen. As discussed in Section 3.1.11, skin sensitization studies involving oxyfluorfen have been conducted. These studies provide information about the potential for oxyfluorfen to act as a skin

sensitizer but they provide no information useful for directly assessing the immunosuppressive potential of oxyfluorfen.

Several studies suggest that oxyfluorfen exposure may trigger an immune response or adversely impact the immune system. Elevated leukocyte counts were seen in rats exposed to 10,000 ppm a.i. high purity technical grade oxyfluorfen in the diet for 13 weeks (Stewart 1997). However, the elevation of leukocyte count at relatively high levels of exposure could simply be a secondary response following cell death in various target organs, rather than a primary immune response. In another subchronic dietary study (Nomura Research Institute 1982), atrophy of the thymus was observed among rats fed 5000 ppm lower purity technical grade oxyfluorfen. Elevated leukocyte and lymphocyte counts were also observed in rats exposed by inhalation to aerosols of Goal 2E for up to 20 days, but the study authors state that the observed values were within the range of normal for Charles River CD rats in their laboratory (Goldenthal et al. 1978). Increased mean white cell counts were observed in rabbits following subchronic dermal exposure to technical grade oxyfluorfen (Cruzan et al. 1978), but the effect in this study is likely secondary to necrotic tissue damage.

3.1.8. Effects on Endocrine System

Assessment of the direct effects of chemicals on endocrine function are most often based on mechanistic studies on estrogen, androgen, or thyroid hormone systems (i.e., assessments on hormone availability, hormone receptor binding or post-receptor processing). The U.S. EPA has not yet adopted standardized screen tests for endocrine disruptors (e.g., U.S. EPA/OPP 2002h).

Dietary exposure to high concentrations of oxyfluorfen has been associated with adverse effects on the adrenal, thyroid and thymus glands. Rats exposed to 10,000 ppm a.i. high purity oxyfluorfen in the diet for 13 weeks had histopathological changes in the adrenal zona reticularis as well as increased thyroid weights (males) (Stewart 1997). Rats exposed to 5000 ppm of lower purity technical grade oxyfluorfen in the diet had decreased adrenal weight and histopathological changes in the adrenals (vacuolation of cells of the zona fasciculata) and atrophy of the thymus cortex (Nomura Research Institute 1982). Male rats exposed for 20 days via inhalation of aerosols of Goal 2E had decreased adrenal weights with respect to controls (Goldenthal et al. 1978).

3.1.9. Reproductive and Teratogenic Effects

3.1.9. 1. Teratology Studies – Developmental studies are used to assess whether the compound has the potential to cause birth defects. These studies typically entail gavage administration to pregnant rats or rabbits on specific days of gestation. Teratology assays as well as studies on reproductive function (Section 3.1.9.2) are typically required for the registration of pesticides. Protocols for developmental studies have been established by U.S. EPA/OPPTS (2005).

Studies which have been conducted in response to U.S. EPA test requirements for pesticide registration comprise a relatively complete data set for the investigation of the potential for oxyfluorfen to adversely affect developing fetuses. These studies are summarized in Appendix 2.

The older studies conducted with the lower purity technical grade oxyfluorfen show effects at lower doses/concentrations than those conducted with the higher purity technical grade oxyfluorfen, but the pattern of results is similar. Rabbits appear to be more sensitive than rats, and most importantly, fetal effects are seen only at doses/concentrations which cause maternal toxicity. Given that the current registration is for oxyfluorfen formulations based on the higher purity technical grade compound (>95% active ingredient), the more recent studies are given precedence. This follows precedent set by U.S. EPA/OPP (2001a).

Pregnant rats given technical grade oxyfluorfen (98% a.i.) by gavage during the critical stage of gestation at concentrations up to 1000 mg a.i./kg/day had no signs of toxicity (Burns 1997b). No adverse effects of any kind were observed among the developing fetuses of these rats. In a parallel study (Burns 1997a), pregnant rabbits dosed by gavage with technical grade oxyfluorfen (98% a.i.) at a concentration of 90 mg a.i./kg/day had reduced food intake and increased fecal output. In addition, decreased mean litter weights, and delayed skeletal ossification and fetal head development were observed at the 90 mg/kg/day dose level. The NOAEL for the rabbit study is 31 mg a.i./kg/day.

3.1.9. 2. Multigeneration Reproduction Studies – Reproduction studies involve exposing one or more generations of the test animal to the compound. Relatively standardized protocols for reproduction studies have been established by U.S. EPA/OPPTS (2005) – i.e., OPPTS 870-3800. The general experimental method involves dosing the parental (P) generation (i.e., the male and female animals used at the start of the study) to the test substance prior to, during mating, after mating, and through weaning of the offspring (F1). In a two-generation reproduction study, this procedure is repeated with male and female offspring from the F1 generation to produce another set of offspring (F2). During these types of studies, standard observations for gross signs of toxicity are made. Additional observations often include the length of the estrous cycle, assays on sperm and other reproductive tissue, and number, viability, and growth of offspring.

Two multi-generation reproduction studies have been conducted with rats, using the lower purity technical grade oxyfluorfen. These studies are summarized in Appendix 2 (page 2-3 and 2-4) in three separate reports, one of which is a preliminary report (Solomon et al 1991, Kileen et al 1977 and Rohm and Haas 1991b). No multiple generation reproduction studies have been conducted with rabbits. The main observation from the available studies is that no adverse effects on reproduction were seen at dietary concentrations which were not associated with parental toxicity. A decrease in the mean number of live offspring and a decrease in fetal body weights was preliminarily reported by Rohm and Haas (1991b), but this observation was made in association with a high dietary concentration (1600 ppm) at which maternal effects (i.e. decreased body weight) also observed.

In a 2-generation dietary study conducted with lower purity technical grade oxyfluorfen (71.4% a.i.) (Solomon et al. 1991; Rohm and Haas 1991b), dose-related kidney effects on parental adults (mineralization of the renal pelvis, reactive hyperplasia and dilation of collecting ducts) was observed at dietary concentrations of 400 ppm and higher, with a NOAEL of 100 ppm. The only treatment-related reproductive effect in this study was a decrease in fetal body weight (a

decreased mean number of live offspring was also reported in the preliminary findings by Rohm and Haas 1991b) at 1600 ppm, yielding a NOAEL 400 ppm for reproductive effects.

In a 3-generation dietary study conducted with 82.2-85.7% pure technical grade oxyfluorfen (Killeen et al. 1977), there was a statistically significant decrease in body weight gain among high-dose (100 ppm a.i. diet) mothers of the F_0 generation during days 14 through 21 of lactation. This effect was not observed in the F_1 or F_2 generation or in any males or non-pregnant females. The offspring of the F_0 mothers had a significant decrease in survival (days 0-4 and 4-14 of lactation) in comparison with controls. This effect was not seen in subsequent generations. There were no statistically significant treatment-related effects on fetal survival, size, sex, malformations or gross pathology. There was no evidence of embryotoxic or teratogenic effects. This study yields a NOAEL of 10 ppm on the basis of the previously discussed observations.

3.1.9. 3. Target Organ Toxicity – As part of most standard acute and chronic toxicity studies, observations are often made on reproductive tissue – e.g., ovaries and testes. No adverse effects on reproductive organs have been reported in any of the available studies on oxyfluorfen.

3.1.10. Carcinogenicity and Mutagenicity

Three kinds of data are commonly used to assess potential carcinogenic hazard. These data include epidemiology studies, bioassays on mammals, and tests for genetic toxicity, including mutagenicity. No epidemiology studies have been encountered in the literature that would permit an assessment of the association of exposure to oxyfluorfen with the development of cancer in humans.

3.1.10.1. Bioassays for Carcinogenicity – Two studies are available which have been conducted in attempt to address the carcinogenic potential of oxyfluorfen. Both studies, summarized in Appendix 3, page 3-7, were conducted with lower purity technical grade oxyfluorfen (85.7% a.i.). It is not possible to draw meaningful conclusions from the study on rats (Auletta et al.1978; Tornaben et al. 1977) due to the occurrence of numerous statistically significant non-cancerous effects which were randomly observed among the various control and treatment groups. As such, no meaningful dose-response could be established for many endpoints quantified in the study. With regard to histopathological changes, no treatment-related effects were found in either low or mid-dose animals at either the interim or final examination points. There were no notable treatment-related differences in the incidence of neoplastic changes between the control and oxyfluorfen-exposed rats.

The study on mice conducted by Goldenthal and Wazeter (1977) suggests that oxyfluorfen could possibly cause liver cancer. U.S. EPA/OPP (2001a; 2002a) classifies oxyfluorfen as a class C (possible human carcinogen) on the basis of this study, and uses the combined incidence of liver adenoma/carcinoma as the basis for deriving a carcinogenic potency factor (Q1*) of 7.3E-02.

3.1.10.2. Mutagenicity – The available studies which address the mutagenicity of oxyfluorfen are summarized in Appendix 4. Studies conducted with the older, lower purity herbicide show more positive results, while studies conducted with the newer, higher purity herbicide are largely

negative. USEPA (2001a) concludes that studies performed with the ≥96% technical grade herbicide satisfy the 1991 mutagenicity guidelines, and that no further testing is required. U.S. EPA (2001a) states: *" The newer technical material (96-99% a.i.) was tested in 12 genetic toxicology studies. All assays were negative, except for one Ames assay which was positive only at high, insoluble levels [Willington et al.1999; Appendix 4 page 2) observed that AG510 (96% a.i.) weakly promoted reverse mutation in Salmonella typhimurium strain TA100 in the presence of S9 metabolic activation, but not in the absence of S9, or in any other strain regardless of metabolic activation.]. A subsequent Ames assay with 96% material was negative [Perhaps not "subsequent, but Everich 1995a (Appendix 4, page 2) saw negative results with AG510 in the same test and strains]. The older72% technical material and a polar fraction were tested in eight genetic toxicology studies. Both Ames assays and a mouse lymphoma study were positive for the 72% technical material. The polar fraction of the 72% technical material was also positive in an Ames assay".*

These results suggest that compounds other than the active ingredient cause most, if not all, of the mutagenic activity observed in these assays. That said, there is one study conducted with high purity technical grade compound which produced a weakly positive result. .

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

Studies on effects of pesticides and pesticide formulations are relatively standardized and include assays for acute eye irritation (OPPTS 870.2400), acute dermal irritation (OPPTS 870.2500), and skin sensitization (OPPTS 870.2600). The acute irritation studies typically involve rabbits. The test material is applied either to one eye of the animal or to an area of the skin (intact or abraded). In the eye irritation studies, the untreated eye of the animal typically serves as the control. In the dermal studies, an untreated area of the skin typically serves as a control. Both eye and skin irritations studies are used to classify pesticides (corrosive to non-irritant) and these classifications reflect how the pesticide or pesticide formulations must be labeled.

3.1.11.1. Skin Irritation **–** Studies which assess the dermal irritation potential of oxyfluorfen and oxyfluorfen formulations are summarized in Appendix 1. Studies conducted with Goal 1.6E and Goal 2XL resulted in moderate to severe irritation (Krzwicki 1983; Lutz and Pano 1993c). Studies conducted with high purity technical grade oxyfluorfen (97% a.i.; e.g., Lampe et al. 1998c) resulted in no irritation (Goal technical grade oxyfluorfen) or mild irritation (AG 510 technical grade oxyfluorfen; Dreher et al. 1995b). On the basis of these studies, U.S. EPA (2001a) classifies oxyfluorfen as a slight (Class IV) dermal irritant.

3.1.11.2. Skin Sensitization **–** Studies which assess the potential for oxyfluorfen to cause allergic skin reactions are summarized in Appendix 1. Based on the negative results seen in these studies, U.S. EPA/OPP (2001a) does not consider oxyfluorfen or oxyfluorfen formulations to be dermal sensitizers. It should be noted that Anderson and Shuey (1994) reported that Goal 2XL caused delayed contact hypersensitivity in Guinea Pigs (Appendix 1, page 1-6).

3.1.11.3. Ocular Effects **–** Studies which assess the potential for oxyfluorfen and oxyfluorfen formulations to irritate the eyes are summarized in Appendix 1 (pages 1-8 to 1-10). Studies

conducted with the higher purity technical grade herbicide (Dreher 1995a; Lampe et al 1988d) and undiluted Goal 2XL (24-25% a.i.) (Lutz et al. 1995; Lutz and Parno 1993d) found no effects or mild irritation. Based on these studies, U.S. EPA/OPP (2001a) classifies oxyfluorfen as a slight (Class IV) eye irritant.

3.1.12. Systemic Toxic Effects from Dermal Exposure

Studies which address the acute systemic dermal toxicity are summarized in Appendix 1. Neither technical grade oxyfluorfen (either 71.4% or 96-97.1% a.i.) nor Goal 2XL (42.2% a.i.) caused death, signs of toxicity or clinical or pathological changes in rats or rabbits exposed to test limit concentrations (2000 - 5000 mg/kg bw, depending on the study).

A subchronic dermal exposure study in rabbits (Cruzan et al. 1978; Appendix 3, page 3-5) is somewhat confounded and flawed by adverse effects seen in the solvent/emulsifier controls and low numbers of rabbits used at each treatment level (4/sex/group). As noted by U.S. EPA/OPP (2001a) this study is unacceptable. Rabbits were exposed to either RH-2915 Technical at 2 g/kg in a solvent emulsifier solution, or to either 24.2 or 96.8 mg a.i. RH-2915 EC in aqueous solution applied to both abraded and intact skin. Negative and solvent/emulsifier controls were also used. Rabbits were exposed 5 days/week for 4 weeks. Significant decreases in body weight, food consumption , hematological variables and pathological changes in the skin and liver were observed among the solvent/emulsifier controls as well as rabbits exposed to the RH-2915 in the solvent/emulsifier. The only treatment-related adverse effects in rabbits treated with the aqueous oxyfluorfen solution were associated with skin pathology (long list, including epidermal hyperplasia and necrosis; significantly increased white cell counts). These effects were seen in rabbits exposed to 96.8 mg a.i./kg body weight. The NOAEL among rabbits exposed via aqueous solution was 24.2 mg a.i./kg body weight). Due to the limitation discussed above, this study (Cruzan et al. 1978) is not considered either qualitatively or quantitatively in the determination of potential hazards due to dermal exposure to oxyfluorfen.

The lack of observed systemic toxicity in these studies is consistent with the findings of Cheng (1999; discussed in Section 3.1.3.1) in rats, which demonstrate that: 1) dermally applied oxyfluorfen is not appreciably absorbed (80-97% not absorbed); 2) what is absorbed, is rapidly and completely eliminated in the feces and urine; and 3) a small amount (2-15%) adheres to the skin.

3.1.13. Inhalation Exposure

Acute inhalation studies are summarized in Appendix 1. Various formulations (e.g. Goal 2XL, Goal/Surflan 2/1G, Goal/Lasso 2/2G) as well as low- and high-purity technical grade oxyfluorfen have been tested. No mortality or abnormal pathology was observed in any study. Transient clinical signs including salivation, hunched posture and piloerection were commonly observed during exposure, and most were resolved quickly following cessation of exposure. The most up-to-date study conducted with high-purity oxyfluorfen (Blagden 1995; Appendix 3, page 3-4) exposed male and female rats to AG510 (96% a.i.) at a measured concentration of 3.71 ± 0.66 mg/L for 4 hours. Other than the transient clinical signs mentioned previously, there were no treatment-related changes (no mortality, no abnormal pathology and no body weight changes) in

the oxyfluorfen-exposed rats. U.S. EPA/OPP (2001a) classifies oxyfluorfen as Class IV, practically nontoxic, with respect to acute inhalation toxicity, on the basis of this study.

There is only one subchronic inhalation study with rats (Goldenthal et al. 1978; Appendix 3; page 3-4). The study was conducted with Goal 2E (23.5% a.i.) and is flawed in so many ways as to be classified as unacceptable by U.S. EPA/OPP (U.S. EPA/OPP 2001a). The LOAEL from the study is ≤0.13 mg/l (33.2 mg/kg/day for males and 34.9 mg/kg/day for females), the lowest dose tested, based on increased liver weight in low-dose but not high dose females and lung pathology. In many cases the low-dose group had more severe toxicity than high-dose animals, and the study authors considered the observed gross pathological deviations to be vehicle-related.

3.1.14. Inerts and Adjuvants

As summarized in Table 2-2, several inert ingredients are listed for certain formulations of oxyfluorfen. Goal, Delta Goal and Galigan contain N-methyl-2-pyrrolidone (8-10% in Galigan; concentration not specified in Goal or Delta Goal). Galigan also contains solvent naptha petroleum heavy aromatic(50-59%), and Goal2XL/Delta Goal contain aromatic solvent and naphthalene (concentrations not specified). Goal Tender contains propylene glycol.

U.S. EPA/OPP (2004b) currently lists N-methyl-2-pyrrolidone as an inert ingredient of unknown toxicity (List 3). A review of secondary sources such as material safety data sheets and readily accessible second-party reviews on the internet are inconsistent with regard to reporting of possible effects. However, a cursory search of TOXLINE, a database of the National Library of Medicine's TOXNET system, reveals the existence of two relatively recent studies published in the open literature, which indicate that N-methyl-2-pyrrolidone is carcinogenic in mice and teratogenic in rats. In an 18-month dietary study with rats and mice, Malley et al. (2001) report statistically significant increases in liver weight; hepatocellular adenoma; increased foci of cellular alteration in the liver; and increased incidence of hepatocellular carcinoma in male mice. Although no carcinogenic response occurred in rats, a dose-related nephropathy and reduced body weight gain occurred in rats. These are effects similar to those reported for rodents in response to oxyfluorfen exposure (see Appendix 3 for detailed summaries). N-methyl 2-pyrrolidone was also shown to cause developmental toxicity at doses not causing toxicity in adults, in rats (Saillenfait et al. 2001). These studies were conducted by researchers affiliated with established organizations (i.e. DuPont's Haskell Laboratory for Toxicology and Industrial Hygiene; and France's Department of Pollutants and Health, National Institute of Research and Safety, respectively) and published in peer-reviewed scientific journals (Malley et al. 2001; Saillenfait et al. 2001). A more detailed review of these and the other published studies available for N-methyl-2-pyrrolidone is beyond the scope of this document.

"Solvent naphtha (petroleum) heavy aromatic" includes naphthalene, and is listed by the U.S. EPA/OPP (2004b) as a potentially toxic agent with a high priority for testing (List 2). There is a large and complex literature on the toxicity of naphthalene and petroleum solvents in general (e.g., ATSDR 1997) and a detailed review of this literature is beyond the scope of the current document. Nonetheless, the primary effect of naphthalene and petroleum solvents involves CNS

depression and other signs of neurotoxicity that are similar to the effects seen in fish exposed to Goal formulations.

Propylene glycol is listed by U.S. EPA/OPP (2004b) as an inert ingredient for which EPA has sufficient information to reasonably conclude that the current use pattern in pesticide products will not adversely affect public health or the environment (List 4B).

The available acute toxicity data for oxyfluorfen formulations, taken from labels and material safety data sheets, are summarized in Table 3-2. Some of these data correspond with studies reported in Appendix 1. Observations from the acute oral toxicity and dermal irritation studies suggests that the inerts in Goal 2XL and Goal 1.6E may cause acute toxicity and skin irritation observed with these formulations (Appendix 1). Acute oral toxicity studies have been conducted on rats with highly pure technical grade oxyfluorfen as well as with Goal 2XL. No signs of toxicity or mortality were observed in response to the highest dose tested in two studies (Dreher 1995d; Lampe et al. 1988a) with highly pure technical grade oxyfluorfen (NOAEL = 5 g/kg). However, 100% mortality was observed at the same dose in a range-finding study with Goal 1.6E (27% a.i.)(Krzwicki 1983), and decreased body weight gain and mortality was observed in rats exposed to Goal2XL at concentrations of 4 and 5 g/kg (Lutz and Parno 1993a). Dermal irritation studies with highly pure technical grade oxyfluorfen yielded either transient mild irritation (AG510; 97% oxyfluorfen; Dreher 1995b) or no irritation at any observation point (Goal technical herbicide (97.1% a.i.; Lampe et al. 1998c). However, parallel studies with Goal 2XL resulted in moderate to severe erythema and edema 24-72 hours post-treatment, which resolved by day 7 (Lutz and Parno 1993c).

3.1.15. Impurities and Metabolites

As discussed in the previous sections, the technical grade oxyfluorfen used in older studies was of lower purity than the currently available technical grade herbicide. According to U.S. EPA/OPP (2001a), the oxyfluorfen formulations currently manufactured by Agan Chemical Manufacturing Corporation and Rohm and Haas Company use 97.4% and 99% pure technical grade oxyfluorfen, respectively. The Rohm and Haas registration was amended in November of 1999 to increase the oxyfluorfen content from approximately 70% to 99%. As part of the pesticide registration process, U.S. EPA/OPP (2001a) reviewed confidential statements of formula and product chemistry reviews, and determined that the new/current technical grade oxyfluorfen products contain similar profiles of impurities in comparison with the older less pure products, but with lower concentrations.

Developmental toxicity studies and sub-chronic/chronic studies have been conducted with both the older, less pure technical grade oxyfluorfen, and newer, higher purity technical grade oxyfluorfen. As summarized in Appendices 2 (Developmental/Reproductive Toxicity) and 3 (Sub-chronic/Chronic Toxicity), studies conducted with the lower purity compound resulted in either toxicity where none was observed with the higher purity material, or in toxic effect levels which were lower than those observed in parallel tests with the higher purity material. This suggests that some of the impurities in technical grade oxyfluorfen may be responsible for some

of the observed toxicity. Similar conclusions can be drawn with regard to mutagenicity (Appendix 4, and Section 3.1.10.1)

There is no information regarding the toxicity of oxyfluorfen metabolites. Studies with metabolites have not been conducted, most likely due to the observation that oxyfluorfen is primarily eliminated in the urine and feces as unchanged compound, and is not appreciably metabolized (see 3.1.3.1).

3.1.16. Toxicologic Interactions

There is no direct information available on the toxicological interaction of oxyfluorfen with other compounds in animals. However, as noted in Sections 3.1.4 and 3.1.15, there are indications that the impurities, inerts and adjuvants in oxyfluorfen formulations will enhance the toxicity of oxyfluorfen in humans. In particular, N-methyl-pyrrolidone has been associated with cancer and teratogenic effects, and solvent naptha inerts have been associated with effects on the liver and central nervous system.

As discussed in Section 3.1.2, oxyfluorfen inhibits heme biosynthesis. As heme groups are essential to cytochrome function, and because cytochromes are important in metabolic processes, this inhibition could affect the metabolism of compounds mediated by cytochromes, such as cytochrome p450. The nature of the impact would depend on the specific compounds involved and could depend on the sequence of exposure.

3.2.EXPOSURE ASSESSMENT

3.2.1. Overview

The exposure assessments for oxyfluorfen are summarized in Worksheet E01 for workers and Worksheet E02 for the general public. All exposure assessments are conducted at the typical application rate for oxyfluorfen of 1 lb/acre. The consequences of using lower or higher application rates are discussed in the risk characterization (Section 3.4). For workers applying oxyfluorfen, three types of application methods are modeled: directed ground spray, broadcast ground spray, and aerial spray. Of these, broadcast ground spray is the method of application that is most likely to be used in Forest Service applications. Aerial applications are not anticipated in Forest Service programs but are included as part of the standard set of exposure assessments used in Forest Service risk assessments in the event that aerial applications might be considered at some point in the future.

Central estimates of exposure for workers are approximately 0.014 mg/kg/day for aerial and backpack workers and about 0.022 mg/kg/day for broadcast ground spray workers. Upper ranges of exposures are approximately 0.15 mg/kg/day for broadcast ground spray workers and 0.08 mg/kg/day for backpack and aerial workers. All of the accidental exposure scenarios for workers involve dermal exposures. Most of these accidental exposures lead to estimates of dose that are in the range of the general exposure estimates for workers. The one exception involves wearing contaminated gloves for one-hour. The upper range of exposure for this scenario is about 2.5 mg/kg bw.

For the general public, the range for acute exposures is about 0.00001 mg/kg bw to about 1.35 mg/kg bw. The upper bound of exposure is associated with the consumption of contaminated vegetation. For chronic or longer term exposures, the modeled exposures are lower than corresponding acute exposures by about a factor of 10. As in acute exposures, the highest longer term exposure is associated with the consumption of contaminated vegetation and the upper range of the estimated dose is about 0.17 mg/kg/day. Because oxyfluorfen is used in tree nurseries that are generally not located in populated or recreational areas, the plausibility of exposures associated with consumption of contaminated vegetation may be low and this supposition does have a substantial impact on the risk characterization. Exposures associated with the longer term consumption of water are very low, with an upper range of about 0.0007 mg/kg/day. Because oxyfluorfen may substantially bioconcentrate in fish, these exposures are much higher – i.e., an upper range of about 0.014 mg/kg/day – than those associated with contaminated water.

3.2.2. Workers

The Forest Service uses a standard set of exposure assessments in all risk assessment documents. While these exposure assessments vary depending on the characteristics of the specific chemical as well as the relevant data on the specific chemical, the organization and assumptions used in the exposure assessments are standard and consistent. All of the exposure assessments for worker as well as members of the general public are detailed in the worksheets on oxyfluorfen that accompany this risk assessment [SERA EXWS 05-43-26-01b]. Detailed documentation for these worksheets is presented in SERA (SERA 2005). This section on workers and the following

section on the general public provide a plain verbal description of the worksheets and discuss oxyfluorfen specific data that are used in the worksheets.

A summary of the exposure assessments for workers is presented in Worksheet E01 of the worksheets. Two types of exposure assessments are considered: general and accidental/incidental. The term *general* exposure assessment is used to designate those exposures that involve estimates of absorbed dose based on the handling of a specified amount of a chemical during specific types of applications. The accidental/incidental exposure scenarios involve specific types of events that could occur during any type of application. The exposure assessments developed in this section as well as other similar assessments for the general public (Section 3.2.3) are based on the typical application rate of 1 lb a.i./acre (Section 2). The consequences of using different application rates in the range considered by the Forest Service are discussed further in the risk characterization (Section 3.4).

3.2.2.1. General Exposures – As described in SERA (2001), worker exposure rates are expressed in units of mg of absorbed dose per kilogram of body weight per pound of chemical handled. These estimates are derived from biomonitoring studies – i.e., studies in which the estimates of absorbed dose are based on measurements of the amount of pesticides excreted by workers. Based on analyses of several different pesticides using a variety of application methods, default exposure rates are estimated for three different types of applications: direct foliar (backpack), boom spray (hydraulic ground spray), and aerial. The general exposure rates used for each group of workers are:

directed foliar	0.003	(0.0003 - 0.01)	mg/kg per lb a.i. handled/day
boom spray	0.0002	(0.00001 - 0.0009)	mg/kg per lb a.i. handled/day
aerial	0.00003	(0.000001 - 0.0001)	mg/kg per lb a.i. handled/day.

General studies of workers involved in nursery applications have been conducted by Lavy (Lavy 1990; Lavy et al. 1993). While these studies generally suggest that nursery workers are not exposed to hazardous levels of pesticides, specific exposure rates for oxyfluorfen are not derived. Thus, the standard absorbed dose rate estimates given above are used to calculate the absorbed doses for workers in ground broadcast applications (Worksheet C01b) and aerial applications (Worksheet C01c).

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.

As summarized in Section 3.1.11, oxyfluorfen and oxyfluorfen formulations may cause slight irritation to the eyes. The available literature does not include quantitative methods for characterizing exposure or responses associated with splashing a solution of a chemical into the

eyes. Consequently, accidental exposure scenarios of this type are considered only qualitatively in the risk characterization (Section 3.4).

Various methods are available for estimating absorbed doses associated with accidental dermal exposure (U.S. EPA/ORD 1992; SERA 2001). Two general types of exposure are modeled: those involving direct contact with a solution of the herbicide and those associated with accidental spills of the herbicide onto the surface of the skin. Any number of specific exposure scenarios could be developed for direct contact or accidental spills by varying the amount or concentration of the chemical on or in contact with the surface of the skin and by varying the surface area of the skin that is contaminated. These variables are discussed below.

Two exposure scenarios are developed for each of the two types of dermal exposure, and the estimated absorbed dose for each scenario is expressed in units of mg chemical/kg body weight. Both sets of exposure scenarios are summarize in Worksheet E01, which references other worksheets in which the specific calculations are detailed. Exposure scenarios involving direct contact with solutions of the chemical are characterized by immersion of the hands for 1 minute or wearing contaminated gloves for 1 hour. Generally, it is not reasonable to assume or postulate that the hands or any other part of a worker will be immersed in a solution of a herbicide for any period of time. On the other hand, contamination of gloves or other clothing is quite plausible. For these exposure scenarios, the key element is the assumption that wearing gloves grossly contaminated with a chemical solution is equivalent to immersing the hands in a solution. In either case, the concentration of the chemical in solution that is in contact with the surface of the skin and the resulting dermal absorption rate are essentially constant.

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

3.2.3. General Public

3.2.3.1. General Considerations **–** Under normal conditions, members of the general public should not be exposed to substantial levels of oxyfluorfen. 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 standard exposure scenarios for members of the general public that are included in Forest Service risk assessments are developed in this section.

Both acute and longer-term or chronic exposure scenarios are developed. 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.

One important factor specific to oxyfluorfen involves the acute and chronic exposure scenarios consumption of contaminated vegetation. Many herbicides used by the Forest Service are applied by either aerial or ground broadcast in areas that may contain edible vegetation (e.g., berries) that may be consumed by members of the general public. As noted in Section 2, however, virtually all applications of oxyfluorfen are made within tree nurseries. Tree nurseries basically consist rows of trees, mostly very small, that are cultivated much in the same way as crops. While herbicides such as oxyfluorfen are used in these areas to prevent weeds, tree nurseries will not typically contain vegetation that members of the general public might harvest and consume. However, it is possible that residences may be found in proximity to Forest Service land, and that these residences may have fruit trees or vegetable gardens. Consequently, while the standard exposure scenarios for the consumption of contaminated vegetation are included in this section, they may be only marginally plausible for oxyfluorfen and this is discussed further in the risk characterization (Section 3.4).

All of the exposure scenarios developed for the general public are summarized in Worksheet E02 of the EXCEL workbook that accompanies this risk assessment. As with the worker exposure scenarios, details of the assumptions and calculations involved in these exposure assessments are given in individual worksheets (Worksheets D01a–D10b). The remainder of this section focuses on a qualitative description of the rationale for and quality of the data supporting each of the assessments.

3.2.3.2. Direct Spray – Direct sprays involving ground applications are modeled in a manner similar to accidental spills for workers (Section 3.2.2.2). In other words, it is assumed that the individual is sprayed with a solution containing the compound and that an amount of the compound remains on the skin and is absorbed by first-order kinetics. For these exposure scenarios, it is assumed that during a ground application, a naked child is sprayed directly with oxyfluorfen. These scenarios also assume that the child is completely covered (that is, 100% of the surface area of the body is exposed) (Worksheet D01a). These are extremely conservative exposure scenarios and are likely to represent upper limits of plausible exposure. An additional set of scenarios are included involving a young woman who is accidentally sprayed over the feet and legs (Worksheet D01b). For each of these scenarios, specific assumptions are made regarding the surface area of the skin and body weight as detailed in Worksheets D01a and D01b along with the sources used for making the assumptions.

3.2.3.3. Dermal Exposure from Contaminated Vegetation – In this exposure scenario, it is assumed that the herbicide is applied at a given 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. 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 data are available on dermal transfer rates for oxyfluorfen and the estimation methods of Durkin et al. (1995) are used as defined in Worksheet D02 of the workbooks for liquid and granular formulations. The exposure scenario assumes a contact period of one hour and assumes that the chemical is not effectively removed by washing until 24 hours after exposure. Other estimates used in this exposure scenario involve estimates of body weight, skin surface area, and first-order dermal absorption rates, as discussed in the previous section. Data are available on dislodgeable residues of oxyfluorfen after applications of Goal formulation to loblolly pine and ponderosa pine (Massey 1990). As summarized in Appendix 11, the dislodgeable residues as a proportion of the application rate ranged from 0.027 to 0.07. Typically, Forest Service risk assessments use a somewhat higher default value of 0.1. This somewhat higher value is reasonably close to the 0.07 value reported by Massey (1990) and a value of 0.1 is used in this risk assessment. As noted in Section 3.4, this modestly conservative approach has no impact on the risk characterization.

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 drift during an application. For this risk assessment, three exposure scenarios are considered for the acute consumption of contaminated water: an accidental spill into a small pond (0.25 acres in surface area and 1 meter deep), accidental direct spray of or incidental drift into a pond and stream, and the contamination of a small stream and pond by runoff, sediment loss, or percolation. In addition, longer-term estimates of concentrations in water are based on a combination of modeling and monitoring data. Each of these scenarios are considered in the following subsections.

3.2.3.4.1. Accidental Spill – 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 the pesticide is considered. This scenario is dominated by arbitrary variability and the specific assumptions used will generally overestimate exposure. The actual concentrations in the water would depend heavily on the amount of compound spilled, the size of the water body into which it is spilled, the time at which water consumption occurs relative to the time of the spill, and the amount of contaminated water that is consumed.

For liquid formulations, Forest Service risk assessments use a standard scenario – the spill of 200 gallons of a *field solution* – i.e., the pesticide diluted with water to the concentration that is anticipated in Forest Service programs (Section 2). Based on the spill scenario for a liquid formulation at an application rate of 1 lbs/acre, the concentration of oxyfluorfen in a small pond is estimated to range from about 0.6 mg/L to 1.5 mg/L with a central estimate of 1 mg/L (Worksheet D05). These concentrations are linearly related to application rate as illustrated in the accidental spill concentrations for Worksheets G03a-c.

3.2.3.4.2. Accidental Direct Spray/drift for a Pond or Stream – These scenarios are less severe but more plausible than the accidental spill scenario described above. The U.S. EPA typically uses a two meter deep pond to develop exposure assessments (SERA 2004). If such a pond is directly sprayed with oxyfluorfen at the nominal application rate of 1 lbs/acre, the peak concentration in the pond would be about 0.06 mg/L (Worksheet D10a). This concentration is a factor of about 17 below the upper bound of the peak concentration of 1 mg/L after the accidental spill. The D05 worksheets also model concentrations at distances of 100 to 500 feet down wind based on standard values adapted from AgDrift (SERA 2005).

Similar calculations can be made for the direct spray of or drift into a stream. For this scenario, the resulting water concentrations will be dependant on the surface area of the stream that is sprayed and the rate of water flow in the stream. The stream modeled using GLEAMS (see below) is about 6 feet wide (1.82 meters) and it is assumed that the pesticide is applied along a 1038 foot (316.38 meters) length of the stream with a flow rate of 710,000 L/day. Using these values, the concentration in stream water after a direct spray is estimated at about 0.09 mg/L. Much lower concentrations, about 0.01 mg/L to 0.00008 mg/L, are estimated based on drift at distances of 25 to 900 feet (Worksheet 10b).

3.2.3.4.3. Gleams Modeling – In addition to drift and direct spray, water contamination may occur from soil runoff, sediment, or percolation. Depending on local conditions, these losses can lead to substantial contamination of ponds or streams. Estimates of concentrations of oxyfluorfen in surface waters is based both on modeling and monitoring data. This section describes the relatively standardized modeling approach used in Forest Service risk assessments. This is followed by subsections on both other modeling efforts and the available monitoring data.

Modeling of concentrations in stream water conducted for this risk assessment are based on GLEAMS (Groundwater Loading Effects of Agricultural Management Systems) modeling. GLEAMS is a root zone model that can be used to examine the fate of chemicals in various types of soils under different meteorological and hydrogeological conditions (Knisel and Davis 2000). As with many environmental fate and transport models, the input and output files for GLEAMS can be complex. The general application of the GLEAMS model and the use of the output from this model to estimate concentrations in ambient water are detailed in SERA (2004).

For the current risk assessment, the application site consists of a 10 hectare square area that drains directly into a small pond or stream. The chemical specific values as well as the details of the pond and stream scenarios used in the GLEAMS modeling are summarized in Table 3-3.

The GLEAMS modeling yielded estimates of runoff, sediment and percolation that were used to calculate concentrations in the stream adjacent to a treated plot, as detailed in Section 6.4 of SERA (2004). The results of the GLEAMS modeling for the small stream are summarized in Table 3-3 and the corresponding values for the small pond are summarized in Table 3-4. These estimates are expressed as both average and maximum concentrations in water. Each table gives the water contamination rates (WCR) – i.e., the concentration of the compound in water in units

of ppb (µg/L) normalized for an application rate of 1 lb/acre. For oxyfluorfen, 1 lb/acre is also the typical application rate.

No surface water contamination is estimated in very arid regions – i.e., annual rainfall of 10 inches of less. At higher rainfall rates, the modeled peak concentrations in streams range from negligible (sand at an annual rainfall rates up to 100 inches) to about 180 ppb (clay soil at an annual rainfall rate of 250 inches per year) (Table 3-4). Modeled peak concentrations in a small pond (Table 3-5) are only somewhat lower than those modeled in the stream. As with the stream modeling, no surface water contamination is expected in very arid regions. For regions with annual rainfall rates of 15 inches or more, the modeled peak concentrations in ponds range from negligible (sand at annual rainfall rates of up to 150 inches) to about 60 ppb (loam soil at an annual rainfall rate of 250 inches per year).

The GLEAMS scenarios do not specifically consider the effects of accidental direct spray. As discussed in Section 3.2.3.4.2, direct spray of a standard pond could result in peak concentrations of about 60 ppb, identical to the peak concentration modeled in ponds as a result of contamination associated with severe rainfall events. For a small stream, the peak concentrations based on GLEAMS modeling (180 ppb) are higher than those estimated for a direct spray (90 ppb or 0.09 mg/L).

3.2.3.4.4. Other Modeling Efforts – A summary of the GLEAMS modeling discussed above as well as modeling of oxyfluorfen conducted by the U.S. EPA/OPP (2001b) is given in Table 3-6. U.S. EPA/OPP (2001b) conducted two modeling efforts, one using PRZM/EXAMS and SCI-GROW and the other using Sci-Grow. As discussed in SERA (2004), these are models developed by the U.S. EPA that are intended to provide estimates of concentrations of a compound in surface water (PRZM/EXAMS) and groundwater (Sci-Grow).

The U.S. EPA/OPP (2001b) conducted several PRZM/EXAMS runs for different agricultural applications and elected to use the results of the scenario for applications to apples in Oregon because this resulted in the highest modeled concentrations of oxyfluorfen in pond water. As indicated in Table 3-6, the peak concentration modeled by U.S. EPA is 11.7 ppb per lb a.i./acre. This is only somewhat below the typical peak concentrations modeled using GLEAMS (Table 3-4). Similarly, the longer term concentrations modeled by U.S. EPA are in the range of 2.85 to 3.55 ppb, which are again in the lower range of longer term concentrations in ponds modeled using GLEAMS. The U.S. EPA/OPP (2001b) modeled much lower concentrations in ground water – i.e., 0.04 ppb. The current Forest Service risk assessment does not explicitly model ground water concentrations. As discussed further in Section 4.2, however, the GLEAMS modeling indicates that very little oxyfluorfen is likely to leach into the soil column under most conditions. The only substantial exception is when oxyfluorfen is applied to predominantly sand soils in areas with high rainfall rates. Thus, except for these conditions, very little contamination of ground water would be anticipated.

3.2.3.4.5. Monitoring Data – Relevant monitoring studies on oxyfluorfen in surface water are summarized in Table 3-6 and the details of these most of these studies are provided in Appendix 12. Several of these studies (Camper et al. 1994; Keese et al. 1994; Riley et al. 1994) are directly relevant to this risk assessment because they involve monitoring of pond water after the application of oxyfluorfen in tree nurseries.

The correspondence between the GLEAMS modeling and the monitoring data from ponds in tree nurseries is striking. The peak concentration of 40 ppm reported by Riley et al. (1994) at an application rate of 2 lbs a.i./acre is virtually identical (when adjusted for differences in application rate) to the typical value from GLEAMS, 20 ppm at an application rate of 1 lb/acre. The peak value reported by Keese et al. (1994) – i.e., 147 ppb at an application rate of 2 lbs/acre – normalizes to a concentration of 73.5 ppb for an application rate of 1 lb/acre. This is only modestly higher than the 57 ppb maximum value modeled using GLEAMS. Similarly, the monitoring studies of longer term concentrations in streams reported by U.S. EPA/OPP (2001b) report concentrations in the range of 0.1 to 1 ppb. These concentrations are encompassed by and very similar to the 0.03 to 1.2 ppb range of longer-term concentrations in streams modeled using GLEAMS.

As with any comparison of modeling and monitoring studies, the apparent correspondence of the modeling and monitoring may be fortuitous. Nonetheless, the correspondence between the GLEAMS modeling and the monitoring studies as well as the consistency of the GLEAMS modeling with the modeling efforts by U.S. EPA/OPP (2001b) enhances confidence in the use of the results from GLEAMS for the current risk assessment.

3.2.3.4.6. Concentrations in Water Used for Risk Assessment – A summary of the concentrations of oxyfluorfen in water that are used for the current risk assessment is given in Table 3-7. The upper part of this table gives the concentrations expected at the typical application rate of 1 lbs a.i./acre in units of micrograms per liter or ppb. The lower part of this table gives the water contamination rates, the normalized concentrations in water converted to units of ppm or mg/L per lb a.i./acre. These latter values are used in the worksheets in the various exposure scenarios involving contaminated water in both the human health and ecological risk assessments.

For oxyfluorfen, the typical application rate is 1 lb/acre and thus the top and bottom sections of Table 3-7 present the same concentrations. The only difference is that the bottom section presents the concentrations in units of mg/L or ppm rather than ug/L or ppb. This conversion of units is necessary because, by convention, the worksheets used in Forest Service risk assessments always present concentrations in water in units of ppm.

The upper range of the expected peak concentration of oxyfluorfen in surface water is taken as 200 ppb/L at the typical application rate of 1 lbs/acre. This corresponds to a water contamination rate of 0.2 mg/L per lb/acre. This is based on the upper range of concentrations estimated in streams from the GLEAMS modeling. As noted in Section 3.2.3.4.5, the monitoring study in ponds by Keese et al. (1994) suggests a water contamination rate of about 0.073 mg/L per lb/acre

and this is somewhat higher than the peak concentrations in ponds modeled using GLEAMS. Thus, the water contamination rate of 0.2 mg/L per lb/acre based on modeling of streams will encompass both the pond modeling as well as pond monitoring data. This concentration also encompasses accidental direct sprays of both a small stream and small pond (Table 3-6).

In most instances, concentrations in surface water are likely to be much lower. At the lower extreme, an argument may be made that concentrations of oxyfluorfen are likely to be essentially zero – i.e., applications at sites that are distant from open bodies of water and in areas in which runoff or percolation are not likely to occur. For this risk assessment, the lower range of the peak water contamination rate will be set at 0.2 ppb or 0.0002 mg/L per lb/acre. This is in the lower range of non-zero concentrations modeled in streams and ponds in relatively arid regions. The central estimate of the peak water contamination rate will be taken as 30 ppb or 0.03 mg/L per lb/acre. This is based on the estimate of the peak concentrations modeled in ponds in areas with clay soil and relatively high rainfall rates.

Most longer term concentrations of oxyfluorfen in surface water will be much lower than peak concentrations. At an application rate of 1 lb/acre, the highest longer term concentration will be taken as 20 ppb or 0.02 mg/L. This is somewhat higher than the maximum longer term concentration modeled using GLEAMS. As with peak concentrations, the lower range of longer term concentrations will approach zero. For this risk assessment, the lower range of longer term concentrations is taken as 0.0002 mg/L per lb/acre. This is based on the concentrations of non-zero values modeled for oxyfluorfen in ponds in areas of predominantly clay or loam soils (Table 3-4). This lower range is arbitrary but has no impact on the risk assessment. The central value for longer term concentrations of oxyfluorfen in water will be taken as 3 ppb or 0.003 mg/L per lb/acre. This is about the mid-range of the central estimates of the longer term concentrations in ponds and streams modeled using GLEAMS.

As noted in Table 3-6, these water contamination rates are likely to encompass non-accidental exposures – i.e., concentrations in water that could be associated with the normal application of oxyfluorfen. Much higher concentrations could occur by accident. These are discussed above in Section 3.2.3.4.1.

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 and is expressed in units of L/kg.

Only one study, Reibach (1990b), has been encountered on the bioconcentration of oxyfluorfen. As summarized in Appendix 11 (page 11-7), bluegill sunfish were exposed to a nominal concentration of 0.01 mg/L of ^{14}C-oxyfluorfen for 40 days followed by a 14 day depuration period. Two sets of studies were conducted, one using a CF_3 position label and a nitrophenyl position label. While the results are similar (Appendix 11), the average BCF values based on the nitrophenyl label are somewhat higher and these values are used in the current risk assessment. It

should be noted that BCF values based on ^{14}C radio-label data will include any metabolites and tend to be higher than BCF data based upon chemical analyses of the parent compound.

For the edible portion (i.e., the muscle), the first measurement of bioconcentration is reported on Day 1 of the study with a value of 0.24 L/kg based on measured concentrations in both fish muscle and water. At equilibrium, the maximum concentration in the edible portion is reported as 605 L/kg. For all human exposures involving the consumption of contaminated fish, a BCF value of 0.24 L/kg is used for acute exposures and a BCF value of 605 L/kg is used for longer-term exposures.

Reibach (1990b) also provides data on concentrations of oxyfluorfen in the viscera and whole fish and the values for viscera are higher than those for whole fish. In the ecological risk assessment, the values for whole fish are used for all exposures involving contaminated fish:0.5 L/kg for acute exposures and 2200 L/kg for longer-term exposures.

For the acute and longer-term exposure scenarios involving the consumption of contaminated fish, the water concentrations of oxyfluorfen used are identical to the concentrations used in the contaminated water scenarios (Section 3.2.3.4.6). The acute exposure scenario is based on the assumption that an adult angler consumes fish taken from contaminated water shortly after an accidental spill into a pond.

Because of the available and well-documented information and substantial differences in the amount of caught fish consumed by the general public and native American subsistence populations, separate exposure estimates are made for these two groups, as illustrated in Worksheet D08a and D08b. The chronic exposure scenario is constructed in a similar way, as detailed in Worksheets D09a and D09b.

3.2.3.6. Oral Exposure from Contaminated Vegetation – Although none of the Forest Service applications of oxyfluorfen will involve the treatment of crops, Forest Service risk assessments typically include standard exposure scenarios for the acute and longer-term consumption of contaminated vegetation. As noted in Section 3.2.3.1, these exposure scenarios may be only marginally relevant for oxyfluorfen because applications of oxyfluorfen will occur almost exclusively on tree nurseries which will not typically contain vegetation that members of the general public might harvest and consume. Nonetheless, these standard exposure scenarios are included in the current risk assessment in the event that residences are in proximity to Forest Service land, and to illustrate the consequences of consuming contaminated vegetation, as discussed further in Section 3.4.

Two sets of exposure scenarios are provided: one for the consumption of contaminated fruit and the other for the consumption of contaminated vegetation. These scenarios are detailed in Worksheets D03a and D03b for acute exposure and Worksheets D04a and D04b for chronic exposure. In most Forest Service risk assessment, the concentration of the pesticide on contaminated fruit and vegetation is estimated using the empirical relationships between application rate and concentration on different types of vegetation (Fletcher et al. 1994). This is

identical to the approach used by U.S. EPA/OPP (2001b). For the current risk assessment, the standard residue rates from Fletcher et al. (1994) are used.

For chronic exposures, both initial concentrations and a halftime on vegetation are required to estimate the time-weighted average exposure (Worksheet D04). As noted in Table 3-3, a halftime of 8 days is used based on the recommended value for GLEAMS modeling (Knisel and Davis 2000). This value may overestimate longer term concentrations for some types of vegetation. As summarized in Appendix 12, much shorter halftimes (in the range of 0.5 days to less than two days) have been reported by Massey (1990) and Frank et al. (1991). Selecting the longer (i.e., more protective) halftime does have an impact on the risk characterization (makes it more health protective), as discussed further in Section 3.4.

3.3. DOSE-RESPONSE ASSESSMENT

3.3.1. Overview

Following standard practices for Forest Service risk assessments, the RfD values and estimates of carcinogenic potency derived by U.S. EPA are used in this risk assessment. U.S. EPA currently has two different chronic RfD values for oxyfluorfen. One value is presented in the Integrated Risk Information System, and the other is presented by U.S. EPA/OPP (2001a, 2002a).

U.S. EPA/OPP has derived a chronic RfD for oxyfluorfen of 0.03 mg/kg/day to assess risks associated with chronic systemic toxicity. This RfD is well-documented and is used directly for all longer term exposures to oxyfluorfen. This value is based on a NOAEL of 3 mg/kg/day in dogs (Rohm and Haas 1981) and mice (Goldenthal and Wazeter 1977), and an uncertainty factor of 100 – two factors of 10 for interspecies and intraspecies variability. The studies from which the NOAEL is derived, summarized in Appendix 3 (page 3-6), used lower purity technical grade oxyfluorfen.

U.S. EPA/OPP (2001a) did not to derive an acute RfD for oxyfluorfen because no adverse effects reflecting a single dose were identified at the highest dose tested in the studies available at the time EPA/OPP (2001a) made this decision. However, a study from the published literature in which mice were shown to develop signs similar to human variegate porphyria following short-term dietary exposure to oxyfluorfen (Krijt 1997) can be used as the basis for a surrogate acute RfD. Dividing the NOAEL of 19.8 mg/kg from Krijt (1997) by an uncertainty factor of 100 (factors of 10 each for intra- and inter-species variability) yields a surrogate acute RfD of 0.20 mg/kg.

U.S. EPA/OPP (2001a) has derived a carcinogenic potency factor (Q1*) of 0.0732 $(mg/kg/day)^{-1}$ for oxyfluorfen. This value is based on combined hepatocellular adenomas and carcinomas observed in male mice in the chronic toxicity/carcinogenicity study of Goldenthal and Wazeter (1997). This value is used to assess risks associated with a one-in-one-million chance of developing cancer over a period of longer-term exposure.

3.3.2. Chronic RfD

The U.S. EPA has derived two different chronic RfD values for oxyfluorfen. One value appears on IRIS. The other was derived by U.S. EPA/OPP (2001a) in the Registration Eligibility Document for Oxyfluorfen.

The U.S. EPA RfD for oxyfluorfen listed on IRIS is 0.003 mg/kg/day (U.S. EPA 1987). This is based on the 20-month mouse dietary study of Goldenthal and Wazeter (1977) summarized in Appendix 3 (cited as "Rohm & Haas, 1977a" in IRIS). This RfD is based on a NOAEL of 0.3 mg/kg/day (2 ppm dietary exposure) and a LEL of 3 mg/kg/day (20 ppm dietary exposure: based ostensibly on increased absolute liver weight; hyperplastic nodules in the liver; and increased incidence of effects at 200 ppm). Dividing the NOAEL of 0.3 by an uncertainty factor of 100 (two factors of 10; one for inter-species variability; one for intra-species variability) yields the RfD of 0.003 mg/kg/day. However, using the same study, U.S. EPA/OPP (2001a) derived an RfD of 0.03 mg/kg/day for chronic exposure. U.S. EPA/OPP identifies a NOAEL of 3

mg/kg/day (20 ppm) a LOAEL of 33-42 mg/kg/day (200 ppm; lower dose is for males, higher dose is for females), and used the same uncertainty factor of 100 that U.S. EPA (1987) used to derive their RfD. U.S. EPA/OPP (2001a; 2002a) use the NOAEL of 3 mg/kg from the 52-week dog study (Appenix 3: Piccirillo 1977; Rohm and Haas 1981, as cited in U.S. EPA 2001a and U.S. EPA 1987) to support this choice. The basis for the difference in RfD values is not apparent upon examination of the documentation provided by U.S. EPA (2001a) and U.S. EPA (1987). An examination of the Goldenthal and Wazeter (1997) study clearly supports the selection of a NOAEL of 3 mg/kg/day (20 ppm dietary exposure). There were no statistically significant and treatment-related changes observed at this level. The only statistically significant and treatment-related changes were observed at the 200 ppm level of exposure, supporting the conclusion drawn by U.S. EPA/OPP (2001a; 2002a) that 3 mg/kg/day is the NOAEL for the study, and hence, the appropriate basis for a chronic RfD of 0.03 mg/kg/day.

This risk assessment uses the chronic RfD of 0.03 mg/kg/day derived by U.S. EPA (2001a; 2002a) to assess risks associated with longer term/chronic exposure to oxyfluorfen.

3.3.3. Acute RfD

U.S. EPA (2001a; 2002a) did not derive an acute RfD for oxyfluorfen because *"appropriate toxicity attributable to a single-dose was not identified"* (U.S. EPA/OPP 2001a, pp. 14). The acute toxicity studies with highly pure technical grade oxyfluorfen yielded NOAEL values at the test limits, and developmental toxicity studies were unsuitable for various reasons. U.S. EPA/OPP 2001a states: "*The HIARC considered a 1997 developmental toxicity study in rabbits (MRID 44933102 [Burns 1997a, Appendix 2]) using the 98% technical oxyfluorfen which is currently registered. The developmental NOAEL in this study was based on increased late resorptions and resulting decreased number of live fetuses/doe in the high-dose group. This endpoint was not considered appropriate for use in risk assessment because the late resorptions were primarily due to late resorptions in one doe and were not statistically significant. The 1981 developmental toxicity study in rabbits (MRID 00094052 {actually there are two studies: Hoberman et al. 1981, 1982, Appendix 2}) was not considered suitable as an endpoint because it used a 26.9% wettable powder formulation from the 71% a.i. technical material which is no longer manufactured."*

Examination of the Burns (1997a) study on rabbits reveals that delayed skeletal ossification, decreased mean litter weights and delayed fetal head development were observed among the fetuses born to high-dose (90 mg a.i./kg/day) dams. Dams at this level of exposure had decreased food intake accompanied by decreased fecal output. None of these effects, on pregnant females or fetuses, were seen at the lower doses (10 or 30 mg a.i./kg/day), and the NOAEL for this study is 30 mg a.i./kg.

However, a short-term dietary study in the open literature(Krijt et al. 1997) indicates that a lower NOAEL should be used. Krijt (1997) fed mice highly pure technical grade oxyfluorfen in the diet for 9 days at concentrations of 125, 200 and 1000 ppm. In comparison with pre-test control levels, statistically significant reductions in protoporphyrinogen oxidase activities in kidney and liver tissues, accompanied by significant increases in liver and kidney porphyrin concentrations,

were seen in mice exposed to 200 and 1000 ppm in the diet. This yields a NOAEC of 200 ppm. Using the mid-point of the range (22-24 g) of experimentally determined mouse body weight (23 g), and the allometric equation provided in the U.S. EPA's Wildlife Exposure Factors Handbook (U.S. EPA 1993, Section 3.1.2, Allometric Equations, Mammals, page 3-6, equation 3-8, food ingestion equation for rodents), it is possible to determine a dose associated with this dietary concentration. Assuming a body weight of 23 grams and that food ingestion rate = 0.061 x $bw^{0.564}$, a dietary concentration of 200 ppm is equivalent to a dose of 19.8 mg/kg/day. Dividing the NOAEL of 19.8 mg/kg/day by an uncertainty factor of 100 (a factor of 10 each to account for differences in sensitivity within the species, and for differences between mice and humans), and rounding to two significant figures, yields a surrogate acute RfD, based on high purity technical grade oxyfluorfen, of 0.20 mg/kg/day.

Based on knowledge of usual EPA/OPP risk assessment methodology, it is possible to conclude that EPA/OPP would not have used the Krijt (1997) study to derive an acute RfD because exposure entailed administration of more than a single dose (i.e. was dietary exposure over a nine-day period). However, this assessment uses the Krijt et al. (1997) study as the basis for a surrogate acute RfD in a conservative attempt to quantify potential effects associated with short-term exposures.

3.3.4. Carcinogenic Potency Factor

U.S. EPA quantifies cancer risk from experimental data through the use of models which estimate a relationship between risk and dose. In most cases, the potency factor is an upper bound limit (e.g. upper 95% confidence limit) on a linearized extrapolation of risk from dose.

Lower purity technical grade oxyfluorfen (85.7% a.i.) has been tested in three chronic feeding studies: one with mice (Goldenthal and Wazeter 1977), one with rats (Auletta et al. 1978) and one with dogs (Rohm and Haas 1981c). The Auletta et al. (1978) study is flawed for many reasons, as discussed in Section 3.3.1, and is not useful in determining whether treatment-related increases in the incidence of tumors occurred in rats. No treatment-related tumors were observed in the dog study. However, a dose-related increase in the incidence of combined hepatocellular adenomas and carcinomas was observed in the mouse study (Goldenthal and Wazeter 1977). Recalling that greater systemic toxicity has been observed with lower purity technical grade oxyfluorfen than with the higher purity herbicide, and given that this study was conducted with lower purity oxyfluorfen, it is not clear whether the oxyfluorfen or the impurities present in the technical grade mixture are actually responsible for the observed outcome.

On the basis of the Goldenthal and Wazeter (1977) study, the U.S. EPA/OPP (2001a) classifies oxyfluorfen as a Class C, possible human carcinogen, and has derived a potency factor of 0.0732 per mg/kg/day. The potency factor is used in this assessment to evaluate potential one-in-one million cancer risks associated with longer-term oxyfluorfen exposure. That said, it is important to keep in mind that the basis for currently registered oxyfluorfen formulations, is the higher purity, generally less toxic, technical grade compound (>95% a.i.) which has never been tested in a long-term cancer bioassay, nor identified as a potential carcinogen in any human case studies or epidemiology studies. On the other hand, that at least one of the inerts known to be present in

oxyfluorfen formulations, N-methyl-pyrrolidone, has been shown to cause the same carcinogenic effect (i.e. increased incidence of hepatocellular adenoma and carcinoma) in mice which was attributed to oxyfluorfen in the Goldenthal and Wazeter (1977) study (see Section 3.1.14 for detailed discussion of inerts).

3.4. RISK CHARACTERIZATION

3.4.1. Overview

In this assessment, risks associated with 1) systemic toxicity; and 2) potential one-in-one million cancer risk are estimated for workers and members of the general public. These risks are presented in detail in the worksheets in Attachment 1 (EXCEL worksheets for Human Health and Ecological Risk Assessments). Summaries of scenarios associated with risks which exceed levels of concern (i.e. HQ values >1) are presented in Tables 3-8 (workers) and 3-9 (general public).

Central and upper bound estimates of risks due to systemic toxicity indicate that workers with contaminated gloves (i.e. leaky or loose gloves which allow the hand to be immersed in herbicide) or not wearing appropriate protective equipment may be at greatest risk due to acute exposure to oxyfluorfen, regardless of application rate.

For members of the general public, the acute exposure scenarios resulting in hazard quotients for systemic toxicity that exceed a level of concern (HQ>1), involve an accidental spill into a small pond, direct spray of a small child, and consumption of contaminated fruit and vegetation by an adult female. Of these scenarios, the only non-accidental acute scenarios which result in hazard quotients that substantially exceed the level of concern are those associated with longer-term exposure to contaminated vegetation after the application of oxyfluorfen at either the typical (1 lb/acre) or maximum (2 lbs/acre) application rates. For members of the general public, the only exposure scenarios resulting in greater than one-in-one-million cancer risk are for adult females consuming contaminated vegetation. While these scenarios yield risks which exceed a level of concern, they are not likely to occur in remote areas where residences are distant from Forest Service land.

Given that oxyfluorfen inhibits protoporphyrinogen oxidase, individuals who are innately deficient in protoporphyrinogen oxidase (i.e. have variegate porphyria) might be uniquely sensitive to oxyfluorfen exposure.

3.4.2. Workers

A quantitative summary of the characterization of risks associated with systemic toxicity and potential carcinogenic risk are presented in the "E" series worksheets in Attachment 1 as follows: Worksheet E02ai (typical application rate), Worksheet E02bi (lowest anticipated application rate), and Worksheet E02ci (highest anticipated application rate) characterize risks associated with systemic toxicity. Worksheet E02aii (typical application rate), Worksheet E02bii (lowest anticipated application rate) and Worksheet E02cii (highest anticipated application rate) address risks associated with a potential one-in-one million cancer risk. A summary of the exposure scenarios which result in hazard quotients exceeding a level of concern (i.e., HQ >1) is shown in Table 3-8.

3.4.2.1. Systemic Toxicity – The quantitative risk for systemic toxicity is expressed as the hazard quotient, which is the ratio of the estimated exposure from Worksheet E01 to the RfD. A hazard quotient which exceeds one indicates that adverse health effects are plausible. For acute accidental/incidental exposures (i.e. contaminated glove and accidental spills on the hands or

lower legs), the acute RfD of 0.2 mg/kg is used (Section 3.3.3). For longer term general exposures – i.e., the general exposure scenarios, that could occur over the course of several days, weeks, or months during an application season – the chronic RfD of 0.03 mg/kg/day is used (Section 3.3.2).

The central and upper bound hazard quotients for workers wearing contaminated gloves for one hour, exceed one, with the central HQ = 2, and the upper bound HQ = 12, regardless of application rate. In terms of general exposure, all upper bound hazard quotients exceed one, for the typical (1 lb/acre) and maximum (2 lbs/acre) application rates, but not the lowest application rate (0.25 lbs/acre). HQ values range from 3 to 5 for the typical rate and from 5 to 10 for the maximum rate. In each case, the highest values are for exposure via ground spray, and the lower values are for general backpack exposure and theoretical aerial spray applications not used by the Forest Service at this time. The only central estimate in excess of one, is an HQ of 1.5 associated with ground spray at the maximum application rate.

These hazard quotients indicate that workers using the typical and maximum application rates need to be particularly aware of glove contamination, and take extra precautions (i.e. use of personal protective equipment and other typical health and safety precautions) to avoid general exposure when spraying oxyfluorfen. Using the lowest application rate would be the most protective course of action with regard to avoiding potential risks from systemic toxicity, given the methods and assumptions used to estimate exposure and risk employed in this assessment.

In addition to hazards associated with systemic toxicity, oxyfluorfen can cause mild skin and eye irritation (Section 3.1.11). Quantitative risk assessments for irritation are not derived; however, from a practical perspective, eye and skin irritation are most likely to occur as a consequence of mishandling oxyfluorfen. These effects can be minimized or avoided by implementing prudent health and safety practices during the handling and application of the herbicide.

3.4.2.2. Carcinogenic Risk – The quantitative potential carcinogenic risk is expressed as a ratio of the estimated exposure from Worksheet E01 to the dose associated with a one-in-one-million cancer risk. Thus, a hazard quotient of one would be equivalent to a lifetime cancer risk of one-in-one million. Hazard quotients for carcinogenic risk which exceed one, indicate the potential for cancer risks to be greater than one-in-one-million. The Forest Service as well as other regulatory agencies generally consider risks less than one-in-one-million to be *de minimis*, and target remedial actions, where warranted, to reduce risks to within a one-in-one-million to one-in-ten-thousand range. With regard to Superfund cleanups, U.S. EPA (1992) states:

> *"EPA uses the general 10(-4) to 10(-6) risk range as a "target range" within which the Agency strives to manage risks as part of a Superfund cleanup. Once a decision has been made to*
> *make an action, the Agency has expressed a preference for cleanups achieving the more protective end of the range (i.e., 10(-6)), although waste management strategies achieving reductions in site risks anywhere within the risk range may be deemed acceptable by the EPA risk manager."*

Because cancer is considered to be something which occurs as a consequence of longer-term exposure, cancer risks are estimated in this assessment only for general exposures. The contaminated glove scenarios are of short duration (one hour exposure), and thus, carcinogenic risks are not estimated for these scenarios.

The estimated hazard quotients shown in the tables indicate no cancer risks in excess of one-in-one million at the lowest application rate (0.25 lbs/acre) for any method of application. However, upper-bound cancer risks on the order of 1.1- to 2-in-one-million are estimated for workers applying oxyfluorfen at the typical application rate of 1 lb/acre, with the highest risk associated with ground spray application. Upper-bound cancer risks ranging from 2-in-one-million to 4-in-one-million are estimated with the maximum application rate of 2 lbs/acre, again, with the highest risk associated with application via ground spray. The only central estimate with a greater than one-in-one-million cancer risk is for ground spray at the maximum application rate. All other lower and other central estimates of cancer risk are below the level of concern of one-in-one-million. As discussed for systemic toxicity, these risks are mitigated by the appropriate use of personal protective equipment and health and safety protocols.

3.4.3. General Public

A detailed quantitative summary of the risk of systemic toxicity for members of the general public is presented in Worksheet E04ai (typical application rate), Worksheet E04bi (lowest anticipated application rate), and Worksheet E04cii (highest anticipated application rate) of the w\Workbook in Attachment 1. Comparable estimates of carcinogenic risk are presented in Worksheets E04aii, E04bii and E04cii, respectively. A summary of the receptors and exposure scenarios with hazard quotients which exceed levels of concern for systemic toxicity and carcinogenicity (HQ> 1) is shown in Table 3-9.

3.4.3.2. Systemic Toxicity - As with the risk characterization for workers, hazard quotients, the ratio of the estimated exposure from Worksheet E02 to the RfD, are used quantitatively to characterize risk of systemic toxicity. For acute accidental/incidental exposures, the acute RfD of 0.20 mg/kg is used (Section 3.3.3). For longer term general exposures – i.e., exposures that could occur over the course of several days, weeks, or months during an application season – the chronic RfD of 0.03 mg/kg/day is used (Section 3.3.2).

Upper bound acute HQ values for adult females consuming contaminated vegetation range from 1.7 at the low oxyfluorfen application rate of 0.25 lbs/acre to 7 at the typical application rate of 1 lb/acre, to 14 at the maximum application rate of 2 lbs/acre. A similar trend for this exposure pathway is seen for chronic exposure, with upper bound chronic HQ values ranging from 1.4 to 6 to 12, respectively. Both acute and chronic upper bound HQ values marginally greater than one are also estimated for adult females consuming contaminated fruit when the maximum oxyfluorfen application rate of 2 lbs/acre is assumed. These findings suggest that in the unlikely event that someone had a vegetable garden or fruit trees growing near a Forest Service nursery where oxyfluorfen was applied, especially at the typical or maximum application rates, adult females who consume the fruit or vegetables from such gardens could be at risk of developing systemic toxicity. The plausibility of the existence of such a scenario is limited by two important

factors. First, the Forest Service uses oxyfluorfen primarily for chemical mowing in areas where proximity to residences, and hence, vegetable gardens and private fruit trees, is remote. Secondly, oxyfluorfen is an effective herbicide which kills nontarget vegetation, such as that which yields fruits and vegetables. Unless the oxyfluorfen contamination were to occur immediately before picking, it is plausible that the accidental contamination would kill the plants or diminish their capacity to yield consumable vegetation.

The only other pathways of potential concern involve a child consuming contaminated water after an accidental spill, or a child being sprayed directly. These scenarios are only of concern when the typical (1 lb/acre) and maximum application rates (2 lbs/acre) are assumed. Upper bound HQ values of 3 and 5 are estimated for the water consumption scenario, for the typical and maximum application rates, respectively. An upper bound HQ value of 1.9 is estimated in association with the maximum application rate of 2 lbs/acre for the direct spray scenario. No other HQ values greater than one were estimated for any other scenario or application rate. These findings suggest that in the unlikely event of a spill into a nearby pond used as a potable water supply, or that the entire body of a small child were sprayed with oxyfluorfen formulated at the maximum application rate of 2 lbs/acre, there could be some risk of adverse systemic toxicity.

3.4.3.3. Carcinogenic Risk - The ratio of the estimated exposure from Worksheet E02 to the dose associated with a one-in-one million cancer risk for oxyfluorfen is used to characterize potential carcinogenic risk. For oxyfluorfen, the dose associated with a one-in-one-million cancer risk is 0.0732 mg/kg/day on the basis of the study by Goldenthal and Wazeter (1977) as discussed in Section 3.3.4.

The only exposure pathway in which a one-in-one million cancer risk is likely exceeded is for adult females eating contaminated vegetation. Upper bound HQ values of 2 (2-in-one million cancer risk) and 5 (5-in-one million cancer risk) are estimated in association with the typical (1 lb/acre) and maximum (2 lbs/acre) application rates, respectively.

3.4.4. Consistency With Prior EPA Risk Assessments

Although many different assumptions and modeling scenarios were used, the risks presented in this assessment, where comparable, are consistent with those determined by U.S. EPA/OPP (2001a) in their Health Effects Division science chapter prepared in support of the re-registration eligibility for oxyfluorfen. HED concluded that the aggregate cancer risk for general population exposure was 1.7 in one-hundred-thousand (1.7×10^{-5}), and that estimates of non-cancer risk were below levels of concern. These estimates take into account exposures from dietary sources, contaminated drinking water and home use of oxyfluorfen in spot-treatment of weeds. EPA concluded that both non-cancer and cancer risks for workers engaged in the application of oxyfluorfen exceed levels of concern unless personal protective equipment (PPE) is used. U.S. EPA/OPP (2001a) states: *"Single layer Personal Protective Equipment (PPE) (which includes gloves, but not respiratory protection) is sufficient to achieve MOEs [margins of error] of greater than 300 for all of the handler/applicator scenarios. The cancer risk is below 1×10^{-4} with single layer PPE and is below 1×10^{-5} or 1×10^{-6} with engineering controls. The PPE*

requirements as listed on the labels range from baseline to double layer with most of the labels requiring waterproof or chemical resistant gloves. Only one of the labels (Scotts OHII) requires respiratory protection."

For post-application re-entry scenarios involving chemical mowing of conifer stands, the cancer risk for all scenarios exceeded one-in-ten-thousand on the day of treatment, but fell to less than one-in-ten thousand on days 1 to 5; and to less than one-in-one million on days 8 to 58 post-treatment (U.S. EPA/OPP, 2001a, pp 41-44). Non-cancer risks for post-application re-entry scenarios were greater than levels of concern (level of concern = margin of error greater than 100 for short-term exposure, and greater than 300 for intermediate-term exposure) for some scenarios involving application rates of 1 and 2 lbs/acre ranging from 1 to 10 days after treatment (U.S. EPA/OPP, 2001a, p 41).

3.4.5. Sensitive Subgroups

There is no indication that oxyfluorfen or oxyfluorfen formulations cause reproductive or teratogenic effects below doses or concentrations which cause general toxicity. Therefore, the general toxicity values used to characterize risk in the above analyses are sufficiently protective of the reproductive process and developing fetuses.

No other reports which discuss subgroups that may be sensitive to oxyfluorfen exposure are available in the open literature. However, one can make a case that oxyfluorfen exposure among individuals who have variegate porphyria, a genetically inherited (autosomal dominant) disease, might exacerbate or bring about the onset of symptoms. Individuals who have variegate porphyria have a 50% deficiency in protoporphyrinogen oxidase (Poh-Fitzpatrick 2005), which is the same enzyme inhibited by oxyfluorfen.

Approximately 60% of the individuals who have variegate porphyria never develop symptoms. The most common presenting sign of disease is photo-sensitivity followed by scarring, blistering and other skin changes, which can be of mutilating severity in children. During an acute attack, high levels of porphyrin precursors are believed to instigate changes in the central, autonomic and peripheral nervous systems, resulting in a cascade of symptoms, including: weakness, excruciating pain, uncontrolled vomiting, unusual behavior, seizures, respiratory and cardiac distress, and coma. The range of expression of symptoms is highly variable, and acute attacks are usually precipitated by environmental influences, such as exposure to drugs or chemicals (Poh-Fitzpatrick 2005).

Given that oxyfluorfen inhibits the same enzyme in which these individuals are innately deficient, it is plausible that oxyfluorfen exposure would exacerbate symptoms in someone with active disease, or induce an acute attack in individuals who might otherwise remain asymptomatic. As discussed in Section 3.1, researchers have been successful in using oxyfluorfen to induce variegate porphyria in mice (Krijt et al. 1997). The Krijt et al. (1997) study is the basis for the acute RfD used in this assessment, and thus is protective of oxyfluorfen-induced symptoms similar to those caused by variegate porphyria. But even though the RfD it

takes into account the range of sensitivity in the population, it is not necessarily protective of individuals who have variegate porphyria.

To know whether workers or members of the general public having variegate porphyria live or work in proximity to any Forest Service operations where oxyfluorfen is employed is not possible at this time. There is no porphyria registry in the United States, and therefore accurate estimates of any form of porphyria in the United States are not available (Poh-Fitzpatrick 2005). Hawkins (2002) estimates an incidence of occurrence of one- to two- in 100, 000 (higher in South Africa: 3 in 10,000) for variegate porphyria, but does not state the basis for the estimate.

Based on these observations, it is prudent to suggest that Forest Service workers known to have variegate porphyria, if any, not be involved in the handling of oxyfluorfen, or involved in operations where oxyfluorfen is used. Noting that many cases of variegate porphyria are undiagnosed, Forest Service personnel should pay particular attention to any complaints of photosensitivity or neurological symptoms among potentially exposed workers or nearby residents, in locations where oxyfluorfen is known to be used.

3.4.6. Connected Actions

Connected actions typically refers to activities other than those associated with the agent of concern (oxyfluorfen in this risk assessment) that might impact an individuals response to the agent of concern. Potentially significant connected actions associated with a chemical risk assessment would include exposures to other agents that might alter an individuals response to the agent of concern.

There is very little information available on the interaction oxyfluorfen with other compounds. As noted in Sections 3.1.14 and 3.1.15, there are indications that the impurities, inerts and adjuvants in oxyfluorfen formulations will enhance the toxicity of oxyfluorfen in humans or mammals. In particular, N-methyl-pyrrolidone has been associated with teratogenic effects in rats and hepatocellular adenoma and carcinoma in mice. In addition, the solvent naphtha inerts in oxyfluorfen formulations are associated with effects on the liver and central nervous system.

As discussed in Section 3.1.2, oxyfluorfen inhibits heme biosynthesis. As heme groups are essential to cytochrome integrity, and because cytochromes are important in metabolic processes, this inhibition could affect the metabolism of many endogenous and xenobiotic compounds which are mediated by cytochromes (e.g. cytochrome p450). Consequently, oxyfluorfen could affect the toxicity of other compounds which are metabolized by liver enzymes such as cytochrome p450. The nature of the potential effect (i.e., synergistic or antagonistic) would depend on the specific compound and perhaps the sequence of exposure.

Oxyfluorfen could worsen the negative effects on health of individuals compromised by other forms of anemia (e.g. sickle cell anemia, thalassemia) or by other predisposing factors such as exposure to compounds which interfere with blood or blood-forming tissues. For example, lead is known to interfere with delta-amino-levulenic acid, which in turn, can lead to anemia. Chlorinated benzenes, such as hexachlorobenzene, have been shown to interfere with heme

biosynthesis through the inhibition of uroporphyrinogen decarboxylase, causing or exacerbating porphyria cutanea tarda.

3.4.7. Cumulative Effects

The consideration of cumulative effects typically refers to the consequences of repeated exposure to the agent of concern (i.e., oxyfluorfen) as well as exposures to other agents that an individual might be exposed to that have the same mode of action as the agent of concern.

To identify and consider all agents that might have the same mode of action as oxyfluorfen is beyond the scope of the current risk assessment. To do so quantitatively would require a complete set of risk assessments on each of the other agents that would be considered. The U.S. EPA similarly declined to consider cumulative risk associated with other chemicals having the same mode of action as part of the recent risk assessment of oxyfluorfen (U.S. EPA/OPP 2001a). The rationale presented by U.S. EPA is as follows:

HED did not perform a cumulative risk assessment as part of this reregistration for oxyfluorfen because HED has not yet initiated a review to determine if there are any other chemical substances that have a mechanism of toxicity common with that of oxyfluorfen. For purposes of this reregistration decision EPA has assumed that oxyfluorfen does not have a common mechanism of toxicity with other substances. - U.S. EPA/OPP 2001a, p. 31

Nonetheless, the current Forest Service risk assessment does specifically consider the effect of repeated exposures to oxyfluorfen for both workers and members of the general public. It should be noted that the half life of elimination in animals is biphasic with values of 9 to 13 hours for the first phase and 26 to 32 hours for the second phase. This means that daily dosing or exposure would result in bioaccumulation. The chronic RfD and carcinogenic potency factor are used as an indices of acceptable longer-term exposures. An acute RfD based on a dietary study involving an exposure period of nine days is used for the risk characterization of exposures occurring in a single day. Consequently, the risk characterizations presented in this risk assessment specifically addresses and encompasses the potential impact of repeated short-term and long-term exposures, and the cumulative effects that could be caused by such exposures.

4. ECOLOGICAL RISK ASSESSMENT

4.1. HAZARD IDENTIFICATION

4.1.1. Overview

Oxyfluorfen is an herbicide which disrupts photosynthesis through interference with chlorophyll production, and inhibition of photosystem II and electron transport. In mammals, oxyfluorfen interferes with heme biosynthesis, which ultimately impacts the blood, liver, and blood-forming tissues such as bone marrow.

The toxicity of oxyfluorfen is fairly well characterized in plants and animals. A comparison of older studies, conducted with less pure technical grade oxyfluorfen, with newer studies conducted with higher purity technical grade oxyfluorfen, demonstrates that impurities are responsible for some of the observed toxicity in the older studies. Similarly, a comparison of studies conducted with oxyfluorfen formulations, with those conducted with highly pure technical grade herbicide (>95% a.i.), demonstrate that inerts in the formulations are responsible for much of the observed toxicity. This latter observation is true for dermal and ocular irritation in mammals, acute toxicity in mammals, acute toxicity in aquatic invertebrates, and acute toxicity in aquatic algae.

Based on classification schemes developed by U.S. EPA on the basis of acute toxicity, oxyfluorfen is practically non-toxic to mammals, birds, and honey bees; highly toxic to fish; and very highly toxic to aquatic invertebrates. Oxyfluorfen does not cause effects on reproduction or fetal development in birds, or mammals at doses/concentrations which do not cause toxic effects in maternal animals. The only available study which addresses the potential for oxyfluorfen to adversely affect early growth and development in fish, was conducted with low-purity technical grade herbicide, and demonstrated adverse effects on growth and survival. Oxyfluorfen causes phytotoxicity in non-target plants at concentrations which are likely used under field conditions, but these effects are often transient and reversible, depending on the species, cultivar and application rates used. A limited number of studies suggest that the effects of oxyfluorfen on soil microorganisms are also likely to be transient, with measured variables in exposed populations ultimately rebounding above those of control levels.

4.1.2. Toxicity to Terrestrial Organisms

4.1.2.1. Mammals – Most of the information on the toxicity of oxyfluorfen in mammals as well as other species comes from unpublished bioassays submitted to the U.S. EPA for the registration of oxyfluorfen. These studies as well as other studies submitted for registration are conducted using methods specified by the U.S. EPA (e.g., U.S. EPA/OPP 2005). While some studies may be conducted directly by the registrant, most toxicity studies are performed by commercial testing laboratories. All studies submitted for registration are independently reviewed by U.S. EPA and all toxicity studies on mammals and other species that are cited in this Forest Service risk assessment were obtained and reviewed in the preparation of this risk assessment.

As summarized in the human health risk assessment (Section 3.1) and detailed in Appendices 1 2, and 3, the toxicity of oxyfluorfen to mammals is relatively well-characterized in a large number of standard studies with a variety of animals.

The mode of action of oxyfluorfen is well characterized in plants and mammals. Oxyfluorfen inhibits protoporphyrinogen oxidase, an important enzyme which catalyzes the production of chlorophyll in plants, and heme in mammals. The disruption of heme biosynthesis in mammals results in the accumulation of hemoglobin precursors, which in turn, causes adverse effects on the liver, blood and blood-forming tissues. In humans, a deficiency in protoporphyrinogen oxidase results in a disease known as variegate porphyria. Krijt et al. (1997) experimentally created variegate porphyria in mice by exposing them to oxyfluorfen in the diet (concentrations $\geq$200 ppm a.i.). The most consistent effects of oxyfluorfen in mammals are on the liver, blood and blood-forming tissues, but only after longer-term exposure.

As noted in Section 3.1.2, the acute oral toxicity of oxyfluorfen in mammals is classified by U.S. EPA/OPP (1994a, 2002g,h) as Category IV: "practically non-toxic". This classification is based on gavage LD_{50} values in rats greater than 5 g a.i./kg body weight (test limits) resulting from tests with both lower purity and higher purity technical grade oxyfluorfen. Tests with Goal 2XL and Goal 1.6E formulations yielded LD_{50} values of 4.337 g/kg and 0.5-5 g/kg, respectively. While no mortality or toxicity was observed with the highly pure technical grade herbicide, mortality and body weight gain reduction were seen in studies with the formulations, probably due to the presence of inerts and impurities (see Sections 3.1.14 and 3.1.15). As mentioned above, a short-term dietary study with mice (Krijt et al. 1997), demonstrated that concentrations of oxyfluorfen at or greater than 200 ppm a.i. cause effects similar to those seen in human variegate porphyria. Statistically significant reductions in protoporphyrinogen oxidase activities, and increases in porphyrin concentrations (with respect to controls) were observed in liver and kidney tissues at dietary concentrations of 200 and 1000 ppm. The individual porphyrin species were identified in liver and kidney tissue from mice fed 1000 ppm, and were consistent with what one would expect following inhibition of protoporphyrinogen oxidase. The NOAEL for the study is 125 ppm a.i.

In terms of sub-chronic and chronic toxicity, mice and dogs are more sensitive than rats (Appendix 3). A NOAEL of 3 mg a.i./kg/day (20 ppm a.i.) is derived from a 52-week chronic dietary study with dogs (Piccirillo 1977; Rohm and Haas 1981, as cited by U.S. EPA 2001a) and a 20-month combined chronic toxicity/carcinogenicity dietary study with mice (Goldenthal and Wazeter 1977). In dogs, the LOAEL is 600 ppm (approximately 19 mg a.i./kg/day) based on decreased body weight gain, and effects on the liver (increased SAP, increased liver weight and increased bile-pigmented hepatocytes). In mice, the LOAEL = 33 mg a.i./kg/day for males; 42 mg a.i./kg/day for females (200 ppm a.i.) on the basis of increased neoplastic and non-neoplastic liver changes as well as some increases in liver enzymes (SGPT and SAP). It should be noted that there is a discrepancy between EFED (U.S. EPA 2001a) and IRIS (U.S. EPA 1987) with regard to interpretation of the effect levels from this study. While the EFED interpretation agrees with the previous statements, IRIS states that the NOAEL for this study is 0.3 mg a.i./kg/day (2 ppm a.i.) and designates 3 mg a.i./kg/day (200 ppm a.i.) as the LOAEL. A review of IRIS and

EFED documentation to uncover this discrepancy is not illuminating. However, a careful review of the original study suggests that the EFED interpretation, which is more recent than the last IRIS update, is consistent with the observed effects reported.

In terms of teratogenicity and reproductive effects, rabbits appear to be more sensitive than rats (Appendix 2). Regardless of the species, adverse effects on the developing fetus or on reproduction are seen only at concentrations which adversely affect the mother. In a teratology study with rabbits (Burns 1997a) using highly pure technical grade oxyfluorfen, the NOAEL for both maternal and fetal effects was 30 mg a.i./kg/day. Effects observed at 90 mg a.i./kg/day included reduced food consumption and decreased fecal output in mothers, and decreased mean litter weights and delayed skeletal ossification and head development in the fetuses. In a three-generation reproduction study with rats (Killeen et al. 1977) a maternal/fetotoxic NOAEL of 10 ppm was established, with a LOAEL of 100 ppm based on decreased lactation in F_0 mothers and a parallel decrease in survival of F_{1a} offspring. It should be noted that this effect was not seen in any subsequent generation, and that no other effects were observed. In addition, this study was conducted with older, less pure technical grade oxyfluorfen (82 - 86% a.i.), which is generally known to be associated with greater toxicity than the current high-purity (>95%) technical grade material.

4.1.2.2. Birds – The toxicity studies on birds are summarized in Appendix 5 and these studies have been reviewed by the U.S. EPA (i.e., U.S. EPA 2001b, 2002). The available toxicity studies in birds include acute gavage studies (Fletcher 1987a; Godfrey and Longacre 1990d; Hoffman et al. 1991a,b), avian acute dietary studies (Fletcher 1987b,c; Godfrey and Longacre 1990e,n); and seven avian reproductive toxicity studies (Frey et al. 2003a,b; Rohm and Haas 1981a,b; Piccirillo and Najarim 1978; Godfrey and Longacre 1990c; Piccirillo and Peterson 1978).

A study from the open literature (Kim-Kang et al. 1994) examined the metabolism of oxyfluorfen in laying hens. Hens were given ^{14}C-labeled oxyfluorfen (both N-pyridinyl ring and C-pyridinyl ring labeled) in the diet for 7 days at a concentration equivalent to 15 ppm. Most of the total radiation partitioned to the fat, with total radioactive residue levels of approximately14 -16 ppm. Total radioactive residues were also detected in whole eggs, liver, breast muscle and thigh muscle at concentrations less than 2 ppm. The majority of the residue identified in the tissues and eggs was unchanged parent compound.

Based LD_{50} values from acute oral and dietary studies in mallard ducks and bobwhite quail, U.S. EPA (2001b; 2002) classifies oxyfluorfen as practically non-toxic. Dietary studies with bobwhite quail and mallard ducks yielded LC_{50} values > 5000 mg a.i/kg and NOAEC values of 1250 mg a.i./kg for both species. These studies used the lower purity technical grade oxyfluorfen (70.2% a.i.). Both a single-dose gavage study and a 21-day repeated gavage study with bobwhite quail yielded LD_{50} values greater than the limit of the test (2150 mg a.i./kg; tests conducted with 70.2% a.i. technical grade oxyfluorfen). A range-finding study using high purity technical grade oxyfluorfen (98.5% a.i.) conducted with the American kestrel (Hoffman et al. 1991a,b) yielded a

NOAEL of 500 mg/kg (test limit). Four nestling kestrels were used in this study, and they were dosed for 10 days.

Avian reproduction studies were conducted with both the older less-pure technical grade oxyfluorfen and the newer high purity technical grade oxyfluorfen (99.3% a.i.). It should be noted that EFED did not have the studies conducted with high purity technical grade oxyfluorfen to evaluate in considering the re-registration of oxyfluorfen (U.S. EPA 2001b; 2002). No effects were observed in the older studies conducted with mallard ducks and bobwhite quail, but the highest test concentration in these studies was only 100 ppm a.i. in the diet. Recent studies have been conducted with high purity technical grade oxyfluorfen (99.3% a.i.) with both mallard ducks (Frey et al. 2003a) and bobwhite quail (Frey et al. 2003b). Bobwhite quail were the least sensitive species, with no effects observed on parental animals or reproductive indicators at the highest dietary concentration tested (NOAEC = 750 ppm a.i.). Mallard ducks were more sensitive, with a dietary NOAEC of 500 ppm a.i. The LOAEL for mallard ducks is 750 ppm on the basis of decreased egg production, embryo development and hatchability.

4.1.2.3. Terrestrial Invertebrates – As is the case with most herbicides, relatively little information is available on the toxicity of oxyfluorfen to terrestrial invertebrates. Under the assumption that herbicides are not generally directly toxic to insects, the U.S. EPA (2001b;2002) required only one direct contact bioassay using the honey bee (Atkins 1992). There is also a study on a predaceous mite (Milligan 2000) which U.S. EPA (2001b) classified as supplemental, as no guideline exists for this species. These studies are summarized in Appendix 6.

The honey bee study used lower purity technical grade oxyfluorfen. There was no mortality and no signs of toxicity at the limit of the test (100 ug/bee). On this basis, U.S. EPA (2001b) classifies oxyfluorfen as practically non-toxic to bees. In the study with predaceous mites, 98% mortality was observed following application of Goal 4F (42.09% a.i.) at a rate equivalent to 1.28 lb a.i./A.

Rovesti and Deseo (1990) demonstrated that concentrations of oxyfluorfen greater than or equal to 5000 ppm caused some immobility in entomopathogenic nematodes; however, the highest concentration tested (10,000 ppm) had no effect on the nematode's ability to infect prey larvae when compared with untreated controls.

Although some diphenyl ether herbicides (e.g. nitrofen) have been shown to kill mosquito larvae, oxyfluorfen was shown to be ineffective (Ikeuchi et al. 1979).

4.1.2.4. Terrestrial Plants (Macrophytes) – The mechanism of action of oxyfluorfen in plants has been well studied. Oxyfluorfen is an effective herbicide which kills both target and nontarget species. Information relevant to nontarget species is discussed in the following sections.

4.1.2.4.1. Mechanism of Action- Oxyfluorfen binds to the membranes of chloroplasts, inhibiting the action of an important enzyme which catalyzes chlorophyll production. This sets off a cascade of effects which results in the inability of the plant to conduct photosynthesis: the

life-sustaining process by which light is transformed to useable chemical energy. As such, oxyfluorfen requires light to work. In more technical terms, Oxyfluorfen is a photo-peroxidizing herbicide which binds to the chloroplast membrane, inhibiting protoporphyrinogen oxidase activity, and disrupting the photosynthetic mechanism of the plant. More details of this process are provided in the following paragraphs in this section.

Early investigators observed that plants treated with oxyfluorfen were not injured when placed in the dark, but noted that the destruction of chlorophyll and amount of injury to the plant increased with light intensity (Vanstone and Stobbe 1979). This led others to investigate the mechanism by which oxyfluorfen inhibited photosynthesis, and based on their observations, to conclude that it did so in a manner different from other herbicides (Pritchard et al. 1980). Sharma et al. (1989a,b) demonstrated that oxyfluorfen causes damage to chloroplast membranes by inhibiting photosystem II and electron transport. They were able to demonstrate a dose-dependent reduction in chlorophyll and a parallel dose-dependent decline in photosystem II (PSII) activity in chloroplasts taken from rice leaves sprayed with oxyfluorfen. A1 ppm exposure caused slight but transient declines in chlorophyll content and PSII activity, while exposure to 3, 5 or 7 ppm caused irreversible and severe reductions in chlorophyll content (80% loss at 7ppm, 5 days post-treatment) and PSII activity (90% reduction at 7 ppm, 5 days post-treatment). More detailed studies with isolated spinach chloroplasts further defined the kinetics of oxyfluorfen inhibition of PSII activity. Investigators such as Lydon and Duke (1988) and Rao and Mason (1988) concluded that the pigments protoporphyrinogen IX, carotene and lycopene were somehow involved in the herbicidal action. Ultimately, investigators demonstrated that chlorophyll inhibition, ethane formation, and protoporphyrinogen oxidase inhibition were correlated with the observed oxyfluorfen-induced toxicity, and that changes in the molecular structure of oxyfluorfen and other diphenyl ether herbicides, cause varying inhibition of protoporphyrinogen oxidase (Sumida et al. 1996; Sato et al. 1999). Disruption of protoporphyrinogen oxidase leads to the accumulation of protoporphyrinogen IX, a precursor for chlorophyll. This disrupts chlorophyll production, and interferes with PSII and electron transport.

Retzlaff and Boger (1996) showed that protoporphyrinogen oxidase also occurs outside the chloroplast, in the endoplasmic reticulum, and that the activity of endoplasmic reticular protoporphyrinogen oxidase plays a role in the phyotoxic accumulation of protoporphyrinogen IX. There is also evidence which demonstrates that naturally occurring pigments, such as lycopene and beta carotene enhance oxyfluorfen's mechanism of toxic action. This is ironic, given that carotenoids such as lycopene and beta carotene evolved as anti-oxidants to protect plants against their own endogenous photosensitizer: chlorophyll (Rao and Mason 1988). However, as discussed in the following paragraphs, plants are not without mechanisms for adapting to the oxidative stress caused by exposure to oxyfluorfen.

Finckh and Kunert (1985) observed that anti-oxidant vitamins which occur naturally in a plant, vitamins A (alpha-tocopherol) and C (ascorbic acid), protect against oxyfluorfen-induced phytotoxicity. Studies with soybeans, tobacco plants, onions, wheat and barley have given insight into how a plant responds to the oxidative stress incurred by exposure to oxyfluorfen, and develops resistance to further exposure and toxicity. Several strategies have been discovered,

including overproduction of mitochondrial protoporphyrinogen oxidase (Warabi et al. 2001; Knowerzer et al. 1996); and induction of the genetic machinery responsible for increasing the production of the anti-oxidative enzymes glutathione reductase, monodehydroascorbate, and glutathione-S-transferase Lederer et al. 1999). Growth and development is initially delayed in onion seedlings sprayed with oxyfluorfen, but as seedlings recover and age, there is a progressive increase in the thickness of the waxy epicuticle of the plant, coupled with a decrease in the retention of sprayed herbicide. Thus, the observed tolerance to oxyfluorfen exposure was attributed to the decreased spray retention as a result of increased wax deposition in the epicuticle of the plant (Akey and Machado 1985).

Choi et al. (1999) studied the differential susceptibility of wheat and barley in response to oxyfluorfen exposure. Wheat is significantly less susceptible to oxyfluorfen exposure than is barley, and although this difference persists regardless of whether treatment is pre- or post-emergence, the difference is greater with post-emergence treatment. The difference in susceptibility is due to a difference in the ability of oxyfluorfen to inhibit protoporphyrinogen oxidase. Oxyfluorfen is less able to bind to protoporphyrinogen oxidase in wheat than in barley, and thus produces less inhibition of protoporphyrinogen oxidase in wheat than in barley. It follows logically from knowledge of oxyfluorfen's mechanism of action, that less inhibition of protoporphyrinogen oxidase = less toxicity/greater resistance.

The protoporphyrinogen oxidase in a strain of bacteria known as *Bacillus subtilis* is resistant to diphenyl ether herbicides such as oxyfluorfen. Lee et al. (2000) demonstrated that the protoporphyrinogen oxidase in *B. Subtilis* could be incorporated into the genome of rice, and creating a genetically modified strain which is in turn, resistant to oxyfluorfen-induced phytotoxicity.

4.1.2.4.2. Toxicity - The U.S. EPA typically relies on standardized bioassays for seed germination, seedling emergence (pre-emergence applications), and vegetative vigor (post-emergence applications) to assess the potential effects of herbicides on non-target plants (U.S. EPA/OPP 2005). These studies were conducted with the lower purity (71.5% a.i.) technical grade oxyfluorfen, as summarized in Appendix 8. A number of studies which address the toxicity of oxyfluorfen to non-target species have been published in the open literature. The relevant studies are summarized briefly in Appendix 8.

Oxyfluorfen is an herbicide, and thus, it is no surprise that it can damage non-target plants as well as target species. In standard laboratory tests conducted according to EPA guidelines, tomatoes were the most sensitive species with regard to both seedling germination (NOAEC = 0.05 lb a.i./A) and vegetative vigor (NOAEC = 0.00066 lb a.i./A). Cabbage, onions, lettuce and ryegrass were equally the most sensitive species with regard to seedling emergence (NOAEC = 0.0024 lb a.i./A). The most tolerant species with regard to seedling germination were cabbage, corn, cucumber, lettuce, oats, ryegrass and soybean (NOAEC = 1.5 lbs a.i./A). Soybeans were the most tolerant with regard to seedling emergence (NOAEC = 0.31 lbs a.i./A), and corn was the most tolerant species with regard to vegetative vigor (NOAEC = 0.034 lbs a.i./A) (Hoberg 1990).

Studies from the open literature (summarized in Appendix 8) support the observation that oxyfluorfen is phytotoxic to non-target species, even when applied at label application rates. Studies from published and non-published sources demonstrate that pre-emergence application is less likely to cause permanent injury than post-emergence application. In fact, oxyfluorfen is relatively ineffective at inhibiting seed germination, but is phytotoxic when applied to soil or sprayed pre- or post-emergence.

There is a common trend in these studies suggesting that plants generally recover from milder initial damage (e.g. cotyledon crinkling and slight growth retardation) following pre-emergence application at lower rates, but incur greater damage which is not reversible (e.g. cotyledon necrosis, seedling death, lower crop yields) at the higher rates. In a greenhouse study conducted with native Australian plants, early phytotoxicity was observed in most of 18 different species (primarily in the Proteaceae and Gramineae families) following pre-emergence application of Goal 24EC at a rate of 1 kg a.i./ha. However, plants recovered from treatment-related injuries by day 85 post-treatment (Jusaitis et al. 1993).

Studies with tomatoes and broccoli demonstrated a difference in susceptibility among different cultivars of the same species (Farnham and Harrison 1995; Harrison and Farnham 1998; Masiunus 1989). In broccoli, later maturing cultivars were less susceptible than earlier maturing cultivars, and were more likely to recover from initial treatment-related injury (Harrison and Farnham 1998). Although application rates are reported in these studies, there is no information on the formulation used or the percent active ingredient.

A field application study with soybeans conducted in India demonstrated that oxyfluorfen (applied as Goal 23.5% EC) reduced nitrogen uptake and seed yield following pre-emergence application at a rate of 0.2 kg/ha.

Pre-emergence application of oxyfluorfen to Elberta Peach groves (0.1, 0.2, and 0.3 kg a.i/ha) resulted in an increase in the uptake of certain micronutrients (potassium, calcium, magnesium and iron), and a decrease in copper in the leaves (Bhargava et al.1987).

A few studies show that oxyfluorfen can potentiate the action of other herbicides. Oxyfluorfen enhances the ability of glyphosate (Roundup) to control yellow nutsedge by increasing the absorption and translocation of glyphosate into the leaves and new tubers (Pereira and Crabtree 1986). The combination of oxyfluorfen and oryzalin leads to greater injury in pansy cultivars, than when oryzalin is applied alone (Kessler et al. 1996).

4.1.2.5. Terrestrial Microorganisms –As summarized in Appendix 6, studies have been conducted to assess the effects of oxyfluorfen treatment on soil microorganisms, but none of these are standard laboratory studies. These are field studies, which taken together, suggest that oxyfluorfen use is probably not harmful at usual application rates, and may even benefit soil microbe populations in ways that are beneficial to plants.

Fungal populations are either not affected or are ultimately increased with respect to controls after pre-emergence application (Nyak et al. 1994; Ahmed and Vyas 1997). Bacterial, fungal and actinomycete populations exposed to 0.03 kg/ha (formulation and % a.i. not reported) were transiently decreased with respect to controls at day 25 post-treatment, but rebounded to equal or exceed controls in samples taken 56 and 75 days post-treatment (Nyak et al. 1994).

Soil taken from a rice paddy and treated with oxyfluorfen (Goal) at a rate of 1.54 l/ha was tested weekly for activities of enzymes indicative of health of microbial populations. With respect to control soil, there was no effect on urease activity, but carbon dioxide output was increased throughout the 5 week sampling period (probably due to degradation of the herbicide). Dehydrogenase activity was increased on day 7 after treatment, then steadily declined below control levels in the following 4 weeks. The meaning of this latter effect is not clear (Barush and Mishra 1986).

A more recent study conducted in Indian rice fields (Das et al. 2003) demonstrated that post-emergence application of oxyfluorfen at a rate of 0.12 kg a.i/ha increased the population of phosphate solubilizing microorganisms, which in turn, increased the amount of phosphorus in the rhizoshpere of the soil available for uptake by plants and use in growth and development. Residues of oxyfluorfen, and the associated effects, persisted in these soils for more than 60 days.

4.1.3. Aquatic Organisms

4.1.3.1. Fish – Standard toxicity bioassays to assess the effects of oxyfluorfen on fish are summarized in Appendix 8. The data available on oxyfluorfen include several standard acute toxicity studies submitted to the U.S. EPA for pesticide registration (Graves and Peters 1990; Graves and Smith 1991a,b), a standard early life stage study in fathead minnows (Godfrey and Longacre 1990f). Some key studies for which fiche were not available, but are cited in U.S. EPA(2001b) are also summarized in Appendix 12.

U.S. EPA/OPP (2001b) classifies oxyfluorfen as highly toxic to fish on the basis of the available acute studies. As with mammals, the higher purity technical grade herbicide (94%) was less toxic than the lower purity material (71.4 - 74%), although both low- and high- purity herbicides yielded 96-hour LC_{50} values which result oxyfluorfen being classified as highly toxic on the basis of acute toxicity. In the flow-through studies conducted with high-purity technical grade oxyfluorfen, bluegills (LC_{50} = 0.2200 mg a.i./L; NOAEC = 0.056 mg a.i./L) were more sensitive than rainbow trout (LC_{50} = 0.410 mg a.i./L; NOAEC = 0.180 mg a.i./L).

The only standard longer term toxicity study of oxyfluorfen in fish is the early life-stage study on fathead minnows by Godfrey and Longacre (1990f). As discussed further in Section 4.3, this study defines a clear NOEC of 0.038 mg/L and an LOEC of 0.074 mg/L. Hassanein (1999; 2002) conducted studies on fish found in the Nile River of Egypt to identify potential bio-markers in response to herbicide exposure. They identified statistically significant increases in heat-shock protein 70 in the liver and kidneys of fish exposed to oxyfluorfen, with respect to unexposed controls. LOAEC values decreased with increasing exposure time (e.g., LOAEC = 0.75 mg a.i./L after 8, 16 and 24 days exposure versus LOAEC = 3 mg a.i./L after days 2, 4 and 6 exposure).

Hassanein (2002) identified statistically significant reduction in brain acetylcholinesterase in freshwater fish exposed for 30 days to oxyfluorfen, with LOAEC values of 0.3 mg a.i./L for *Oreachromis niloticus*, and 0.43 mg/L for *Gambusia affinis*.

4.1.3.2. Amphibians – No information is available on the toxicity of oxyfluorfen to amphibians.

4.1.3.3. Aquatic Invertebrates – The available information on the toxicity of oxyfluorfen to aquatic invertebrates includes studies submitted to the U.S. EPA for pesticide registration and a study on sea urchin development published in the open literature. All of these studies are summarizes in Appendix 9. On the basis of acute LC_{50} values in both freshwater and saltwater species, U.S. EPA classifies oxyfluorfen as very highly toxic to aquatic invertebrates (U.S. EPA, 2001b;2002). All the available studies were conducted with lower purity technical grade oxyfluorfen, and one acute study with Daphnia was conducted with Goal 2XL formulation.

For species tested with technical grade oxyfluorfen, a freshwater clam, *Elliptio complanata*, (96-hour EC_{50} of 9.57 ug/L with a LOAEC of 3.2 ug/L; Godfrey and Longacre 1990b) and Eastern oyster, *Crassostrea virginica*, (48-hour LC_{50} value of >32 ug a.i./L, with a NOAEC of 3.2 ug a.i./L; MRID 96881 as cited by U.S. EPA 2001b) were the most sensitive species. Grass shrimp (96-hour LC_{50} of 32 ug/L and a NOAEC values of 18 ug/L; cited by U.S. EPA 2001b) and *Daphnia* (48-hour LC_{50} of 1500 ug/L and a NOAEC of 100 ug/L; cited U.S. EPA 2001b) were next in sensitivity, followed by Mayflies (unspecified species; 48-hour LC50 = 420 ug/L; Swigert 1986) and Fiddler crabs were least sensitive (96-hour LC50>1000 mg/L and a NOAEC of 320 mg/L; cited in U.S. EPA, 2001b). Goal 2XL was more toxic to *Daphnia* (NOAEC = 20 ug a.i./L; 48-hour EC_{50} = 80 ug/L; Sutherland et al. 200a) than technical grade oxyfluorfen, suggesting that the inerts in the formulation play a role in the observed acute toxicity.

As summarized in Appendix 9, one reproduction study in *Daphnia magna* is available: Godfrey and Longacre (1990g). This study was conducted with low purity technical grade oxyfluorfen (71.8% purity) and yielded a NOAEC of 13 ug a.i./L and LOAEC of 28 ug a.i./L on the basis of adult survival, growth and reproduction.

One additional study from the open literature (Medina et al. 1994) demonstrated that oxyfluorfen delays early egg development in sea urchins by interfering with the development of the mitotic apparatus during early division. Goal herbicide (240 grams a.i./L) was used in the study at a concentration of 2.7×10^{-4} M (equivalent to 97.7 mg/l, based on an oxyfluorfen molecular weight of 361.7 g/mole).

4.1.3.4. Aquatic Plants – Studies on the effects of Oxyfluorfen on aquatic plants are summarized in Appendix 10. Oxyfluorfen is an effective herbicide and the mechanism of action of oxyfluorfen, the inhibition of photosynthesis (Section 4.1.2.4), affects aquatic plants (Geoffroy et al. 2003; Kunert et al. 1985; Kunert and Goeger 1984) as well as terrestrial plants. This is true of most herbicides. Consequently, the U.S. EPA requires a relatively standard group of studies on both unicellular aquatic algae as well as aquatic macrophytes. These studies are typically conducted over a 5-day period under controlled laboratory conditions.

As in studies conducted with animals, the studies on aquatic plants conducted with lower purity technical grade oxyfluorfen and oxyfluorfen formulations yielded greater toxicity than those conducted with highly pure technical grade oxyfluorfen. As discussed below, this suggests that both the inerts in formulations and the impurities in the older technical grade herbicide are responsible for a significant portion of the observed toxicity in algae and diatoms.

Based on the standard bioassays of algal cell growth conducted with lower purity technical grade oxyfluorfen, relatively substantial differences in sensitivity to oxyfluorfen are apparent. The differences span a factor of 8,333 based on the EC_{50} values and 20,000 based on the NOAEC values. The most sensitive species appear to be *Navicula pelliculosa* (a freshwater diatom; 5-day-EC_{50}: 0.00024 mg/L and a corresponding NOAEC of 0.0001 mg/L; Giddings 1990) and *Selenastrum capricornutum* (a freshwater green alga; 5-day-EC_{50}: 0.00035 mg/L and a corresponding NOAEC of 0.00032 mg/L; Giddings 1990). The least sensitive species appears to be *Anabaena flos-aquae* (a freshwater blue-green alga) with a 5-Day EC_{25} of >2 mg/L and a corresponding NOAEC of 2 mg/L (Giddings 1990).

A single 10-day toxicity test conducted with *Pseudokirchneriella subspicata* (freshwater green alga) and highly pure technical grade oxyfluorfen (Goal Technical purified herbicide; 99.19% a.i.) (Hoberg 1999) suggests that impurities in the older technical grade herbicide were responsible for the observed toxicity in the previously mentioned 5-day growth and biomass studies with *Selanastrum capricornutum*. No inhibition of growth or biomass were noted in the Hoberg (1999) study in comparison with controls at the highest dose tested (0.0029 mg/L). This leads to a freestanding NOAEC value of 0.0029 mg/L and a 10-day EC_{50} of >0.0029 mg/L.

A standard EPA growth and biomass study was conducted with *Selanastrum capricornutum* to assess the potential impacts of Goal 2XL on a sensitive freshwater alga (Sutherland et al. 2000b). The study yielded a 96-hour EC_{50} of 0.0012 mg formulation/L and a NOAEC of 0.00043 mg formulation/L. Assuming that Goal 2XL is 23% a.i., these values translate to an EC_{50} of 0.00028 mg a.i./L and a NOAEC of 0.000099 mg a.i./L.

The relative sensitivity of green algae and tolerance of blue-green algae to formulations of Oxyfluorfen (in this case, Goal 2E) is confirmed in the open literature. Rojickova-Padrtova and Marsalek (1999) conducted 96-hour biomass and growth assays similar to the standard EPA studies with six species of green algae and one species of blue-green algae. The most sensitive species was *Scenedesmus subspicatus* (green algae), with an EC_{50} of 0.000676 mg formulation/L. The most tolerant species was *Synechoccus leopoliensis* (blue-green algae) with an EC_{50} of 49.676 mg formulation/L. Assuming an oxyfluorfen purity of 22.2%, these values translate to an EC_{50} of 11.028 mg a.i./L for *Synechoccus leopoliensis* and an EC_{50} of 0.000150 for *Scenedesmus subspicatus*. As with the previous study with Goal 2XL, this study supports the notion that oxyfluorfen formulations are more toxic to algae than highly pure technical grade oxyfluorfen, and that the inerts and impurities in the formulation may be responsible for a significant portion of the observed toxicity.

Relatively little information is available on the toxicity of oxyfluorfen to macrophytes. As summarized in Appendix 14, only one study is available on duckweed (i.e., *Lemna* sp.). The standard bioassay on *Lemna gibba* submitted to U.S. EPA (Giddings 1990) was conducted with low purity technical grade herbicide (71.5% a.i.), and yields an EC_{50} of 0.0014 mg a.i./L and a LOAEC of 0.00055 mg a.i./L. A no-observed-effect level was not defined in the study.

4.2. EXPOSURE ASSESSMENT

4.2.1. Overview

A number of different exposure scenarios are developed mammals, birds, terrestrial invertebrates, terrestrial plants and aquatic species. The specific levels of exposure for each group of organisms are summarized in the G-Series worksheets in the EXCEL workbook that accompanies this risk assessment. In many respects, these exposures parallel the exposure scenarios used in the human health risk assessment and the scenarios fall into two general groups: exposures that may be anticipated in the normal use of oxyfluorfen and atypical exposures that could occur as a result of mischance or misapplication. In some cases, the atypical exposures have somewhat different interpretations. The direct spray of a human is regarded as accidental. The direct spray of a small mammal or insect during any broadcast application, however, is more plausible. Nonetheless, it is highly unlikely that a substantial proportion of small mammals or insects would be directly sprayed. Exposures would likely be reduced both by animal behavior as well as foliar interception.

For terrestrial animals, exposure assessments are developed for direct spray, the ingestion of contaminated media (vegetation, prey species, or water), grooming activities, or indirect contact with contaminated vegetation. Not all exposure scenarios are developed for all groups of animals because toxicity data are not available in all groups to support the use of such exposure assessments in the risk characterization. For terrestrial plants, exposure assessments are developed for direct spray, spray drift, and off-site movement of the compound by percolation, runoff, wind erosion of soil. For aquatic species, the concentrations in water are identical to those used in the human health risk assessment.

Also as in the human health risk assessment, the major route of exposure for most terrestrial species involves the consumption of contaminated vegetation rather than the consumption of contaminated water.

4.2.2. Terrestrial Animals

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

In the exposure assessments for the ecological risk assessment, estimates of oral exposure are expressed in the same units as the available toxicity data. As in the human health risk assessment, these units are usually expressed as mg of agent per kg of body weight and abbreviated as mg/kg for terrestrial animals. For dermal exposures to terrestrial animals, the units of measure 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. As with the human health exposure assessment, the exposure scenarios are provided in an EXCEL workbook and the

exposure assessments for terrestrial animals are summarized in Worksheet G01. The computational details for each exposure assessment presented in this section are provided as scenario specific worksheets (Worksheets F01 through F16b).

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

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

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

For this risk assessment, three groups of direct spray or broadcast exposure assessments are conducted (Worksheets F01, F02a, and F02b). The first spray scenario, 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. This scenario assumes first-order dermal absorption. The second exposure scenario, detailed in Worksheet F02a, is developed in which complete absorption over day 1 of exposure is assumed. This very conservative assumption is likely to overestimate exposure and is included to encompass any increase in exposure due to grooming. The third exposure assessment is developed using a body weight of a honey bee, again assuming complete absorption of the compound. Direct spray scenarios are not given for large mammals. Allometric relationships dictate that large mammals will be exposed to lesser amounts of a compound in any direct spray scenario than smaller mammals.

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. Unlike the human health risk assessment in which transfer rates for humans are available, there are no transfer rates available for wildlife species. Wildlife, compared with humans, are likely to spend longer periods of time in contact with contaminated vegetation. It is reasonable to assume that for prolonged exposures an equilibrium may be reached between levels on the skin, rates of absorption, and levels on contaminated vegetation. No data regarding the kinetics of such a process, however, are available. In the absence of such data, no quantitative assessments are made for this scenario in the ecological risk assessment.

4.2.2.3. Ingestion of Contaminated Vegetation or Prey – Since oxyfluorfen 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). The use of oxyfluorfen on tree nurseries may reduce the likelihood of wildlife consuming contaminated vegetation. Nonetheless, tree nurseries may be inhabited and/or frequented by various types of animals and contaminated vegetation is a plausible route of exposure.

The consumption of contaminated insects is modeled for a small bird (Worksheet 14a) and a small mammal (Worksheet 14b). No monitoring data have been encountered on the concentrations of oxyfluorfen in insects after applications of oxyfluorfen. The empirical relationships recommended by Fletcher et al. (1994) are used as surrogates as detailed in Worksheets F14a and F14b. A similar set of scenarios is provided for the consumption of small mammals by either a predatory mammal (Worksheet 16a) or a predatory bird (Worksheet 16a). In addition to the consumption of contaminated vegetation, insects, and other terrestrial prey, oxyfluorfen may reach ambient water and fish. Thus, a separate exposure scenario is developed for the consumption of contaminated fish by a predatory bird in both acute (Worksheet F08) and chronic (Worksheet F09) exposures. Details of each scenario are given in the cited worksheets.

Multi-route exposures (e.g., the consumption of contaminated vegetation and contaminated water) are likely. Any number of combinations involving multiple routes of exposure could be developed. Such scenarios are not developed in the current risk assessment because the predominant route of plausible exposure is either contaminated vegetation (for herbivores) or the consumption of small mammals (for carnivores). Explicit considerations of other routes of exposure would have no impact on the characterization of risk.

4.2.2.4. Ingestion of Contaminated Water – Estimated concentrations of oxyfluorfen in water are identical to those used in the human health risk assessment (Worksheet B04). The only major differences involve the weight of the animal and the amount of water consumed. These differences are detailed and documented in the worksheets that involve the consumption of contaminated water (F05, F06, F07).

Unlike the human health risk assessment, estimates of the variability of water consumption are not available. Thus, for the acute scenario, the only factors affecting the estimate of the ingested dose include the field dilution rates (i.e., the concentration of the chemical in the solution that is spilled) and the amount of solution that is spilled. As in the acute exposure scenario for the human health risk assessment, the amount of the spilled solution is taken as 200 gallons for liquid formulations. For granular formulations, the amount spilled (in lbs) is calculated based on the number of acres that would be treated with the corresponding liquid formulation(s) and the range of application rates covered by this risk assessment.

In the exposure scenario involving contaminated ponds or streams due to contamination by runoff or percolation, the factors that affect the variability are the water contamination rate, (see Section 3.2.3.4.2) and the application rate. As in the human health risk assessment, exposures involving the consumption of contaminated water are much lower than exposures involving contaminated vegetation or contaminated fish.

4.2.3. Terrestrial Plants

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

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

4.2.3.2. 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 U.S. EPA, the Forest Service, and the Spray Drift Task Force, a coalition of pesticide registrants.

For aerial applications, AgDrift permits very detailed modeling of drift based on the chemical and physical properties of the applied product, the configuration of the aircraft, as well as wind speed and temperature. For ground applications, AgDrift provides estimates of drift based solely on distance downwind as well as the types of ground application: low boom spray, high boom spray, and orchard airblast. Representative estimates based on AgDrift (Version 1.16) are given in Worksheets G05a-c for low boom applications and Worksheets G06a-c for aerial applications. 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 (Teske et al. 2001).

While backpack drift is likely to be less and probably much less than any form of broadcast application, comparable methods of quantifying drift after backpack applications are not available.

4.2.3.3. Runoff – Oxyfluorfen or any other herbicide may be transported to off-site soil by runoff, sediment loss, or percolation. All of these processes are considered in estimating contamination of ambient water. For assessing off-site soil contamination, however, only runoff and sediment losses are considered. This approach is reasonable because off-site runoff and sediment loss could contaminate the off-site soil surface and could impact nontarget plants. Percolation, on the other hand, represents the amount of the herbicide that is transported below the root zone and thus may impact water quality but should not impact off-site terrestrial vegetation.

Based on the results of the GLEAMS modeling (Section 3.2.3.4.2), the proportion of the applied oxyfluorfen lost by runoff and sediment loss is estimated for clay, loam, and sand at rainfall rates ranging from 5 inches to 250 inches per year. Note that the GLEAMS modeling is based on the assumption that rainfall occurs uniformly every tenth day (SERA 2004). Thus, the annual rainfall rates correspond to rainfall events ranging from 0.14 inches to 6.94 inches. These values are summarized in Table 4-1 and are used in Worksheets G04a-c to estimate functional off-site exposure rates to nontarget plants that are associated with runoff and sediment losses.

The pesticide that is not washed off in runoff or sediment will penetrate into the soil column and the depth of penetration will depend on the properties of the chemical, the properties of the soil, and the amount of rainfall. GLEAMS outputs concentrations in soil layers of varying depths. These concentrations are output by GLEAMS in mg pesticide/kg soil (ppm). The minimum non-zero value that GLEAMS will output is 0.000001 mg/kg, equivalent to 1 nanogram/kg soil or 1 part per trillion (ppt). The deepest penetration of oxyfluorfen in clay, loam, and sand modeled using GLEAM is summarized in Table 4-2. Based on the GLEAMS modeling, oxyfluorfen may penetrate to about 12 inches in clay soils and to about 24 inches in loamy soils. In sand, detectable residues are modeled to occur at 60 inches. Because the GLEAMS modeling used a 60 inch root zone, the actual penetration in loam or sand could be greater than 60 inches.

4.2.3.4. Contaminated Irrigation Water – Unintended direct exposures of nontarget plant species may occur through the use of contaminated ambient water for irrigation. Effects on nontarget vegetation have been observed with irrigation water contaminated by other herbicides (e.g., Bhandary et al. 1997). The levels of exposure associated with this scenario will depend on the concentration of oxyfluorfen in the ambient water used for irrigation and the amount of irrigation water that is applied.

The amount of irrigation water that may be applied will be highly dependent on the climate, soil type, topography, and plant species under cultivation. Thus, the selection of an irrigation rate is somewhat arbitrary. Typically, plants require 0.1 to 0.3 inch of water per day (Delaware Cooperative Extension Service 1999). In the absence of any general approach of determining and expressing the variability of irrigation rates, the application of one inch of irrigation water

per day will be used in this risk assessment. This is somewhat higher than the maximum daily irrigation rate for sandy soil (0.75 inches/day) and substantially higher than the maximum daily irrigation rate for clay (0.15 inches/day) (Delaware Cooperative Extension Service 1999).

Based on the estimated concentrations of oxyfluorfen in ambient water and an irrigation rate of 1 inch per day, the estimated functional application rate of oxyfluorfen to the irrigated area is about 7×10^{-4} (1×10^{-6} to 9×10^{-3}) lb/acre (Worksheet F15). This level of exposure is generally below those associated with offsite drift after low boom ground applications [Worksheets G05a-c]. Thus, specific worksheets characterizing risk for this exposure scenario are not developed.

4.2.3.5. Wind Erosion – Wind erosion is a major transport mechanism for soil (e.g., Winegardner 1996). Although no specific incidents of nontarget damage from wind erosion have been encountered in the literature for oxyfluorfen, this mechanism has been associated with the environmental transport of other herbicides (Buser 1990).

Wind erosion leading to off-site contamination of pesticides will be highly site specific. The amount of oxyfluorfen 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 oxyfluorfen would be neither substantial nor significant.

For this risk assessment, the potential effects of wind erosion are estimated in Worksheets G07a-c. In these worksheets, it is assumed that oxyfluorfen is incorporated into the top 1 cm of soil. This is identical to the depth of incorporation used in GLEAMS modeling. Average soil losses are estimated at from 1 to 10 tons/ha·year with a typical value of 5 tons/ha·year. These estimates are based on field studies conducted on agricultural sites that found that wind erosion may account for annual soil losses ranging from 2 to 6.5 metric tons/ha (Allen and Fryrear 1977; USDA 1998). As indicated in Worksheets G07a-c, wind erosion for oxyfluorfen is inconsequential relative to other sources of exposure.

4.2.4. Soil Organisms

Limited data are available on the toxicity of oxyfluorfen to soil invertebrates as well as soil microorganisms. For both soil invertebrates and soil microorganisms, the toxicity data are expressed in units of soil concentration – i.e., mg oxyfluorfen/kg soil which is equivalent to parts per million (ppm) concentrations in soil. The GLEAMS modeling discussed in Section 3.2.3.4 provides estimates of concentration in soil as well as estimates of off-site movement (runoff, sediment, and percolation). Based on the GLEAMS modeling, concentrations in clay, loam, and sand over a wide range of rainfall rates are summarized in Table 4-2 for the top 60 inches of soil and Table 4-3 for the top one foot of soil. Peak soil concentrations in the top one foot of soil in the range of about 0.1 to 0.5 ppm at an application rate of 1 lb/acre, with the upper bound of this range occurring in very arid areas. As rainfall rate increases, maximum soil concentrations

decrease to the lower bound of this range. The potential consequences of such exposures for soil invertebrates and microorganisms are discussed in Section 4.4 (Risk Characterization).

4.2.5. Aquatic Organisms

The plausibility of effects on aquatic species is based on estimated concentrations of oxyfluorfen in water that are identical to those used in the human health risk assessment. These values are summarized in Table 3-7 and are discussed in Section 3.2.3.4.6.

4.3. DOSE-RESPONSE ASSESSMENT

4.3.1. Overview

The specific toxicity values used in this risk assessment are summarized in Table 4-5 and the derivation of each of these values is discussed in the various subsections of this dose-response assessment. The first column in Table 4-5 specifies the organism to which the toxicity value applies. The available toxicity data support separate dose-response assessments in eight classes of organisms: terrestrial mammals, birds, terrestrial invertebrates, terrestrial plants, fish, aquatic invertebrates, aquatic algae, and aquatic macrophytes. Different units of exposure are used for different groups of organisms depending on how exposures are likely to occur and how the available toxicity data are expressed.

As with the human health dose-response assessment, priority is given to studies which used highly pure technical grade oxyfluorfen, as this is the basis for currently registered end-use products. Special consideration is given to studies conducted with end-use products for certain species (e.g. aquatic invertebrates and algae) in which oxyfluorfen formulations appear to be more toxic than the highly pure technical grade herbicide.

Based on both acute and chronic dietary toxicity values, mammals appear to be more sensitive to oxyfluorfen than birds. On the basis of acute toxicity, mammals are approximately 10 times more sensitive than birds. On the basis of chronic toxicity, mammals are approximately 3 times more sensitive than birds. For mammals, the dose-response assessment for chronic toxicity is based on the same data as the human health risk assessment (i.e., a chronic NOAEL of 3 mg/kg/day). As discussed in the human health risk assessment, U.S. EPA has not derived an acute RfD for oxyfluorfen. However, a study from the open literature yields a NOAEL value of 19.8 mg/kg/day which was used to derive an acute RfD. These NOAEL values and a full discussion of their selection are detailed in Section 3.3. An acute NOAEL of 200 mg/kg is selected for birds on the basis of a dietary study with Mallard ducks. No lifetime toxicity studies on birds have been encountered. Based on the reproduction study, the chronic NOAEL for birds is set at 64.7 mg/kg/day. Relatively little information is available on terrestrial insects. A contact toxicity value of 1075 mg/kg bw (for honey bees) is taken as a NOAEC for terrestrial invertebrates.

The toxicity of oxyfluorfen to terrestrial plants can be characterized relatively well and with little ambiguity. Oxyfluorfen is relatively ineffective in inhibiting seed germination but is toxic after either direct spray or soil application. Based on toxicity studies in which exposure can be characterized as an application rate, oxyfluorfen is more toxic in pre-emergent soil applications than direct spray. In pre-emergent soil applications, the NOAEC values for the most sensitive and tolerant species are 0.0024 lb/acre and 0.31 lb/acre, respectively. The corresponding values for direct spray (post-emergent bioassays) are 0.00066 lb/acre and 0.034 lb/acre.

Oxyfluorfen is highly toxic to aquatic animals. The acute NOAEC values for sensitive and tolerant species of fish vary three-fold, with a range of 0.056 mg/L to 0.180 mg/L. For longer term exposures, the data are not sufficient to identify tolerant and sensitive species and a single NOAEC value of 0.038 mg/L is used. A much greater variability is apparent in aquatic

invertebrates, with acute NOAEC values ranging from 0.0001 mg/L to 2 mg/L. This is not an artifact of comparisons between freshwater and saltwater species, because the large range of sensitivities is apparent upon examination of either freshwater or saltwater data sets. The NOAEC of 0.013 mg/L from the sole reproduction study (in *Daphnia*) is used to assess the effects of longer-term exposures in tolerant aquatic invertebrates, while an estimated value of 0.0022 mg/L is used to assess longer term exposure in sensitive species. The latter value is based on the Daphnid NOAEC, but adjusted for relative sensitivity between *Daphnia* and Eastern oyster from acute toxicity studies.

Aquatic algae are more sensitive than fish but are equal in sensitivity with aquatic invertebrates. Oxyfluorfen formulations appear to be more toxic than technical grade herbicide, regardless of purity, although the lower purity material is more toxic than higher purity herbicide. NOAEC values of 0.001 mg/L and 2 mg/L are used to assess sensitive (green algae) and tolerant species (blue-green algae) and to account for the more toxic end-use product.

Aquatic macrophytes are equally sensitive to oxyfluorfen with respect to algae, as demonstrated by the only available study, which was conducted with duckweed. Since only one study was available, the LOAEC of 0.00055 for both sensitive and tolerant macrophytes is derived from this standard 5-day growth bioassay. This value is used for the assessment of both acute and chronic exposures. A NOAEC was not identified in the study due to adverse effects on growth at the lowest concentration tested.

4.3.2. Toxicity to Terrestrial Organisms

4.3.2.1. Mammals – Forest service risk assessments customarily use EPA-derived RfD values, where available, as the basis for selecting NOAEL values to assess acute and chronic exposure. As summarized in the dose-response assessment for the human health risk assessment (Section 3.3), the Office of Pesticide Programs of EPA has derived a chronic RfD of 0.03 mg/kg/day for oxyfluorfen, but has not derived an acute RfD. A chronic RfD of 0.003 appears on U.S. EPA's Integrated Risk Information System (IRIS). And although the IRIS value and the OPP value are based on the same study and use the same uncertainty factors, OPP and IRIS disagree upon the choice of a NOAEL from the study. Based on an assessment of the original study, as discussed in the next paragraph, and given that the OPP value is more recently derived, this assessment uses the OPP NOAEL of 3 mg/kg/day.

The chronic NOAEL of 3 mg/kg/day is based on the 20-month dietary study of Goldenthal and Wazeter (1977) with mice, and the 52-week dietary study of Rohm and Haas (1981c), as summarized in Appendix 3. An examination of tabulated data from the Goldenthal and Wazeter (1997) study clearly supports the selection of a NOAEL of 3 mg/kg/day (20 ppm dietary exposure). There were no statistically significant and treatment-related changes observed at this level. The only statistically significant and treatment-related changes were observed at the 200 ppm level of exposure, supporting the conclusion drawn by U.S. EPA (2001a; 2002a) that 3 mg/kg/day is truly the NOAEL for the study. Although the original study was not available for examination, U.S. EPA (1987) and OPP (U.S. EPA 2001a, 2001b) are in agreement that the NOAEL from the Rohm and Haas (1981c) study with dogs is 3 mg/kg/day.

It should be noted that the Registration Eligibility Document (RED) for Oxyfluorfen (U.S. EPA/OPP 2002a) which is based on the EFED science chapter (U.S. EPA/OPP 2001b) uses a NOAEL of 400 ppm a.i. to assess the impacts of oxyfluorfen on terrestrial mammals. This NOAEL is derived from the 2-generation reproduction study with rats (Solomon et al. 1991; MRID 42014901; summarized in Appendix 2). This study used lower purity technical grade oxyfluorfen (71.4%). A treatment-related decrease in fetal body weight was observed at 1600 ppm, resulting in a NOAEC of 400 ppm a.i. for reproductive variables. A NOAEC of 100 ppm a.i. for adult toxicity is based on dose-related histological changes in the kidneys of P1 and P2 males exposed to concentrations of 100 ppm or higher in the study. In spite of these results and the results obtained in the 20-month dietary study with mice and the 52-week dietary study with dogs, described above, neither U.S. EPA/OPP (2001b) nor U.S. EPA/OPP (2002a) give a clear rationale for the selection of a NOAEC of 400 ppm to assess the effects of chronic exposures of oxyfluorfen on mammals. Since the study used lower purity technical grade oxyfluorfen, one cannot construct the argument that the study was selected over other studies on the basis of using high purity technical grade oxyfluorfen (generally less toxic), which is the basis for the current end use products. Furthermore, lower LOAEC values of 200 ppm are derived from both the short-term dietary mouse study by Krijt (1997) and from the 20-month dietary mouse study by Goldenthal and Wazeter (1977), both of which used higher purity technical grade oxyfluorfen (99.4% in the case of Krijt 1997, and 85.7% in the case of Goldenthal and Wazeter 1977). EFED does not explicitly state whether they considered the study of Goldenthal and Wazeter (1977) or Krijt (1997) in their dose-response assessment, but it is known that EFED gives preference to multigeneration rat studies in their selection of a NOAEL for the assessment of mammalian toxicity in ecological risk assessments. Nevertheless, it is Forest Service protocol to adopt the NOAEL from the same study used as the basis for the chronic human RfD to assess risks to mammals. As such, this risk assessment uses the chronic NOAEL of 3 mg/kg/day (based on 20 ppm dietary exposure) to evaluate the potential impact of longer-term exposures to oxyfluorfen on terrestrial mammals.

As discussed previously, EPA/OPP has not derived an acute RfD to evaluate the potential short-term risks of exposure to oxyfluorfen, and thus, does not evaluate short-term risks to mammals in the RED for oxyfluorfen (U.S. EPA/OPP 2002a). This is based on EPA's conclusion that none of the available studies provided a single dose which was appropriate for assessing acute toxicity. The LD_{50} studies under EPA's consideration yielded LD_{50} values in excess of test limit concentrations, and no mortality or signs of toxicity were observed in the acute oral studies under consideration (MRIDs 447120-10 and 448289-03); U.S. EPA OPP, 2001b, page 37).

As summarized in Appendix 1 and discussed in Section 3, the standard acute oral toxicity studies on technical grade oxyfluorfen, regardless of purity, yield NOAEL or NOAEC values at the test limits. A study with Goal 2XL (24.2% a.i.) with rats yields an LD_{50} value of 4.37 g formulation/kg (Lutz and Parno 1993). No mortality was seen at doses up to and including 3 g formulation/kg. Dose-related salivation, lacrimation, passiveness, ataxia and diarrhea were seen at doses of 4 and 5 g/kg, but as discussed previously (Section 3.1.15) some of the inert ingredients in this end-use product could be responsible for these effects. Nevertheless, Goal2XL

is of a low order of acute toxicity within EPA's toxicity classification scheme based on these results. However, a short-term dietary study in the open literature (Krijt et al. 1997) demonstrated adverse effects at much lower doses. Krijt (1997) fed mice highly pure technical grade oxyfluorfen in the diet for 9 days at concentrations of 125, 200 and 1000 ppm. In comparison with pre-test control levels, statistically significant reductions in protoporphyrinogen oxidase activities in kidney and liver tissues, accompanied by significant increases in liver and kidney porphyrin concentrations, were seen in mice exposed to 200 and 1000 ppm. This yields a NOAEC of 125 ppm. Using the mid-point of the range (22-24 g) of experimentally determined mouse body weight (23 g), and the allometric equation provided online in the U.S. EPA's Wildlife Exposure Factors Handbook (U.S. EPA 1993, Section 3.1.2, Allometric Equations, Mammals, page 3-6, equation 3-8, food ingestion equation for rodents), it is possible to determine a dose associated with this dietary concentration. Assuming a body weight of 23 grams, and that the food ingestion rate = $0.061 \times bw^{0.564}$, a dietary concentration of 125 ppm is equivalent to a dose of 19.8 mg/kg/day. Using the same body weight and equations, the LOAEC of 200 ppm is equivalent to a dose of 31.7 mg/kg/day. These values are used in this risk assessment to evaluate risks to mammals associated with short-term exposure to oxyfluorfen.

4.3.2.2. Birds –Standard laboratory studies on birds are usually conducted with bobwhite quail and mallard ducks. Studies with these species have only been conducted with lower purity technical grade oxyfluorfen. On the basis of 5-day dietary studies with bobwhite quail and mallard ducks, lower purity technical grade oxyfluorfen yielded NOAEC values of 1250 ppm a.i.(as discussed below, is equivalent to 200 mg/kg for duck) for both studies (Appendix 5, Fletcher 1987a,c). The highest concentration tested, 5000 ppm, was associated with decreased body weight or body weight gain in both species. A multiple gavage study with American Kestrel was located in the open literature (Hoffman et al. 1991a, b). In this study 4 nestlings were exposed by gavage to highly pure technical grade oxyfluorfen for 10 days, the NOAEL for the study was the test limit, 500 mg/kg bw.

Reproduction studies are generally used to assess the consequences of longer-term exposures for birds. As shown in Appendix 5, the dietary reproduction studies (twenty weeks) conducted with highly pure technical grade oxyfluorfen suggest that mallards are more sensitive than quail. No effects on reproduction or parental animals were seen in quail at the highest concentration tested, yielding a NOAEC of 750 ppm a.i. for both reproductive and toxic effects (Frey et al. 2003b). In ducks, decreases in egg production, hatchability, and embryo development were observed at a concentration of 750 ppm a.i. The NOAEC for reproductive effects was 500 ppm, which was associated with a measured dose of 64.7 mg/kg/day (Frey et al. 2003a).

Based on the above considerations, a NOAEL of 64.7 mg/kg/day is used in this assessment to evaluate chronic avian exposure to oxyfluorfen. Given that this value is based on a study on ducks, and that toxicity in ducks and quail is equivalent in comparable studies, the acute NOAEC for ducks is chosen to evaluate acute avian exposure to oxyfluorfen. As detailed in Appendix 5 (Fletcher 1987c), the acute NOAEC of 1250 ppm is converted to a NOAEL of 200 mg/kg based on the body weights and food consumption rates measured in the experiment. The NOAEL of 200 mg/kg is used in this assessment to evaluate acute avian exposure to oxyfluorfen.

4.3.2.3. Terrestrial Invertebrates – There is very little information on the toxicity of oxyfluorfen to terrestrial insects. This is the case with most herbicides, which are generally presumed to be relatively nontoxic to insects and other invertebrates. Based on the study by Atkins (1992), the acute contact LD_{50} for oxyfluorfen is reported as greater than 0.100 mg/bee, a dose which corresponds to about 1075 mg/kg bw (authors state this dose is equivalent to an application rate of 8.93 lb a.i./acre). This is consistent with the low dermal toxicity observed in mammals. There is a study which tested the impact of Goal 4F on predacious mites (Milligan 2000), and identified a LOAEC of 1.44 kg a.i./ha (1.28 lb a.i/acre). Mite proto-nymphs were exposed to plates sprayed with Goal 4F and observed for 7 days. Mortality was 98% in the Goal exposed group in comparison with 5% of the unexposed controls. However, it is not possible to convert the application rate to a dose on the basis of information provided in the study. Thus, the value of 1075 mg/kg bw derived from the bee study is used to characterize risks for honey bees.

4.3.2.4. Terrestrial Plants (Macrophytes) – As discussed in Section 4.1.2.4, oxyfluorfen is phytotoxic when applied to soil (pre-emergence) or directly to plants by spraying (post-emergence).

For assessing the potential consequences of exposures to nontarget plants via runoff or direct soil treatment, the seedling emergence (pre-emergence application) bioassays by Hoberg (1990) are used (Appendix 7). In this bioassay, the most sensitive species were cabbage, lettuce, onion and ryegrass, with an NOAEC for all effects of 0.0024 lb/acre. The most tolerant species was soybean, with an NOAEC for all effects of 0.31 lb/acre. These values are used in all worksheets assessing the consequences of soil treatment (Attachment 1, Worksheets G04a-c).

For assessing the impact of drift, the post-emergent (vegetative vigor) bioassays by Hoberg (1990) are used. In this series of bioassays, the most sensitive species was tomato, with an NOAEC of 0.00066 lb/acre for all endpoints. The least sensitive species was corn, with an NOAEC of 0.034lb/acre. These values are used to characterize risks to non-target terrestrial vegetation in all worksheets assessing the consequences of accidental direct spray or drift (Worksheets G05a-c, G06a-c, and G07a-c).

4.3.2.5. Terrestrial Microorganisms – As summarized in Appendix 6, studies have been conducted to assess the effects of oxyfluorfen treatment on soil microorganisms. These are field studies, which taken together, suggest that oxyfluorfen use is probably not harmful at usual application rates, and may even benefit soil microbe populations in ways that are beneficial to plants. This information is considered directly in the risk characterization for terrestrial microorganisms (Section 4.4.2.5).

4.3.3. Aquatic Organisms

4.3.3.1. Fish – As with mammals, the higher purity technical grade herbicide (94%) was less toxic to fish than the lower purity material (71.4 - 74%), although both low- and high- purity herbicides yielded LC_{50} values which classify oxyfluorfen as highly toxic on the basis of acute toxicity (studies discussed in Section 4.1.3.1 and summarized in Appendix 8). In the short-term studies conducted with higher purity oxyfluorfen, bluegills were the most sensitive, while rainbow trout were the most tolerant. The NOAEC values used to evaluate acute exposure to sensitive and tolerant species of fish are 0.056 mg/L (MRID 95585 cited by U.S. EPA 2001b) and 0.180 mg/L (MRID 95585 cited by U.S. EPA 2001b), respectively.

The only available early life stage study (Godfrey and Longacre 1990f) was conducted with fathead minnows and lower purity technical grade oxyfluorfen. This study yielded a NOAEC of 0.038 mg/L, with concentrations of 0.074 mg/L and higher causing reduced survival, total length and average weight of fry in comparison with controls. The only other longer term studies available were conducted with species from the Nile River in Egypt for purposes of identifying markers of exposure. In these studies (Hassanein et al. 1999, 2002), fish were exposed to Goal herbicide (23.6 % a.i.) for up to 30 days. In *Oreochromis niloticus*, a 30-day LOAEC of 0.3 mg/L was identified for reduced brain acetylcholinesterase activity in comparison with unexposed controls (Hassanein 2002). In another study with the same species (Hassanein et al. 1999), heat shock proteins indicative of exposure were induced in kidney and liver tissue, with a study LOAEC of 0.75 mg a.i./L following 8 to 24 days of exposure.

A method commonly employed by EPA in human health risk assessment is to derive a NOAEC from a LOAEC by dividing the LOAEC by an uncertainty factor of 10. Similarly, a NOAEC of 0.03 mg/L can be derived from LOAEC of 0.3 mg/L from the Hassanein studies. The NOAEC derived in this manner concurs with the experimentally derived NOAEC of 0.038 mg/L from the standard egg and fry bioassay with fathead minnows. Based on these considerations, the NOAEC of 0.038 mg/L from the fathead minnow study is chosen as the reference toxicity value with which to assess long-term exposure to oxyfluorfen among fish. Because the study was conducted with lower purity oxyfluorfen, which was shown to be more toxic than the higher purity technical grade herbicide in the acute studies, and was conducted with the most sensitive species identified in acute studies, the NOAEC value is expected to be protective of sensitive species, but is used in this assessment to evaluate both sensitive and tolerant species (Worksheet G03a-c). Whether an end-use formulation could yield greater toxicity in the rainbow trout than the fathead minnow has not been determined experimentally.

4.3.3.2. Amphibians –No studies which address the toxicity of oxyfluorfen to amphibians are available. Given the lack of studies, it is not possible to conduct a dose-response assessment and ultimately, to characterize risks of oxyfluorfen exposure to amphibians.

4.3.3.3. Aquatic Invertebrates – The available studies were conducted with lower purity technical grade oxyfluorfen, and one acute study with *Daphnia* was conducted with Goal 2XL formulation (Appendix 9). Based on a comparison of technical grade oxyfluorfen (48-hour NOAEC = 1.5 mg a.i./L; MRID 96881 cited by U.S. EPA 2001b) versus Goal 2XL formulation

(48-hour NOAEC = 0.0197 mg a.i./L; Sutherland et al. 2000a) in acute toxicity studies with *Daphnia*, oxyfluorfen formulations are likely more toxic than even the lower purity technical grade herbicide. Even so, *Daphnia* was neither the most sensitive nor the most tolerant aquatic invertebrate species tested.

A much greater range of sensitivities is apparent in aquatic invertebrates than fish. Based on standard acute (48- and 96-hour) bioassays, the most sensitive species are bivalve mollusks: the Eastern oyster (MRID 96881 cited by U.S. EPA 2001b) and a freshwater clam (*Elliptio complanata*) (Godfrey and Longacre 1990b), both with a NOAEC values of 0.0032 mg/L . Other species of aquatic invertebrates are much less sensitive. As noted in Section 4.1.3.3, the fiddler crab, a large crustacean, is much less sensitive, with a NOEC for mortality of 320 mg/L (MRID 96811 cited by U.S. EPA 2001b). These values encompass the range of sensitivities for aquatic invertebrates in both freshwater and saltwater, and thus are used to evaluate sensitive (NOAEC = 0.0032 mg/L) and tolerant (NOAEC = 320 mg/L) species in either a freshwater or saltwater environment. As with fish, it is impossible to know without further testing whether the NOAEC values for these sensitive and tolerant species would be lower if the studies had been conducted with Goal 2XL formulation.

The only study from which chronic toxicity data are available is a 21-day life cycle study with *Daphnia magna* reported by Godfrey and Longacre (1990g) and Forbis (1986). The NOAEC from this study is 0.013 mg/L. This value is much higher than the acute NOAEC of 0.0032 mg/L selected to evaluate sensitive species and much lower than the acute NOAEC of 320 mg/L selected to evaluate tolerant species. As mentioned previously, the study was conducted with lower purity technical grade oxyfluorfen.

Given that the toxicity of a compound generally increases with increasing duration of exposure (i.e. the dose tolerated without adverse effects gets smaller), it would be inappropriate to use 0.013 mg/L to evaluate sensitive species, but would be appropriate to use for tolerant species. Therefore, for purposes of this assessment, 0.013 mg/L is taken as a reference toxicity value to evaluate chronic exposure of tolerant species.

A reference toxicity value for use in evaluation of chronic exposure of sensitive species is derived as follows. Dividing the acute NOAEC for *Daphnia*, by the acute NOAEC for the most sensitive species, the Eastern oyster, results in a ratio of 6 (i.e. Easter oyster is 6 times more sensitive than *Daphnia* on an acute basis). Using this ratio, it is possible to adjust the chronic Daphnid NOAEC downward to account for the relative sensitivity between *Daphnia* and eastern oyster by dividing the chronic Daphnid NOAEC of 0.013 mg/L by 6, to arrive at an adjusted chronic NOAEC of 0.0022 mg/L. The NOAEC of 0.0022 is used to evaluate chronic exposure of sensitive aquatic invertebrates in this assessment. A similar adjustment is not made between Daphnia and the fiddler crab to derive a chronic value for tolerant species because of the large size differences and variability between the juvenile and adult phases of the crab, relative to *Daphnia*, and the large differences in acute toxicity. As noted above, the daphnid NOAEC of 0.013 is used to evaluate tolerant species.

The assumptions and uncertainties inherent in the above derivation of a NOAEC for chronic exposure of sensitive species are threefold. First, the approach assumes that the ratios of acute toxicity among species are equivalent with respect to ratios of chronic toxicity among the same species. Secondly, the approach assumes that the acute to chronic ratio is consistent between species. And lastly, the differences in inerts and impurities in the various studies, and their impact on toxicity, as stated above, is not taken into account (i.e. studies to determine this are not available).

4.3.3.4. Aquatic Plants – The relevant data on the toxicity of oxyfluorfen to aquatic plants are discussed in Section 4.1.3.4 and summarized in Appendix 10. With this herbicide, the toxicity values for aquatic plants are much lower than those for fish, but the values for aquatic plants encompass the range of toxicity values for aquatic invertebrates.

Based on the standard bioassays of algal cell growth conducted with lower purity technical grade oxyfluorfen, relatively substantial differences in sensitivity to oxyfluorfen are apparent. The differences span a factor of 8,333 based on the EC_{50} values and 20,000 based on the NOAEC values. The most sensitive species appear to be *Navicula pelliculosa* (a freshwater diatom; 5-day-EC_{50}: 0.00024 mg/L and a corresponding NOAEC of 0.0001 mg/L; Giddings 1990) and *Selenastrum capricornutum* (a freshwater green alga; 5-day-EC_{50}: 0.00035 mg/L and a corresponding NOAEC of 0.00032 mg/L; Giddings 1990). The least sensitive species appears to be *Anabaena flos-aquae* (a freshwater blue-green alga) with a 5-Day EC_{25} of >2 mg/L and a corresponding NOAEC of 2 mg/L (Giddings 1990).

There is only one standard bioassay for algal cell growth (Hoberg 1999) which was conducted with highly pure technical grade oxyfluorfen (99.19% a.i.), and it was conducted with *Pseudokirchneriella subspicata* (freshwater green alga). While this green alga was somewhat less sensitive than the diatom in the above studies with lower purity oxyfluorfen, it is still on the more sensitive end of the spectrum of species tested with regard to toxicity. The NOAEC from the Hoberg (1999) study is 0.0029 mg/L, which is approximately 10-fold higher than the NOAEC of 0.00032 obtained in the study with lower purity technical herbicide. A standard EPA growth and biomass study conducted with *Selanastrum capricornutum* and Goal 2XL (Sutherland et al. 2000b) yielded a 96-hour NOAEC of 0.00043 mg formulation/L. As Goal 2XL is 23% a.i., these values translate to an EC_{50} of 0.00028 mg a.i./L and a NOAEC of 0.000099 mg a.i./L. The relative sensitivity of green algae and tolerance of blue-green algae to formulations of Oxyfluorfen (in this case, Goal 2E) is confirmed in the open literature (Appendix 10). Taken together, these studies demonstrate that lower purity technical grade oxyfluorfen and oxyfluorfen formulations are more toxic to aquatic algae than the highly pure technical grade herbicide. As such, the GOAL 2XL NOAEC of 0.00099, rounded to 0.0001 mg/L, is used to evaluate sensitive species. The NOAEC of 2 mg/L from the Hoberg (1990) assay with *Anabaena flos-aquae* is used to evaluate tolerant algal species.

There is only one study to evaluate the toxicity of oxyfluorfen to aquatic macrophytes (Section 4.1.3.4). The seven-day LOAEC of 0.00055 mg/L from the study with duckweed (Giddings 1990) is used to evaluate both sensitive and tolerant species. The study was conducted with

lower purity oxyfluorfen, and thus should be somewhere in the range of toxicity values that could be expected if tests on macrophytes had been conducted with highly pure technical grade herbicide (would expect lower toxicity) and oxyfluorfen formulations (would expect greater toxicity).

4.4. RISK CHARACTERIZATION

4.4.1. Overview

Oxyfluorfen has been tested in a variety of organisms. However, by necessity, the available tests represent a limited number of species, and the conditions of the tests may not represent actual conditions of exposure in the wild. These are limitations inherent to any risk characterization, and may result in underestimates or overestimates of actual risk. The methods used in both the exposure and dose-response assessments are intended to consider these uncertainties by using protective assumptions in developing both the exposure and dose-response assessments which form the basis of the risk characterization.

Because oxyfluorfen is an effective herbicide, unintended effects on nontarget vegetation are plausible. The effective use of oxyfluorfen is achieved by applying it to target vegetation at a time and in a manner which will minimize effects on nontarget plant species. If this is done properly and with care, effects on nontarget vegetation could be minor. Nonetheless, in the normal course of applications of formulations at rates that are effective in weed control, adverse effects on terrestrial plants are plausible due to either drift or runoff. Depending on local conditions and the proximity of streams or ponds to oxyfluorfen applications, damage to aquatic vegetation is also plausible and could be substantial.

Over the range of application rates used in Forest Service programs (0.25 to 2 lbs/acre), adverse effects on aquatic vegetation and invertebrates are highly likely if steps are not taken to prevent oxyfluorfen from entering nearby ponds or streams. Adverse effects in fish are likely only in association with the maximum application rate of 2 lbs/acre.

Over the range of application rates used in Forest Service programs, adverse effects are plausible in mammals consuming contaminated vegetation and insects following application at the typical and maximum application rates, but not likely at the lower application rate. There is no indication that substantial numbers of mammals would be subject to lethal exposure to oxyfluorfen. Consequently, adverse effects such as weight loss and reproductive impairment could occur but might not be readily apparent or easy to detect. Birds appear to be much more tolerant to oxyfluorfen than mammals and adverse effects on birds do not seem plausible.

In addition to the direct effects mentioned above, both terrestrial and aquatic animals could be impacted secondarily by the adverse effects of oxyfluorfen on vegetation. These secondary effects associated with the depletion of vegetation would likely be variable over time and among different species of animals. Some effects could be detrimental for some species – i.e., a reduction in the supply of preferred food or a degradation of habitat – but beneficial to other species – i.e., an increase in food or prey availability or an enhancement of habitat.

4.4.2. Terrestrial Organisms

The quantitative risk characterization for mammals and other terrestrial animals is summarized in Worksheets G02a-c of the EXCEL workbook (Attachment 1). These worksheets summarize the hazard quotients for the range of application rates specifically considered in this risk assessment: a typical rate of 1 lb/acre (Worksheet G02a), the lowest anticipated application rate of 0.25

lbs/acre (Worksheet G02b), and the highest anticipated application rate of 2 lbs/acre (Worksheet G02c). In this and all other similar worksheets, risk is characterized as the hazard quotient, the estimated dose (taken from Worksheet G01) divided by toxicity value. The toxicity values used for each group of animals – mammals, birds, and insects – are summarized in Table 4-5 and the specific toxicity values used for mammals are discussed in Section 4.3.2.1. These toxicity values are repeated in the last column of the worksheets. A hazard quotient of one or less indicates that the estimated exposure is less than the toxicity value. When this is the case, there is no basis for asserting that adverse effects are plausible.

4.4.2.1. Mammals – No hazard quotient exceeds the level of concern for terrestrial mammals exposed via scenarios involving the lowest oxyfluorfen application rate (Worksheet G02b). However, hazard quotients greater than one are estimated for small and large mammals under certain acute and long-term conditions of exposure involving the typical (1 lb/acre) and maximum (2 lbs/acre) application rates, respectively (Worksheets G02a and G02c), as follows:

Small mammal, acute exposure, direct spray, HQ = 1.2 to 2.0;
small mammal, acute exposure, contaminated insects, HQ = 1.2 to 7;
large mammal, acute exposure, contaminated grass, upper bound HQ = 2 to 5;
large mammal, longer term exposure, on-site ingestion of contaminated vegetation, upper bound HQ = 2 to 4.

A basis for the acute hazard quotients is the acute NOAEL of 19.8 mg/kg. This NOAEL is derived from the Krijt et al. (1997) study on mice, in which a LOAEL of 31.7 mg/kg was estimated (Section 4.3.2.1). Given that the LOAEL is less than a factor of 2 greater than the NOAEL, HQ values of 2 and higher indicate that adverse effects are highly plausible. These effects would include a decrease in protoporphyrin oxidase levels and subsequent increases in kidney and liver uroporphyrins. Such changes are consistent with interference in heme biosynthesis, and potential liver and kidney damage, and could possibly affect growth, and survival.

A basis for the chronic HQ values is the chronic NOAEL of 3 mg/kg/day from the studies of Goldenthal and Wazeter (1977) on mice, and Rohm and Haas (1981c) on dogs. The LOAELs from these studies are approximately 33 mg/kg/day for male mice, and 18.5 mg/kg/day for male dogs. This translates to a thee- to six-fold difference between the NOAEL and the LOAEL values in these studies (three-fold for mice; six-fold for dogs; see Appendix 3 for details). The upper bound HQ values of 2 and 4 were estimated for large mammals ingesting contaminated vegetation on-site where application rates were 1 lb/acre and 2 lbs/acre, respectively. The HQ value associated with the lower typical application rate of 1 lb/acre is less than 3-to-6-fold above the NOAEL, suggesting that mammals under these conditions are not likely to achieve LOAEL doses, but could still have adverse effects because the anticipated exposure exceeds the NOAEL. However, the HQ of 4 associated with the 2 lbs/acre application rate, is within the 3- to 6-fold range above the NOAEL, suggesting that LOAEL doses could be achieved, and that the expression of adverse effects is probable. For mice, these effects include pathological liver

changes, including tumors. For dogs, these effects include decreased body weight and liver changes.

In summary, the estimates of risk for mammals indicate that growth and survival could be adversely affected at the typical application rate of 1 lb/acre, and probably would be adversely affected at the highest application rate of 2 lbs/acre. This risk characterization for terrestrial mammals is consistent with the risk assessments by the U.S. EPA/OPP (2001b; 2002a) in which hazard quotients for chronic exposure exceed the level of concern for mammals feeding on short grass and insects, in scenarios involving an application rate of 2 lbs/acre (U.S. EPA/OPP 2001b, p. 37). Had U.S. EPA/OPP (2001b) used the same chronic NOAEL used in this assessment (they used 400 ppm, this assessment uses 20 ppm converted to a dose of 3 mg/kg/day; see Section 4.3.2.1 for details), they would have also predicted adverse effects in mammals for scenarios involving application rates less than 2 lbs/acre. U.S. EPA/OPP (2001b; 2002a) did not characterize risks associated with acute exposures due to the stated lack of an appropriate acute NOAEL, for reasons discussed previously (Sections 3.3.3 and 3.4.3.2.1).

As noted in Section 4.1.2.1, the effect of oxyfluorfen on vegetation may alter habitat and these alterations may increase or decrease food availability. These secondary effects are likely to be variable over time and among different species of mammals.

4.4.2.2. Birds – Worksheets G02a-c of the EXCEL workbook in Attachment 1summarize the risk characterization for birds. As noted in Section 4.3.2.2 and summarized in Table 4-5, birds appear to be substantially more tolerant of oxyfluorfen than mammals, in terms of both the acute NOAEL (10 times higher in birds) and the longer-term NOAEL (21.5 times higher in birds).

At the highest anticipated application rate and the at the upper limit of exposure, none of the hazard quotients exceed a level of concern (HQ=1). Thus, there is no basis for asserting that any adverse effects are plausible in birds following exposure to oxyfluorfen in association with Forest Service activities. This unambiguous risk characterization, however, is not consistent with the risk characterization for birds given by the U.S. EPA/OPP (2001b; 2002a) in the re-registration eligibility document for oxyfluorfen. In their assessment, U.S. EPA concluded that application rates of 0.25 lbs a.i./acre and higher would result in adverse effects on birds. The reason for this discrepancy is that U.S. EPA did not have the MRID studies of Frey et al. (2003a,b, Appendix 5). Frey et al (2003a, b) used high purity technical grade oxyfluorfen (99.3% a.i.) in their studies. As noted previously, the high purity technical grade oxyfluorfen is the basis for the currently manufactured oxyfluorfen formulations, and is basis for the chronic NOAEL used in this risk assessment. U.S. EPA's assessment is based on the data they had at the time, which in the case of chronic avian studies, consisted solely of studies conducted with lower purity technical grade herbicide. In keeping with precedent set by U.S. EPA (2001a,b, 2002a), this risk assessment gives priority to studies conducted with high purity technical grade oxyfluorfen, which is the basis for the currently registered end-use herbicides. As such, adverse effects are not plausible for birds, even in association with exposure to oxyfluorfen at the highest application rate of 2 lbs/acre.

As with mammals, secondary effects on some species of birds may occur through changes in vegetation that may impact food availability and habitat (Section 4.1.2.2). These effects may be beneficial or detrimental and are likely to vary over time. There is no basis for asserting, however, that negative impacts on populations of birds will be substantial or severe.

4.4.2.3. Terrestrial Invertebrates – Three studies which assess the effects of oxyfluorfen on terrestrial invertebrate species are available. These studies, summarized in Appendix 6, involve honey bees, predacious mites and entomopathogenic nematodes. Given the large number of terrestrial invertebrate species, this severely limits the risk characterization.

The study on honey bees yields information which can directly be used to estimate hazard quotients for risk characterization. These data, shown in Worksheets G02a through G02c, suggest that honey bees will not be adversely affected by oxyfluorfen use, even at the highest application rate (i.e., all HQ values less than one).

In a series of laboratory studies with an unspecified Goal formulation, Rovesti and Desceo (1990) report limited mobility among entomopathogenic nematodes exposed to 5000 ppm, but not 625 ppm. However, the highest application of Goal (10,000 ppm) had no effect on the ability of the nematodes to infect their prey. The nematodes and larvae in these experiments were exposed to oxyfluorfen under highly artificial conditions (e.g. in water solutions or in dishes with moistened fine sand) which are not clearly described in the paper. As such, it is not possible to translate these conditions of exposure into meaningful estimates which could reflect exposure under field conditions. However, given these limitations, it is likely that oxyfluorfen concentrations which could result in soil following Forest Service use scenarios, are likely to be significantly lower than those encountered in these laboratory studies. Table 4-2 indicates that concentrations are likely to be no higher than 60 ppm, even in conditions which favor high concentrations (e.g. sand, high rainfall).

Data provided in the study by Milligan (2000) suggest that predacious mites might be affected by oxyfluorfen use near the typical application rate of 1 lb/acre. In this study, Goal 4F adversely affected survival and reproduction in *Typhlodromus pyri* protonymphs when exposed to plates sprayed with Goal 4F at a concentration equivalent to an application rate of 1.44 kg/ha (1.28 lbs a.i./acre).

In addition to the above considerations, oxyfluorfen may have effects on nontarget vegetation that result in secondary effects on terrestrial invertebrates. The extent with which such effects would be regarded as beneficial or detrimental is speculative. No field studies to determine whether changes in the distribution of soil invertebrates occurs following oxyfluorfen use are available. See Section 4.4.2.5 for a discussion of the impacts of oxyfluorfen exposure on soil microorganisms.

4.4.2.4. Terrestrial Plants – A quantitative summary of the risk characterization for terrestrial plants is presented in Worksheets G04a-c for runoff, Worksheets G05a-c for drift after low boom ground applications, G06a-c for drift after aerial applications, and Worksheets G07a-c for

off-site contamination due to wind erosion. As with the worksheets for terrestrial animals, the a-c designations represent groups of three worksheets for the typical application rate (a), the lowest anticipated application rate (b), and the highest anticipated application rate (c). Also analogous to the approach taken for terrestrial animals, risk in these worksheets is characterized as a ratio of the estimated exposure to a benchmark exposure (i.e., exposure associated with a defined response). The benchmark exposure is a NOAEC, as derived in Section 4.3.2.4, for both sensitive and tolerant species.

Oxyfluorfen is an effective herbicide and adverse effects on some nontarget plant species due to direct application or drift are likely. Direct spray or direct application is likely to damage both tolerant and sensitive plant species. Spray drift will affect sensitive species under most modeled conditions, and tolerant species within up to 50 feet of application, depending on the application method and rate used. For low boom ground applications (Worksheets G05a-c), damage to off-site sensitive species may occur at distances beyond 900 feet at the highest application rate and up to about 100 feet at the lowest application rate. For aerial spray application (not currently employed by the Forest Service for oxyfluorfen) the HQ values are much higher for distances between 25 and 100 feet of the site in comparison with low boom ground applications. As with ground application, damage to sensitive species could be apparent at distances beyond 900 feet at the highest application rate and up to about 100 feet at the lowest application rate (Worksheets G06a-c).

Whether or not damage due to drift would actually be observed after the application of oxyfluorfen would depend on a several site-specific conditions, including wind speed and foliar interception by the target vegetation. In other words, in applications conducted at low wind speeds and under conditions in which vegetation at or immediately adjacent to the application site would limit off-site drift, damage due to drift could be inconsequential or limited to the area immediately adjacent to the application site.

Thus, all of these risk characterizations for drift should be viewed as only a crude approximation of the potential for damage during any actual application. AgDrift is a highly parameterized model and the output of the model is sensitive to a number of site-specific and application specific variables – e.g., wind speed, type of aircraft, and elevation at which the pesticide is released. It is not feasible and would not be particularly useful to elaborate a large number of different drift scenarios based on the many variables that could be modified. The generic drift modeling presented in Worksheets G05a-c and Worksheets G06a-c suggests that efforts should be made to minimize drift. This is supported by the study of Holmdal 1984b (summarized in Appendix 8) in which phytotoxicity was observed in lettuce plants located 35 to 800 meters from the site of application. If threatened or endangered species are in the area to be treated, the site-specific application of AgDrift or some other appropriate drift model should be considered.

In contrast to drift that could occur during application, relatively conservative estimates of pesticide transport by wind erosion of soil (Worksheets G07a-c) suggest that wind erosion is not likely to result in exposures that would be of concern. At the highest application rate (Worksheet G07c), the upper bound of the hazard quotient for the most sensitive species is only 0.4.

As summarized in Worksheet G04a-c, the off-site transport of oxyfluorfen by runoff and sediment losses could cause substantial damage to sensitive, but not tolerant, species under conditions that favor runoff and sediment loss – i.e., high rainfall rates and clay or loam soil. Based on the generic GLEAMS modeling for off-site pesticide losses (Table 4-4), adverse effects in sensitive species could be expected across the range of application rates in clay and loam soils. In predominantly sandy soils, the major transport mechanism is percolation into the soil with very little risk of off-site loss due to runoff or sediment loss. As with AgDrift, GLEAMS is a highly parameterized model that is designed for site-specific assessments (Knisel and Davis 2000; SERA 2004b). The use of the generic modeling in the current risk assessment is simply to illustrate factors that may need to be considered in assessing the potential for significant off-site movement. For oxyfluorfen, the potential appears to be high, particularly for predominantly loam and clay soils.

This risk characterization is reasonably consistent with the risk characterization given by U.S. EPA/OPP (2001a), though the numeric estimates of risk differ between this assessment and U.S. EPA's, due to differences in toxicological endpoints (i.e., EC_{25} values rather than NOEC values) and modeling scenarios. In their assessment, U.S. EPA concludes that oxyfluorfen exposure is of concern for nontarget plant species for all the scenarios they modeled. They concluded further that spray drift plays an important role in damage to nontarget species, with aerial applications having an approximate 5-fold increase in risk quotients over other methods. U.S. EPA/OPP 2001b, pp. 40-41) risk quotients range from less than 1 to over 183. The risk quotients estimated in the worksheets for the current Forest Service risk assessment range from less than 1 to over 3,000.

In summary, this assessment and U.S. EPA (2001b; 2002a) conclude that nontarget plant species could be adversely affected by the runoff, sediment loss, or off-site drift of oxyfluorfen under a variety of different scenarios depending on local site-specific conditions that cannot be generically modeled. If oxyfluorfen is applied in proximity to sensitive crops or other desirable sensitive plant species, site-specific conditions and anticipated weather patterns will need to considered if unintended damage is to be avoided.

4.4.2.5. Soil Microorganisms – As discussed in Section 4.1.2.5, and summarized in Appendix 6, several studies have been conducted on the toxicity of oxyfluorfen to soil bacteria and fungi. Though insufficient information is provided in these studies to reach definitive conclusions with a high degree of confidence, taken together, the studies suggest that oxyfluorfen application at rates lower than those typically used by the Forest Service can affect soil microorganisms.

A field study by Nayak (1994) suggests that after an initial reduction following application of oxyfluorfen to soil at a rate of 0.03 kg/ha (formulation and a.i. not specified) bacterial, fungal and actinomycete populations equaled or exceeded to those of controls on days 56 and 75 post-treatment. In a similar study, fungal populations were not affected at a pre-emergence application rate of 0.25 kg a.i./ha (formulation not specified; equivalent to 0.22 lb a.i./acre) but increased with respect to controls in sandy loam soil treated with 0.5 kg a.i./ha (0.45 lb a.i./acre) (Ahmed and Vyas 1997). A study by Das et al. (2003) showed that post-emergence use of

oxyfluorfen in a rice field at a rate of 0.12 kg a.i./ha (0.11 lb a.i./acre) increased the number of phosphate-solubilizing microorganisms in the rhizosphere of the soil and increased the available phosphate content of the soil.

4.4.3. Aquatic Organisms

The risk characterization for aquatic organisms is presented in Worksheets G03a, G03b, and G03c, in Attachment 1 for typical (1 lb/acre), lower (0.25 lbs/acre) and maximum (2 lbs/acre) application rates, respectively. Risks to both tolerant and sensitive species are presented where appropriate toxicity data are available (discussed in Section 4.3.3.1). Risk estimates suggest that aquatic plants and invertebrates are the most sensitive, and fish are the least sensitive.

4.4.3.1. Fish –The risk characterization for acute exposure suggests that an accidental spill would cause adverse effects in both sensitive and tolerant fish, regardless of application rate, unless precautions are taken. The range of upper bound HQ values for sensitive species is from 20 for an application rate of 0.25 lbs/acre, to 162 for 2 lbs/acre. For acute exposure based on peak estimated concentrations following drift from herbicide application, HQ values indicate that risks are plausible only in association with the maximum application rate (upper bound HQ values = 7 for sensitive species, and 2 for tolerant species). These HQ values are based on NOAEL values from studies conducted with high purity technical grade herbicide (MRID 95585, as cited by U.S. EPA 2001b, summarized in Appendix 8). As noted previously (Section 4.3.3.1) end-use formulations are likely to be more toxic than highly pure technical grade oxyfluorfen.

The risk characterization for longer-term exposure suggests that adverse effects on fish are not plausible in association with the use of oxyfluorfen at even the highest application rate of 2 lbs/acre. The upper bound HQ for sensitive species is only 1.1. A basis for this HQ is the long-term NOAEL of 0.038 mg/L from the early life-stage study of fathead minnows conducted with lower-purity technical grade oxyfluorfen (Godfrey and Longacre 1990f, summarized in Appendix 8). As discussed in Section 4.3.3.1, bluegills are more sensitive than rainbow trout in terms of acute toxicity. As there were no studies of acute toxicity conducted with fathead minnows, it is not possible to know whether fathead minnows are more or less sensitive than either bluegills or rainbow trout. As such, it is not possible to determine whether the chronic NOAEL from the fathead minnow study is representative of either sensitive or tolerant species, and whether risks characterized with this value are over- or under-protective of most fish species. In addition, since the acute studies indicate that formulations are more toxic than technical grade oxyfluorfen, it is not possible to say whether risks associated with an end-use product would be higher or lower than those estimated on the basis of the existing fathead minnow study.

It should be noted that secondary effects on fish could be associated with damage to aquatic invertebrates and vegetation (Sections 4.4.3.3 and 4.4.3.4). The nature of these effects could be beneficial or detrimental and could be variable over time and probably among different species of fish.

Although different modeling scenarios and toxicity endpoints were used, the risk characterization for fish in this assessment is generally consistent with that conducted by U.S. EPA (2001b; pp

23-24). U.S. EPA (2001b) shows acute risk quotients in excess of a level of concern (acute restricted use) for application rates of 1.2 and 2 lbs/acre, and no longer term risks above levels of concern for scenarios involving application rates up to and including 2 lbs/acre.

4.4.3.2. Amphibians –A risk characterization for amphibians is not possible due to a lack of data on the toxicity of oxyfluorfen to amphibians.

4.4.3.3. Aquatic Invertebrates – Sensitive aquatic invertebrates, such as bivalve mollusks and *Daphnia*, are likely to be adversely affected by oxyfluorfen under normal conditions of use, if steps are not taken to eliminate contamination of nearby aquatic habitats. More tolerant species, such as the fiddler crab, are unlikely to be affected.

The risk characterization for sensitive aquatic invertebrates in response to acute exposure parallels that for fish, but with higher HQ values. For an accidental spill, upper bound HQ values for sensitive species greatly exceed a level of concern (HQ = 1), ranging from 365 to 2839 in association with the lower (0.25 lbs/acre) to maximum (2 lbs/acre) application rates, respectively. For non-accidental acute exposure, upper bound HQ values range from 16 to 125 for lower and maximum application rates, respectively.

Longer-term risk is marginally enhanced above the level of concern for sensitive species at the lower application rate (upper bound HQ = 2), and is elevated above the level of concern at the typical (1 lb/acre, HQ = 9) and maximum (2 lbs/acre, HQ = 18) application rates. For tolerant species, risk is marginally elevated above the level of concern for the typical (HQ = 1.5) and maximum application rates (HQ = 2).

Many ecologically important aquatic invertebrates are primary consumers of aquatic vegetation. It is virtually certain that effects on aquatic vegetation (Section 4.4.3.4) would enhance the detrimental effects on aquatic invertebrates anticipated in association with direct toxicity.

As with fish, and with the same caveats regarding modeling and toxicity endpoints, this risk characterization for aquatic invertebrates is consistent with that of U.S. EPA/OPP (2001b). U.S. EPA/OPP (2001b) characterizes risks to aquatic invertebrates as greater than those for fish, with risk quotients in excess of levels of concern as follows. Acute risk quotients for freshwater invertebrates exceed levels of concern for endangered species and restricted use in association with application rates of 0.25 and higher; estimates for non-endangered species and non-restricted use exceeded levels of concern in scenarios involving application rates of 0.8 lb/acre and higher. Chronic RQ values exceed a level of concern for non-threatened/non-endangered species in scenarios involving application rates of 0.8 lb/acre and higher.

4.4.3.4. Aquatic Plants – Adverse effects on aquatic vegetation are virtually certain unless steps are not taken to eliminate contamination of nearby aquatic habitat.

Based on the estimated concentrations in water used in other parts of this risk assessment for non-accidental exposures, hazard quotients for aquatic vegetation substantially exceed the level

of concern across all application rates. For algae, even at the lowest application rate (0.25 lbs/acre), the hazard quotients for sensitive species range from a low value of 8 for the central estimate of longer term exposure, to a high value of 500 as the upper bound estimate for acute non-accidental exposure. At the highest application rate (2 lbs/acre), the corresponding hazard quotients range from 60 to 4000. A similar pattern is observed for macrophytes, such as duckweed. Exposures resulting from an accidental spill scenario result in central hazard quotients in the range of 4542 (0.25 lbs/acre) to over 36,000 (2 lbs/acre) for sensitive species of algae, and corresponding values of 826 to over 16,000 for macrophytes such as duckweed. This risk characterization is consistent with that of U.S. EPA/OPP (2001b, p. 25) which concludes:

"The risks to aquatic plants are of the greatest concern as the Acute Risk LOC [level of concern] is exceeded for all modeled scenarios, even for the lowest application rates of 0.25 lb ai/acre/application with only one application per year."

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TABLES

Table 2-1. Selected physical and chemical properties of oxyfluorfen (additional studies in Appendices 11 and 12)

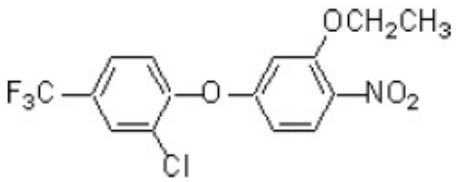
Structure	
Appearance, ambient	Orange crystalline solid (Tomlin 2004)
CAS number	42874-03-3
Synonyms	2-chloro-a,a,a-trifluoro-p-tolyl 3-ethoxy-4-nitrophenyl ether (IUPAC) (Tomlin 2004) 2-chloro-1-(3-ethoxy-4-nitrophenoxy)-4-(trifluoromethyl)benzene (CAS) (Tomlin 2004)
Development codes	RH-2915 (Tomlin 2004)
Field dissipation halftime (days)	30(30-40) (recommended values)(USDA/ARS 1995) 8.8 (Das et al. 2003)
Foliar half-time (days)	8 (Knisel and Davis 2000)
Foliar wash-off fraction	0.4 (Knisel and Davis 2000)
Formulation pH	7.2 - 7.5 (C&P Press 2005 Delta Goal,)
Hydrolysis	Stable, pH 5-9 (Tomlin 2004) Stable (USDA/ARS 1995)
$K_{o/c}$	2891 (Sand) (USDA/ARS 1995) 32381 (Silty clay loam) (USDA/ARS 1995) 100,000 (recommended value)(Knisel and Davis 2000 ; USDA/ARS 1995)
$K_{o/w}$	29,512 (Log Ko/w 4.47 experimental) (Tomlin 2004; USDA/ARS 1995)
Odor	Floral (C&P Press 2005)
Molecular weight	361.7 (Tomlin 2004)
Molecular formula	$C_{15}H_{11}ClF_3NO_4$ (Tomlin 2004)
Photolysis half-time(days)	27.7 days ($k=0.025\ day^{-1}$) in soil (USDA/ARS 1995) 3 days ($k=0.231\ day^{-1}$) in water (USDA/ARS 1995)
Soil half-time (days)	291-296 (aerobic) (USDA/ARS 1995) 554-603 (anaerobic) (USDA/ARS 1995) 35 (Knisel and Davis 2000)
Soil sorption, K_d	10 to about 850 depending on soil type. See Appendix 11.
Smiles Notation	CCOc1cc(Oc2ccc(cc2Cl)C(F)(F)F)ccc1[N+](=O)[O-] (Tomlin 2004)
Vapor pressure	0.0267 mPa (25 ˚C)(Tomlin 2004)

Table 2-1. Selected physical and chemical properties of oxyfluorfen (additional studies in Appendices 11 and 12)

Water solubility (mg/L)	0.116 (Tomlin 2004; USDA/ARS 1995) 0.1 (Knisel and Davis 2000)

TABLE 2-2: Commercially Available Formulations of Oxyfluorfen [1]

Brand Name/ Company/ Composition	Application Rate (lb a.i./acre) (Specified by Label) [2]	Inerts (Specified)
With Forestry Labeled Applications		
Galigan 2E/Makhteshim-Agan of North America, Inc./22.2%, 2 lbs a.i./gal, EPA Reg. # 66222-28 Label recommends use of nonionic surfactant	**Ground Application, General:** Minimum volume of 5 gal. water/acre. **Aerial Application, General:** Minimum volume of 10 gal. water/acre, droplets >100 microns, 6-10 feet above soil surface. **Preemergence in conifer seedbeds:** 0.25-1.0 lb a.i./acre , 20 - 50 gals total volume/acre. Use lower rates in soils with <1% OM. At least 0.25" of rain within 3 to 4 weeks after application. **Conifer transplants:** 1-2 lbs a.i./acre, a minimum of 20 gals total volume/acre. No more than 2 lbs a.i./year. Not for use in conifer release. **Field-Grown Deciduous Trees:** 0.5 - 2 lbs/acre applied to soil surrounding plants. **Spot Treatments:** Applications equivalent to 2 lbs/acre in 110 gallons of spray solution made to soil prior to bud swell.	N-methyl-2-pyrrolidone (CAS No. 872-50-4, 8-10%) Solvent naphtha (petroleum), heavy aromatic (CAS No. 6474-94-5), 54-59%.
Goal 2XL/Dow AgroSciences/23%, 2 lbs a.i./gallon EPA Reg. # 62719-424 Label recommends use of nonionic surfactant	**General Rates:** 0.25-2 lbs/acre, maximum annual rate of 2 lbs/acre. Minimum of 20 gallons total volume/acre. Maximum annual rate of 2 lbs a.i./acre. **Preemergence:** 0.25-1 lb/acre. **Postemergence**: 0.25-0.5 lb/acre. At least 5 weeks after conifer emergence. **Conifer Transplants:** 1-2 lbs/acre. Two applications may be necessary. **Field-Grown Deciduous Trees:** 0.5-2 lb/acre directly to soil. **Spot Treatments:** Applications equivalent to 2 lbs/acre in 110 gallons of spray solution made to soil prior to bud swell.	N-methylpyrrolidone (CAS No. 872-50-4), %N.S. Aromatic solvent (CAS No. 6474-94-5), %N.S. Naphthalene (CAS No. 91-20-3), %N.S.

TABLE 2-2: Commercially Available Formulations of Oxyfluorfen [1]

Brand Name/ Company/ Composition	Application Rate (lb a.i./acre) (Specified by Label) [2]	Inerts (Specified)
Goal Tender/Dow AgroSciences/41%, 4 lbs a.i./gallon EPA Reg. # 62719-447 Label recommends use of nonionic surfactant	**General Preemergence:** At least 0.25" of rain or irrigation within 3-4 weeks after application. Apply directly to soil. **General Postemergence**: Thorough coverage of weed foliage up to 4-leaf stage. Most effective to seedling grasses not exceeding 2-leaf stage. **Conifer seedbeds:** Preemergence rate of 0.25-2 lb/acre in a minimum of 20 gals water/acre. No more than 2 lbs/acre per season. Postemergence rate of 0.25-0.5 lb/acre in a minimum of 20 gals water/acre. Multiple applications may be necessary. **Conifer transplants:** 1 to 2 lb/acre in a minimum of 20 gallons water/acre. **Selected deciduous trees**: 0.5-2 lb/acre applied to soil. Label specifies spot treatments equivalent to 1 gallon product (4 lbs a.i.) in 110 gallons of water per acre. This may be an error because it exceeds the maximum rate of 2 lb a.i./acre.	Propylene glycol (CAS No. 57-55-6), %N.S.
Weedfree 63 [4] Herbicide/Harrell's, Inc/ 2% granular, EPA Reg No. 52287-16 **Conditional label**	**General Preemergence:** At least 0.25" of rain or irrigation within 3-4 days after application. Apply directly to soil. Apply with drop or rotary spreader. **Conifer Seedbeds:** 0.25 to 1 lb/acre for preemergence weed control. **Conifer transplants:** 1 to 2 lb/acre applied to soil and not conifer foliage. **Selected deciduous trees**: 0.5 to 2 lb/acre for preemergence weed control.	Not identified

Continued on next page

TABLE 2-2: Commercially Available Formulations of Oxyfluorfen [1]

Brand Name/ Company/ Composition	Application Rate (lb a.i./acre) (Specified by Label) [2]	Inerts (Specified)
Continued from previous page		
Other Formulations		
Delta Goal/Dow AgroSciences/23%, 2 lbs a.i./gallon EPA Reg. # 707-234	**Cotton**: 0.25-0.5 lb a.i./acre Maximum annual rate of 0.5 lb a.i./acre	Same as Goal 2XL

[1] Unless otherwise noted, information is taken from the product labels and material safety data sheets (C&P Press 2005; Pro-Serve Inc. 2004). All application rates expressed as pounds active ingredient (a.i.) Per acre.
[2] All application specified in this column are in units of formulation (oz, gallons, or pounds) per acre. Application rates used in Forest Service programs are discussed in Section 2.4.
[3] The information submitted to U.S. EPA has been reviewed in the conduct of this risk assessment. This information, however, is classified as CBI (confidential business information) under Section 7(d) and Section (10) of FIFRA and cannot be disclosed in this document. See Section 3.1.14 for a discussion of the potential significance of inerts and adjuvants and Section 3.1.15 for a discussion of the potential significance of impurities.
[4] Only a conditional label has been found at http://oaspub.epa.gov/pestlabl/ppls.srchreslt. Unclear that this formulation is available.

Table 2-3: Uses of oxyfluorfen by the Forest Service between 2000 and 2003 by management objective [1].

Management Objective	Pounds	Acres	Pounds/Acre	Proportion	
				lbs	acres
Nursery Weed Control	768.57	916.02	0.84	0.71	0.72
Noxious Weed Control	239.30	275.60	0.87	0.22	0.22
Research	56.00	55.00	1.02	0.05	0.04
Insect Suppression	10.88	21.75	0.50	0.01	0.02
Facilities Maintenance	7.70	8.00	0.96	0.01	0.01
Totals [2]	1082.45	1276.37	0.85		

Source: http://www.fs.fed.us/foresthealth/pesticide/reports.shtml. One application in 2003 (Region 9, Forest 7) is reported only as 2.14 gallons applied to 36.89 acres. This is not included in the analysis for Forest Service use.

[1] The maximum reported application rate at a single site was 2 lbs/acre (Forest 10 in Region 5 in 2000).

[2] For comparison, the total annual use in the U.S. from 1990 to 1990 was 761000 lbs on 1167000 acres for an average application rate of about 0.65 lbs/acre.

Table 2-4: Uses of oxyfluorfen by the Forest Service between 2000 and 2003 by Forest Service Region.

Region (No.: Name)	Pounds	Acres	Average lb a.i./acre	Proportion	
				Pounds	Acres
1: Northern	53.25	213.53	0.25	0.049	0.167
2: Rocky Mountain	36.26	72.80	0.50	0.034	0.057
4: Intermountain	27.10	45.60	0.59	0.025	0.036
5: Pacific Southwest	458.00	344.45	1.33	0.423	0.270
6: Pacific Northwest	449.70	508.10	0.89	0.415	0.398
8: Southern	56.00	55.00	1.02	0.052	0.043
9: Eastern	2.14	36.89	0.06	0.002	0.029
Total for All Regions	1082.45	1276.37	0.85		

Source: http://www.fs.fed.us/foresthealth/pesticide/reports.shtml

Table 2-5: Use of oxyfluorfen between 2000 and 2003, Forest Service and Agricultural Use In California [1,2].

Year	Forest Service, All Regions, lbs	California, Agricultural Use, lbs
2000	354.75	463,337.47
2001	300.81	347,588.59
2002	295.74	425,816.76
2003	131.15	469,166.73

[1] Source: Forest Service use taken from http://www.fs.fed.us/foresthealth/pesticide/reports.shtml. Agricultural use in California taken from California Department of Pesticide Regulation 2001-2004.
[2] Total use in U.S. from 1990 to 1999 estimated at 761,000 lbs/year by U.S. EPA (2001g).

Table 3-1. Nomenclature and Chemical Structures of Oxyfluorfen and Oxyfluorfen Metabolites [1]

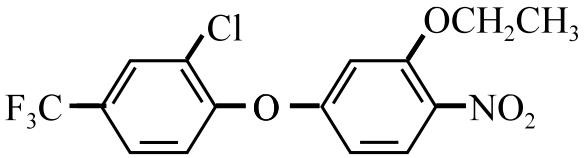
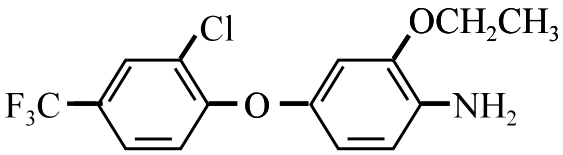
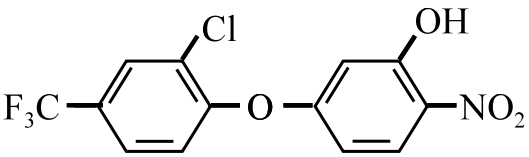
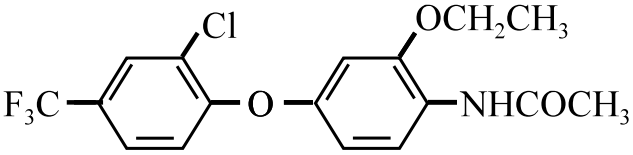
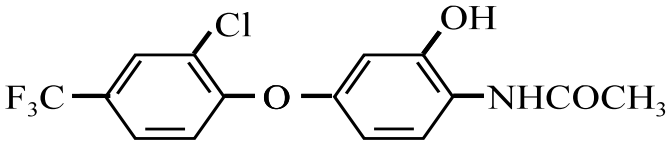
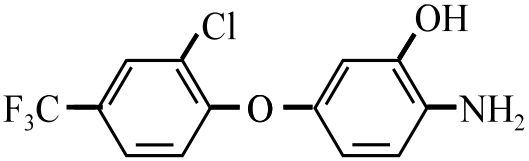
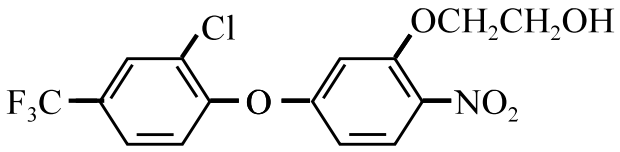
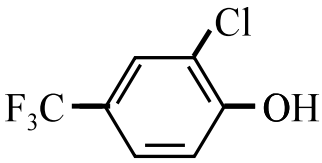
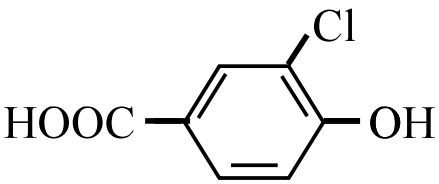
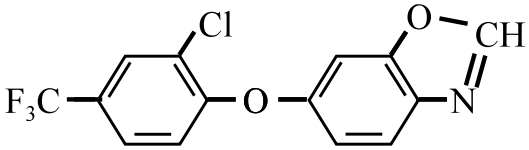
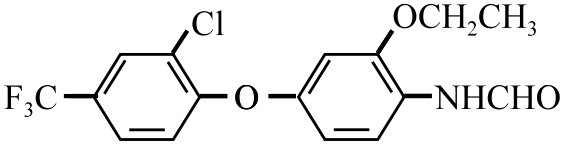
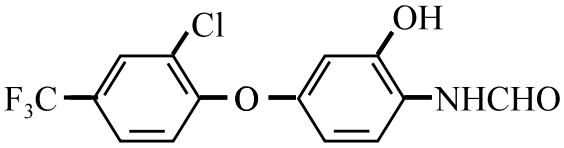
Code	Common Name	Structure
RH-2915 RH-32915 AG510	Oxyfluorfen, technical Oxyfluorfen, 99.4% Oxyfluorfen, technical	
RH-35451	Amino-Goal	
RH-34670		
RH-35450	N-Acyl Goal	
RH-45469	Acyl-670	
RH-45298	Amino-670	

Table 3-1. Nomenclature and Chemical Structures of Oxyfluorfen and Oxyfluorfen Metabolites [1]

Code	Common Name	Structure
RH-34980		
RH-34800	4-Trifluoromethyl-2-chlorophenol	
RH-31680	3-Chloro-4-hydroxy benzoic acid	
RH-120832		
RH-120162		
RH-120450		

[1] Codes and structures taken from Zhang (1993) unless otherwise specified.

Table 3-2: Toxicity data on commercial formulations of oxyfluorfen that may be used in Forest Service Programs[1]

Formulation [2]	Toxicity (M: Male, F: Female) All units are formulated product unless otherwise specified
Galigan 2E/Makhteshim Agan of North America, Inc./22.2%, 2 lbs a.i./gal	Oral LD_{50} in Rats: >2000 mg/kg Dermal LD_{50} in rabbit: >4000 mg/kg Aerosol LC_{50} (species not specified): >4.8mg/L x 4 hours Inhalation: Respiratory irritation, CNS depression (narcosis) Eyes: Moderately irritating (rabbit) Skin: Moderately irritating (rabbit) Skin sensitization: Causes allergic reaction.
Goal 2XL/Dow AgroSciences/23%, 2 lbs a.i./gallon	Oral LD_{50} in rats: 2985 mg/kg (F), 4594 mg/kg (M) Dermal LD_{50} in rats: >4000 mg/kg Aerosol LC_{50} in rats: >4.8mg/L x 4 hours Inhalation: Respiratory irritation, CNS depression (nacosis). Eyes: Moderate irritation Skin: Severe skin irritation with pain and redness Skin sensitization: Causes allergic reaction
Goal Tender/Dow AgroSciences/41%, 4 lbs a.i./gallon	Oral LD_{50} in Rats: >5000 mg/kg Dermal LD_{50} in rabbit: >5000 mg/kg Aerosol LC_{50} in rats: >0.39mg/L x 4 hours Inhalation: Respiratory irritation, headache, and nausea. Eyes: Temporary eye irritation. Skin: Brief contact non-irritating Skin sensitization: No entry.
Delta Goal/Dow AgroSciences/23%, 2 lbs a.i./gallon	**Entries identical to those for Goal 2XL/Dow**

[1] Unless otherwise specified, the data are taken from MSDS sheets available at C&P Press, http://www.greenbook.net/; CDMS Label System, http://www.cdms.net/manuf/manuf.asp; U.S. EPA Label System, http://www.epa.gov/pesticides/pestlabels/index.htm , and http://www.mauget.com/mlinks/pdf/imicmsds.pdf. Also unless otherwise specified, toxicity data are on the formulation and expressed in units of formulation.

[2] All formulations are liquid

Table 3-3: Chemical and site parameters used in GLEAMS modeling for oxyfluorfen.

Chemical Specific Parameters

Parameter	Clay	Loam	Sand	Comment/ Reference
Halftimes (days)				
Aquatic Sediment		230		Walker et al. 1988
Foliar		8		Note 1
Soil		870.5		Note 2
Water		1741		Note 3
Ko/c, mL/g		5,585		Note 4
K_d, mL/g	755	52	9.44	Note 5
Water Solubility, mg/L		0.116		Knisel and Davis (2000) and Tomlin (2005)
Foliar wash-off fraction		0.4		Knisel and Davis 2000
Fraction applied to foliage		0.5		Note 6

Note 1	Value recommended by Knisel and Davis (2000). Much shorter halftimes, on the order of 0.5 days, have been reported by Massey (1990) and Frank et al. (1991). See Appendix 12.
Note 2	Reference value used by U.S. EPA/OPP (2001b) based on upper 90th percentile from Reibach (1990f). Much shorter halftimes have been measured. The use of the longer halftime will accommodate the consideration of metabolites.
Note 3	Reference aerobic aquatic degradation rate used by U.S. EPA/OPP 2001b based on one-half of the aerobic soil degradation rate.
Note 4	Reference value used by U.S. EPA/OPP (2001b). A value of 100,000 is recommended by Knisel and Davis (2000) and USDA/ARS (1995).
Note 5	Value for loam taken from Yen et al. (2003). Value for sand taken from Reibach (1988). Value for clay taken as the value for silty clay from Yen et al. (2003).
Note 6	A foliar fraction of 0.5 is used a standard value for liquid formulations.

Site Parameters (see SERA 2004b for details)

Pond	1 hectare pond, 2 meters deep, with a 0.01 sediment fraction. 10 hectare square field (1093' by 1093') with a root zone of 60 inches.

Stream	Base flow rate of 710,000 L/day with a flow velocity of 0.08 m/second or 6912 meters/day. Stream width of 2 meters (about 6.6 feet'). 10 hectare square field (1093' by 1093') with a root zone of 60 inches.

Table 3-4: Summary of modeled concentrations in streams (all units are ug/L or ppb per lb/acre applied)

Annual Rainfall (inches)	Clay		Loam		Sand	
	Average	Maximum	Average	Maximum	Average	Maximum
5	0	0	0	0	0	0
10	0	0	0	0	0	0
15	0.208	3.34	0	0	0	0
20	0.45	7.24	0	0	0	0
25	0.688	11.3	0	0	0	0
50	1.2	29.8	0.00653	0.198	0	0
100	1.13	75.5	0.385	10.9	4.35e-09	5.12e-07
150	0.935	117	0.545	28.4	0.00015	0.0327
200	0.789	151	0.566	49.7	0.00551	0.355
250	0.68	179	0.54	71.8	0.0255	1.54

Table 3-5: Summary of modeled concentrations in ponds (all units are ug/L or ppb per lb/acre applied)

Annual Rainfall (inches)	Clay		Loam		Sand	
	Average	Maximum	Average	Maximum	Average	Maximum
5	0	0	0	0	0	0
10	0	0	0	0	0	0
15	3.45	5.86	0	0	0	0
20	7.06	11	0	0	0	0
25	10.4	14.9	0	0	0	0
50	16.5	19.5	0.203	0.229	0	0
100	14.7	22.8	8.95	14.2	5.17E-09	1.19E-07
150	12.2	26.8	11.6	29.4	0.00013	0.00319
200	10.4	29.8	11.7	43.7	0.0125	0.101
250	9.04	32.6	11.1	57	0.216	0.93

Table 3-6: Summary of concentrations of oxyfluorfen in surface and groundwater based on modeling and monitoring (all units in µg/L or ppb) .

Scenario	Peak	Long-Term Average
GLEAMS MODELING FOR THIS RISK ASSESSMENT (1 lb/acre)		
Accidental spill (Worksheet D05)	1,000 (600-1,500)	N/A
Direct Spray of Pond (Worksheet D10a)	56	N/A
Pond, drift at 100 feet (Worksheet D10a)	1.1	N/A
Direct Spray of Stream (Worksheet D10b)	91	N/A
Stream, drift at 100 feet (Worksheet D10b)	1.8	N/A
GLEAMS Pond, Table 3-5	20 (0.2 - 57)	10 (0.2 - 17)
GLEAMS, Stream, Table 3-4	30 (3 - 180)	0.5 (0.03 - 1.2)
OTHER MODELING (U.S. EPA/OPP 2001b adjusted to 1 lb/acre)		
PRZM/EXAMS, Pond	11.7	2.85 to 3.55
Sci-Grow 2.3, groundwater	0.04	N/A
MONITORING		
Area	Concentrations	Reference
Estimated concentrations in San Joaquin River based on sediment data	0.1 to 1 ppb	U.S. EPA/OPP 2001b
Peak stream concentration after accidental spill	541 ppb	U.S. EPA/OPP 2001b
Pond water near container production nursery. Appl. rate N.S.	9 ppb peak concentration	Camper et al. 1994 [1]

Pond water near container production nursery after application of 2 lb/acre	147 ppb peak at 1 DAT [73.5 ppb @ 1 lb/acre] <40 ppb at 3 DAT	Keese et al. 1994 [1]
Pond water at a commercial nursery after application of 2 lb/acre	40 ppb peak	Riley et al. 1994 [1]

[1] Additional details given in Appendix 12.

Table 3-7: Concentrations of oxyfluorfen in surface water used in this risk assessment (see Section 3.2.3.4.6 for discussion).

At application rate:	**1**	**lb/acre**	
		Peak Concentration (ppb or µg/L)	Longer Term Concentration (ppb or µg/L)
	Central	30	3
	Lower	0.2	0.2
	Upper [2]	200	20
Water contamination rate [1]		**mg/L per lb/acre applied**	
		Peak Concentration (mg/L per lb/acre)	Longer Term Concentration (mg/L per lb/acre)
	Central	3.00e-02	3.00e-03
	Lower	2.00e-04	2.00e-04
	Upper	2.00e-01	2.00e-02

[1] Water contamination rates – concentrations in units of mg/L expected at an application rate of 1 lb/acre.
[2] Encompasses normal variability but may not encompass extreme or accidental exposures. These are addressed in different Worksheet D05 and discussed in Section 3.2.3.4.1.

Table 3.8. Summary of Risks Exceeding Level of Concern (HQ=1): Workers

Application Rate/Exposure Scenario	HQ for Systemic Toxicity			HQ for one-in-one million Cancer Risk		
	Central	Lower	Upper	Central	Lower	Upper
Typical Application Rate: 1 lbs/acre						
Contaminated Gloves, 1 hour	2		1.2	NA	NA	NA
General Exposure, Backpack Spray			3			1.1
General Exposure, Ground Spray			5			2
General Exposure, Aerial Spray			3			1.1
Maximum Application Rate, 2 lbs/acre						
Contaminated Gloves, 1 hour	2		12	NA	NA	NA
General Exposure, Backpack Spray			5			2
General Exposure, Ground Spray	1.5		10			4
General Exposure, Aerial Spray			5			2
Low Application Rate, 0.25 lbs/acre						
Contaminated Gloves, 1 hour	2		12	NA	NA	NA
General Exposure, Ground spray			1.3			

NA = Not applicable. Cancer risk not estimated for short-term exposure
Note: empty cells indicate HQ values less than 1. Only scenarios with at least one HQ values >1 are shown in this table.

Table 3.9. Summary of Risks Exceeding Level of Concern (HQ=1): General Public

Application Rate/Exposure Scenario/Receptor	HQ for Systemic Toxicity			HQ for one-in-one million Cancer Risk		
	Central	Lower	Upper	Central	Lower	Upper
Typical Application Rate: 1 lbs/acre						
Acute Expsoure						
Contaminated Vegatation, Adult Female			7	NA	NA	NA
Water Consumption, Spill, Child			3	NA	NA	NA
Chronic/Longer Term Exposures						
Contaminated Vegetation, Adult Female			6			2
Maximum Application Rate, 2 lbs/acre						
Acute Expsoure						
Contaminated Fruit, Adult Female			1.9	NA	NA	NA
Contaminated Vegatation, Adult Female	1.6		14	NA	NA	NA
Direct Spray, Entire Child			1.9	NA	NA	NA
Water Consumption, Spill, Child	1.4		5	NA	NA	NA
Chronic/Longer Term Exposures						
Contaminated Fruit, Adult Female			1.6			
Contaminated Vegetation, Adult Female	1.4		12			5
Low Application Rate, 0.25 lbs/acre						
Acute Expsoure						
Contaminated Vegatation, Adult Female			1.7	NA	NA	NA
Chronic/Longer Term Exposures						

Contaminated Vegetation, Adult Female	1.4	

NA = Not applicable. Cancer risk not estimated for short-term exposure
Note: empty cells indicate HQ values less than 1. Only scenarios with at least one HQ values >1 are shown in this table.

Table 4-1: Summary of the cumulative loss from soil runoff and sediment as a proportion of the application rate

Annual Rainfall (inches)	Clay	Loam	Sand
5	0	0	0
10	0	0	0
15	0.0182	0	0
20	0.0372	0	0
25	0.0534	0	0
50	0.0819	0.000585	0
100	0.0786	0.0472	0
150	0.0714	0.0767	0
200	0.0661	0.0858	0
250	0.0622	0.0874	0.00259

Table 4-2: Summary of modeled maximum depth of chemical in the soil column.

Annual Rainfall (inches)	Clay	Loam	Sand
5	6.5	6.5	6.5
10	6.5	6.5	6.5
15	12	12	18
20	12	12	18
25	12	12	24
50	12	18	36
100	12	24	54
150	12	24	60
200	6.5	24	60
250	6.5	24	60

Table 4-3: Summary of modeled concentrations in the entire 60 inch soil column (all units are mg/kg soil or ppm per lb/acre applied)

Annual Rainfall (inches)	Clay		Loam		Sand	
	Average	Maximum	Average	Maximum	Average	Maximum
5	0.0676	0.114	0.0603	0.102	0.0609	0.103
10	0.0692	0.118	0.0625	0.106	0.0624	0.106
15	0.0633	0.106	0.0623	0.105	0.0619	0.105
20	0.0555	0.0929	0.0621	0.105	0.0614	0.103
25	0.0471	0.0792	0.0619	0.104	0.0609	0.103
50	0.0207	0.0449	0.0611	0.103	0.0603	0.102
100	0.00695	0.0312	0.042	0.0752	0.0608	0.103
150	0.0033	0.0281	0.0269	0.0559	0.0616	0.105
200	0.00173	0.0271	0.018	0.0437	0.0624	0.107
250	0.00101	0.0268	0.0128	0.0367	0.062	0.107

Table 4-4: Summary of modeled concentrations in the top 12 inches of the soil column (all units are mg/kg soil or ppm per lb/acre applied)

Annual Rainfall (inches)	Clay		Loam		Sand	
	Average	Maximum	Average	Maximum	Average	Maximum
5	0.338	0.571	0.301	0.508	0.304	0.515
10	0.346	0.588	0.312	0.53	0.312	0.529
15	0.316	0.532	0.312	0.527	0.31	0.523
20	0.278	0.464	0.311	0.525	0.307	0.517
25	0.235	0.396	0.309	0.522	0.304	0.51
50	0.104	0.225	0.306	0.515	0.288	0.474
100	0.0347	0.156	0.209	0.374	0.246	0.387
150	0.0165	0.141	0.133	0.276	0.207	0.319
200	0.00866	0.135	0.089	0.215	0.176	0.272
250	0.00504	0.134	0.0632	0.181	0.151	0.239

Table 4-5: Summary of oxyfluorfen toxicity values used in ecological risk assessment (all amounts expressed as a.i.)

Organism	% a.i.	Endpoint	Toxicity Value	Reference
Mammals (mice)	99.4	Acute NOAEL, 125 ppm 9-day dietary	19.8 mg/kg[1]	Krijt et al. 1999
dogs, mice	85.7 (mouse study)	Chronic NOAEL, toxicity, 20 ppm 20 month mouse dietary; 100 ppm 52-week dog dietary	3 mg/kg/day[2] (measured dose, both studies)	U.S.EPA 2001b; Goldenthal and Wazeter 1977
Birds (Mallard duck)	70.2	Acute NOAEL, 1250 ppm, 5-day dietary	200 mg/kg[3]	Fletcher 1987c; Godfrey and Longacre 1990n
	99.3	Chronic NOAEL, 500 ppm, Reproduction	64.7 mg/kg/day	Frey et al. 2003a
Terrestrial Invertebrates				
Honey bee	?	NOAEC for mortality, >100 ug/bee	1075 mg/kg[4]	Atkins 1992
Terrestrial Plants - Pre-emergence assay (seedling emergence study: soil treatment)				
Sensitive (cabbage, lettuce, onion, rytgrass)	71.5	NOAEC, all effects	0.0024 lb/acre	Hoberg 1990
Tolerant (soybean)	71.5	NOAEC, all effects	0.31 lb/acre	Hoberg 1990
Terrestrial Plants - Post-emergence assay (vegetative vigor study: direct spray)				
Sensitive (tomato)	71.5	NOAEC, all effects	0.00066 lb/acre	Hoberg 1990
Tolerant (corn)	71.5	NOAEC, all effects	0.034 lb/acre	Hoberg 1990
Fish Acute				

Table 4-5: Summary of oxyfluorfen toxicity values used in ecological risk assessment (all amounts expressed as a.i.)

Organism	% a.i.	Endpoint	Toxicity Value	Reference
Sensitive (bluegill)	94	NOAEC for mortality	0.056 mg/L	MRID 95585 cited by U.S. EPA 2001b
Tolerant (Rainbow trout)	94	NOAEC for mortality	0.180 mg/L	MRID 95585 cited by U.S. EPA 2001b
Fish Chronic				
Sensitive/Tolerant (Fathead Minnows)	71	NOAEC, egg-and-fry development	0.038 mg/L	Godfrey and Longacre 1990f
(Continued on next page)				
(Table 4-5 continued from previous page)				
Aquatic Invertebrates, Acute				
Sensitive (Freshwater clam, Eastern oyster)	74	NOAEC	0.0032 mg/L	Godfrey and Longacre 1990b; MRID 96881 as cited by U.S. EPA 2001b
Sensitive (Freshwater clam, Eastern oyster)	74	NOAEC	0.0032 mg/L	Godfrey and Longacre 1990b; MRID 96881 as cited by U.S. EPA 2001b
Tolerant (Fiddler crab)	74	NOAEC	320 mg/L	MRID 96811 as cited by U.S. WPA 2001b
Aquatic Invertebrates, Chronic				
Sensitive		Daphnid NOAEC, reproduction, 0.013 mg/L adjusted for relative acute sensitivity to Eastern Oyster[5]	0.0022 mg/L[5]	Daphnid chronic value from Godfrey and Longacre 1990g; Acute toxicity values from Sutherland et al. 2000a and Godfrey and Longacre 1990b[MRID 96881 as cited by U.S. EPA 2001b]
Tolerant (*Daphnia*)	71.8	NOAEC, reproduction	0.013 mg/L	Godfrey and Longacre 1990g
Aquatic Algae				
Tolerant (*Anabaena flos-aquae*)	71.5	NOAEC, 5-day growth	2 mg/L	Giddings 1990
Selanastrum capricornutum	Goal 2XL (23)	NOAEC, 4-day growth, 0.00043 mg formultion/L	0.000099 mg/L, rounded to 0.0001 mg/L	Sutherland et al. 2000b
Aquatic Macrophytes				
Sensitive/Tolerant (*Lemna gibba*)	71.5	LOAEC, 7-day growth	0.00055 mg/L	Giddings 1990

Table 4-5: Summary of oxyfluorfen toxicity values used in ecological risk assessment (all amounts expressed as a.i.)

Organism	% a.i.	Endpoint	Toxicity Value	Reference

[1] Food ingestion rate = $0.621(23g\ bw)^{0.564}$ = 3.64 g/day; 125 mg/day x 0.00364 kg diet/day x 1/0.023 kg = 19.8 mg/kg/day

[2] U.S. EPA/OPP (2001b; 2002) chronic NOAEL used to derive chronic RfD.

[3] See Appendix 5 for conversion of dietary concentration to dose from experimental data

[4] 100 ug/bee ÷ 9.3E-5 kg/bee x 1E-3 mg/ug = 1075 mg/kg bw

[5] 0.0197 ÷ 0.0032 = factor of 6 difference in *Daphnia*/oyster acute toxicity. 0.013 mg/L ÷ 6 = 0.0022 mg/L

FIGURES

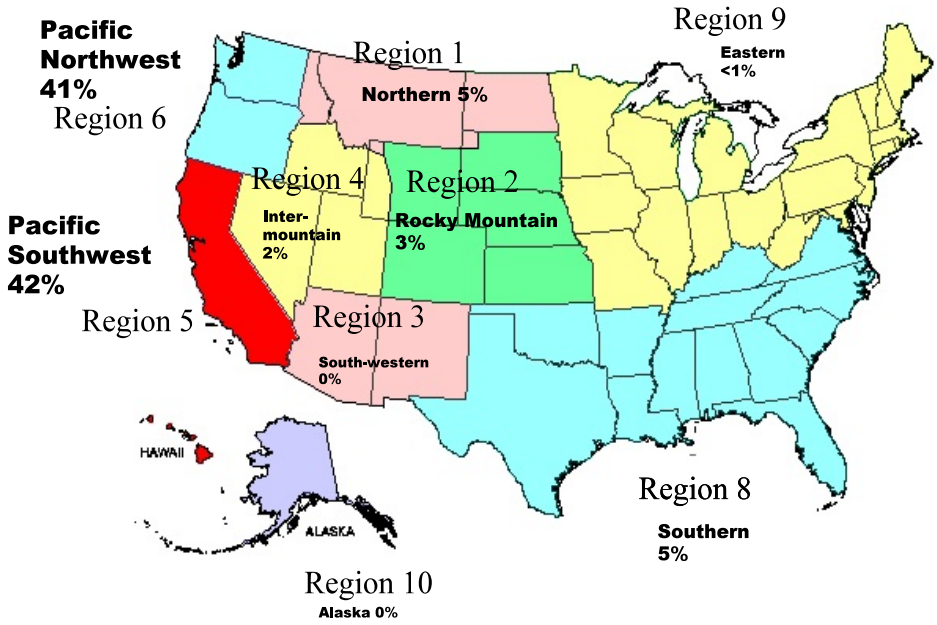


Figure 2-1: Use of oxyfluorfen by the Forest Service between 2000 and 2003 by region of the country as a percentage of the total pounds used in all Forest Service programs (see Table 2-4 for data).

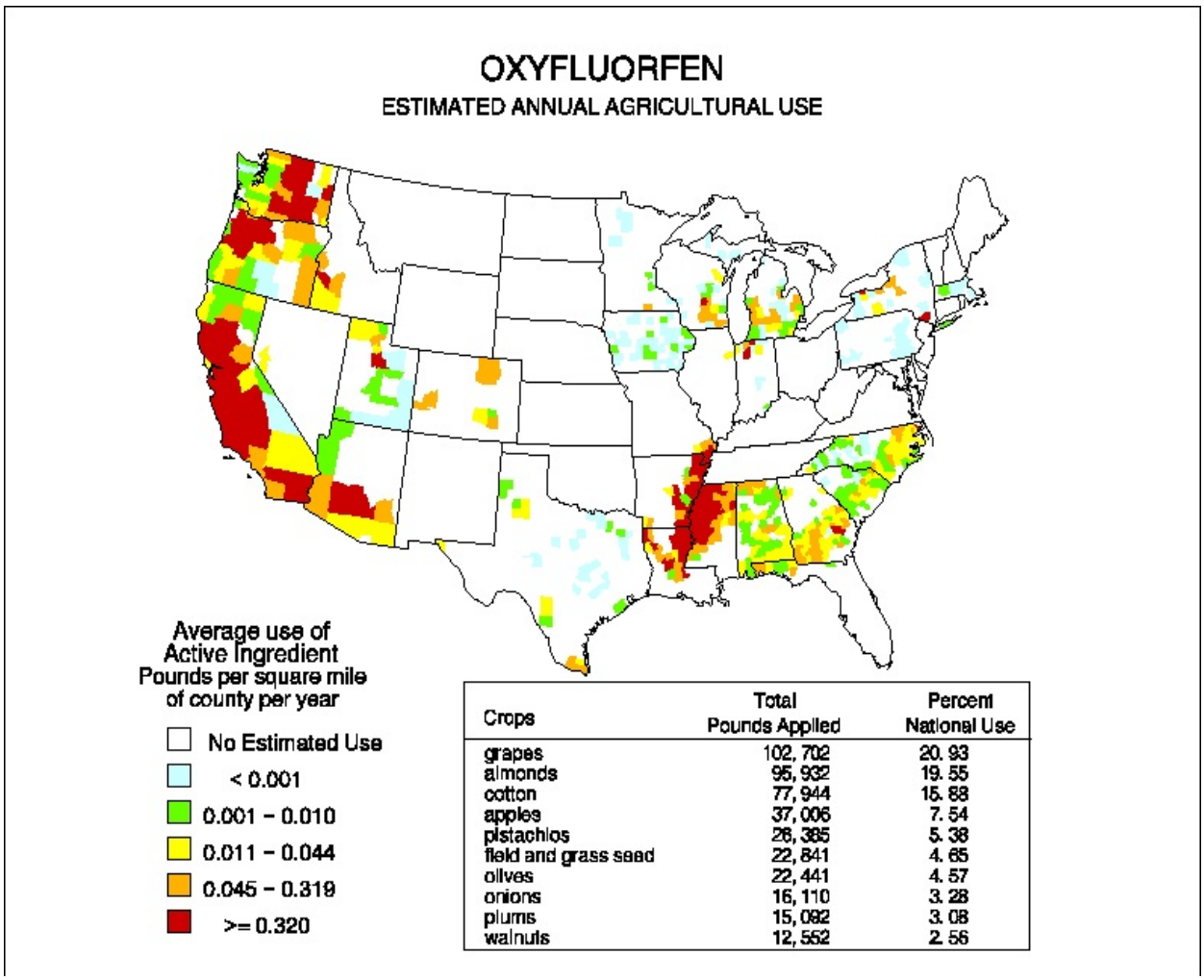


Figure 2-2: Agricultural uses of oxyfluorfen in the United States (USGS 1998).

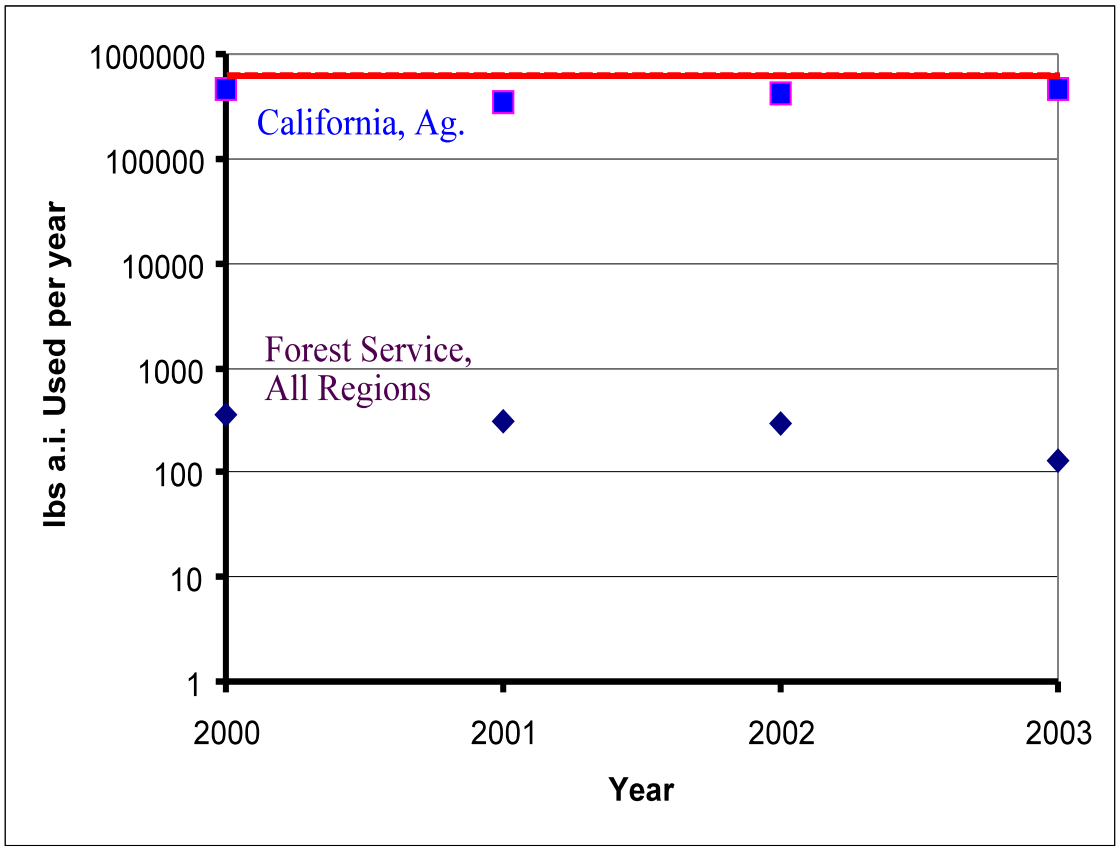


Figure 2-3: Use of oxyfluorfen between 2000 and 2003 by the Forest Service and agricultural use in California. *[The flat solid line is the U.S. EPA (2001g) estimate of total use in U.S. during the 1990's.]* (See Table 2-5 for data).

APPENDICES

Appendix 1: Acute toxicity of oxyfluorfen and oxyfluorfen formulations to experimental mammals.

Species	Exposure	Response	Reference
		ORAL	
Rats, Gavage			
rat, Sprague-Dawley, 5 male, 5 female	Acute toxicity limit test with AG510 (96% a.i.) in arachis oil	NOAEL: 5000 mg a.i./kg No deaths, no signs of toxicity, no pathological changes	Dreher 1995d MRID 44712010
rats, male, CRCD (3 per group)	Range finding study. Goal 1.6E (27% a.i.) administered by gavage at single doses of 0.05, 0.5, and 5.0 g/kg [does not indicate if this is formulation or a.i.]. No control group. No vehicle used.	0.05 g/kg: no mortality; no signs of toxicity; no gross pathological changes. 0.5 mg/kg: no mortality; signs of toxicity – passiveness and stained muzzle; no gross pathological changes. 5.0 g/kg: 100% mortality; signs of toxicity include – passiveness, ataxia, prostration; gross pathological changes to lungs, stomach, intestines, liver and bladder. LD_{50} between 0.5 and 5 g/kg (slightly toxic)	Krzywicki 1983 MRID 00159811
rats, Crl:CD BR, 6 males/6 females	Goal Technical Herbicide (71.4% a.i.) administered by gavage at a dose of 5.0 g formulation/kg [equivalent to 3.57 g a.i/kg]. Corn oil vehicle.	No mortalities. Signs of toxicity: stained genital area, red-stained fur around eyes and muzzle, salivation, soft feces. No apparent body weight effects. No gross pathological changes. LD_{50} > 5.0 g formulation/kg (practically non-toxic)	Gingrich et al. 1990a MRID 41601001

Appendix 1: Acute toxicity of oxyfluorfen and oxyfluorfen formulations to experimental mammals.

Species	Exposure	Response	Reference
rats,Crl:CDBR, 6/sex/group	Goal 2XL (24.2 5 a.i.) administered by gavage at doses of 2.0, 3.0, 4.0, and 5.0 g formulation/kg. No control group.	Animals observed for 14 days after treatment. Mortality: No deaths in 2.0 and 3.0 g/kg group;2/6 deaths in 4.0 g/kg group; 4/6 deaths in 5.0 g/kg group. Dose-related signs of toxicity: salivation, lacrimation, passiveness, ataxia, scant feces, diarrhea. Decreased body weight at 4.0 and 5.0 g/kg groups. Gross pathology: No gross pathological changes in surviving animals. In dead animals, gross pathological changes related to gastric irritation. **LD_{50} = 4.337 g formulation/kg** (95% CL 3.682 – 5.964)	Lutz and Parno 1993a MRID 43149802
rats, Crl:CDBR, males and females,	Single dose of Goal Technical 95 administered by gavage at 5.0 g a.i./kg in corn oil. Corn oil control group included.	No deaths or treatment related signs of toxicity were observed over the 14 days after administration. **LD_{50} >5 g a.i./kg**	Lampe et al. 1988a MRID 44828903

Short Term Dietary (5-15 days)

Appendix 1: Acute toxicity of oxyfluorfen and oxyfluorfen formulations to experimental mammals.

Species	Exposure	Response	Reference
Mouse, BALB/c, 4 males per group, 22-24g	control, 125, 200, 1000 ppm a.i. oxyfluorfen (99.4% a.i.) in the diet for 9 days	Dose-related increase in relative liver weight (9.2±0.8% at 1000 ppm vs. 5.0±0.4% control); Statistically significant reductions in protoporphyrinogen oxidase activities in liver and kidney tissue at 200 and 1000 ppm; statistically significant increase in liver and kidney porphyrin concentrations (200 and 1000 ppm). In liver from mice fed 1000 ppm, uroporphyrin I, uroporphyrin III and protoporphyrin accounted for 55%, 20% and 15-25% of liver porphyrins, respectively. In kidney tissue, protoporphyrin accounted for 85% of total porphyrins. No porphyrin increase was found in the brain, adrenals or testes. Statistically significant increase in liver pentoxyresorufin dealkylation (PROSD) activity at 200 and 1000 ppm. **NOAEC = 125 ppm**. **LOAEC = 200 ppm**	Krijit et al. 1997

DERMAL – Systemic Effects

Appendix 1: Acute toxicity of oxyfluorfen and oxyfluorfen formulations to experimental mammals.

Species	Exposure	Response	Reference
rabbits, male, New Zealand White (2 animals)	Range finding study. Goal 1.6E (27% a.i.) applied to clipped intact skin for 24 hours at 5.0 g/kg [does not indicate if this is formulation or a.i.].	dermal effects: erythema, hair loss, irritation systemic effects: no mortality; signs of toxicity – passiveness, prostration; no gross pathological changes. **LD_{50} > 5.0 g/kg** (practically non- toxic)	Krzywicki 1983 MRID 00159811
rat, Sprague-Dawley, 5 male, 5 female	Acute dermal toxicity limit test. AG510 (96%) in arachis oil to shaved skin at concentration of 2000 mg/kg	No mortality, no clinical signs, normal body weight gain, no dermal irritation, no abnormalities at necropsy. NOAEL = 2000 mg/kg	Dreher 1995e MRID 44712011
rats, Crl:CD BR, 6 males/6 females	Goal Technical Herbicide (71.4% a.i.) applied to clipped intact skin at a dose of 5.0 g formulation/kg [equivalent to 3.57 g a.i/kg] for 24 hours.	No mortalities. No clinical signs of toxicity. No affect on body weight. No gross pathological changes. **LD_{50} > 5.0 g formulation/kg** (practically non-toxic)	Gingrich et al. 1990b MRID 41601002
rats, Crl:CDBR 6 males/6 females	Goal 2XL (42.2% a.i.) applied undiluted to shaved intact skin at does of 4g formulation/kg for 24 hours	No deaths of treatment related effects were observed. No changes in body weight or gross pathological changes. LC_{50} >4 g formulation/kg	Lutz and Parno 1993b MRID 43149803
rabbits, New Zealand White, 6 males	Single 24-hour dermal application of 5.0 g Goal Technical 95 Herbicide (97.1% a.i.) to clipped intact skin. Control group included.	No deaths, treatment-related signs of toxicity or gross pathological changes observed during the 14-day observation period. LD_{50} >5.0 g a.i./kg	Lampe et al.1988b MRID 44828904

Appendix 1: Acute toxicity of oxyfluorfen and oxyfluorfen formulations to experimental mammals.

Species	Exposure	Response	Reference
rats, Sprague-Dawley, 5 males/5 females	5000 mg/kg Weedfree 75 (containing 2% oxyfluorfen and 3% trifluralin) was moistened with saline and applied for 24 hours. Note: this appears to be an oxyfluorfen combination product)	Animals were observed for 14 days after application. No moralities,, signs of toxicity or gross pathological findings. **LD_{50} >5000 mg formulation/kg**	Merkel 2002 MRID 46250501
DERMAL – Skin Irritation			
rabbits, male, New Zealand White (6 animals)	Range finding study. 0.5mL of test substance (Goal 1.6E, 27% a.i.) applied to clipped intact skin for 4 hours [does not indicate if this is formulation or a.i.].	72-hour mean irritation score = 6.2, indicating that test substance is severely irritating to skin. Observations: erythema, edema, dryness, sloughing.	Krzywicki 1983 MRID 00159811
rabbits, female, New Zealand White (6 animals)	0.5mL of test material (Goal Technical Herbicide. 71.4% a.i.) applied to clipped intact skin for 4 hours.	Skin irritation evaluated according to Draize procedure at 1, 24, 48, and 72 hours and 7 days after application. Very slight to moderate erythema and very slight to slight edema observed at 1 to 48 hours. No skin irritation observed at 72 hours.	Gingrich et al. 1990c MRID 41601003

Appendix 1: Acute toxicity of oxyfluorfen and oxyfluorfen formulations to experimental mammals.

Species	Exposure	Response	Reference
rabbits, New Zealand White, 6 males	Goal 2XL (24.2% a.i.) applied undiluted (0.5 ml) to shaved intact skin for 4 hours.	Skin irritation evaluated according to Draize criteria at 1, 24, 48, and 72 hours and 7 days after application. At 1 hour, well defined erythema and very slight edema. At 24 hours, moderate erythema and slight to severe edema. At 48 hours, moderate to severe erythema and edema. At 72 hours, severe erythema and edema. No irritation or edema at day 7.	Lutz and Parno 1993c MRID 43149804
rabbits, New Zealand White, 6 (4 females.2 males)	Single 4-hour dermal application of 0.5 g of AG 510 (containing ~97% a.i.) to semi-occluded intact skin.	Test site examined 1, 24, 48, and 72 hours after application. Mild irritation noted at 1, 24, and 48 hours. No irritation at 72 hours. No corrosive effects were observed at any time point. AG 510 classified as a mild irritant.	Dreher 1995b MRID 44712015
rabbits, New Zealand White, 6 males	0.5 g Goal Technical Herbicide (97.1 % a.i.) applied to clipped intact skin for 4 hours.	Skin irritation assessed at 1, 24, 48, and 72 hours and 7 days after application. No skin irritation (erythema or edema) observed at any time point.	Lampe et al. 1998c MRID 44828906

Appendix 1: Acute toxicity of oxyfluorfen and oxyfluorfen formulations to experimental mammals.

Species	Exposure	Response	Reference
		DERMAL – Sensitization	
guinea pigs (Hartley)	Three 6-hour induction (1dose/week) doses of 0.4mL Goal Technical Herbicide at 50% (w/w) in acetone. Challenge tests conducted 7 days after initial dosing at 1, 6.25, 12.5, and 25% Goal in acetone.	In naive animals, all concentrations produced erythema. In induced animals, erythema developed at all test concentrations, but no evidence of hypersensitivity. No evidence that Goal Herbicide produces contact sensitization in guinea pigs	Anderson and Kyle 1991 MRID 41891802
guinea pigs, albino, Crt(HA)BR strain, 20 test, 10 irritation control, 10 positive control, 10 positive control irritation control	Sensitization maximization test. Goal 2XL(P). Two initial irritation tests to determine definitive study conditions. In the definitive study, test animals: intradermal injection with 5% w/v Goal 2XL(P) in sterile water; followed by topical induction with 25% w/v Goal 2XL(P) in sterile water topical induction; followed by challenge with 10% w/v Goal 2XL(P) in sterile water.	No sensitization among animals induced and challenged with Goal 2XL(P). Sensitization was observed in positive controls (hehexylcinnamaldehyde in mineral oil). Conclusion: Goal 2XL(P) is not a dermal sensitizer	Glaza 1996 MRID 44814901

Appendix 1: Acute toxicity of oxyfluorfen and oxyfluorfen formulations to experimental mammals.

Species	Exposure	Response	Reference
guinea pigs (Hartley), 10 males/10 females	Goal 2XL (24.5% a.i.). Three 6-hour induction doses of 0.4 ml (1 dose/week) of Goal 2XL (undiluted). Challenge dose 0.4 ml undiluted Goal 2XL. DNCM positive control group included.	Delayed contact hypersensitivity test. Goal 2XL produced delayed contact hypersensitivity.	Anderson and Shuey 1994 MRID 43149807
Albino guinea pigs, (Dunkin Hartley)	Sensitization test with AG 510 (containing ~97% a.i.) Induction phase: intradermal 25% w/v in arachis oil; topical induction 50% w/w in arachis oil. Challenge phase: topical challenge 5, 10, 25 and 50% in arachis oil.	Test material did not produce any sensitization effects and was classified as a non-sensitized to guinea pig skin.	Dreher 1995c MRID 44712015
	DERMAL – Absorption		
rats, Crl:CDBR, 4 males/group	^{14}C-Goal Technical Herbicide applied to skin at three dose levels – 0.24 mg/animal (0.02 mg/cm^2), 1.2 mg/animal (0.1 mg/cm^2), and 18 mg/animal (1.44 mg/cm^2)	The majority (80 - 97.5%) of ^{14}C was not absorbed. 2.18 to 14.6% of ^{14}C was adsorbed on/in skin at test site. The predominant route of elimination of absorbed dose was feces.	Cheng 1989 MRID 42142306
	INTRAPERITONEAL		

Appendix 1: Acute toxicity of oxyfluorfen and oxyfluorfen formulations to experimental mammals.

Species	Exposure	Response	Reference
		INHALATION	
rats, CrlCDBR, 6 males/6 females per group	4-hour nose-only inhalation exposure to Goal Technical (71.4%) at concentrations of 0.58 and 5.4 mg formulation/L.	Animals observed for 14-day post-exposure. No deaths, signs of toxicity or gross pathological changes for any treatment group. **4-hour LC_{50} >5.4 mg formulation/L** (practically non-toxic)	Wanner and Hagan 1991 MRID 42000001
rats, Crl:CDBR, 5 males/5 females	4-hour nose-only inhalation exposure to Goal 2XL (24.2% a.i.)) at 4.8 mg formulation/L	Animals evaluated for 14 days after exposure. No deaths occurred. No gross pathological findings. Sings of toxicity – immediately after exposure: decreased activity, labored breathing, increased salivation. At 7-days after exposure: decreased body weight gain. At 14-days after exposure: decreased activity and labored breathing **LC_{50} >4.8 mg formulation/L**	Ulrich 1993 MRID 43149806
rat, Sprague-Dawley, 5 male, 5 female	1-hour inhalation exposure to Goal/Surflan 2/1G(MB-83-6897): mean (standard deviation) measured concentration off 7.18(±0.23) mg	No mortality. All rats gained weight over the 14-day post-exposure observation period. No unusual behavioral, no abnormal gross pathology in major organs examined. No controls were used	Tansy 1983b MRID 00163582

Appendix 1: Acute toxicity of oxyfluorfen and oxyfluorfen formulations to experimental mammals.

Species	Exposure	Response	Reference
rat, Sprague-Dawley, 5 male, 5 female	1-hour inhalation exposure to Goal/Lasso 2/2G (MB 83-6896) at mean measured concentration (standard deviation) of 7.25 (±0.38) mg/L	No mortality. All rats gained weight over the 14-day post-exposure period, and all displayed "normal" exploratory behavior. No abnormal gross pathology in major organs examined. No controls were used.	Tansy 1983a MRID 00163584
rat, Sprague-Dawley, 5 male, 5 female	4-hour nose-only exposure to AG510 (96% a.i.) at measured concentration of 3.71 ± 0.66 mg/L (27.5 mg/L nominal) with mean mass median aerodynamic diameter of 3.8 uM, and inhalable fraction of 52.2% < 4 uM	No mortality, normal body weight gain, no abnormal pathology. Transient clinical signs (piloerection, wet fur, hunched posture, staining with test material) during exposure and resolved by 1 hour post-exposure	Blagden 1995 MRID 44712012
	OCULAR		
rabbits, male, New Zealand White (9 animals)	Eye irritation study. 0.1mL of test substance (Goal 1.6E, 27% a.i.) applied to corneal surfaces [does not indicate if this is formulation or a.i.].	Irritation to iris and cornea for up to 72 hours after administration of test substance. Based on duration of effects, test substance is rated as severely irritating to eyes.	Krzywicki 1983 MRID 00159811

Appendix 1: Acute toxicity of oxyfluorfen and oxyfluorfen formulations to experimental mammals.

Species	Exposure	Response	Reference
rabbits, male, New Zealand White (9 animals)	0.1mL of test material (Goal Technical Herbicide. 71.4% a.i.) applied to conjunctival sac. For 3 rabbits, eyes were irrigated after dosing.	Eye irritation evaluated according to Draize procedure at 1, 24, 48, and 72 hours and 7 and 14 days after application. Irritation of conjunctiva (chemosis and redness). No effect noted for iris or cornea. Treatment-related effects observed at 1 through 72 hours. No effects observed at 7 days after application. Irritation was not reduced by irrigation.	Gingrich et al. 1990d MRID 41601004
rabbits, New Zealand White, 6 males	Undiluted (0.1 ml) Goal 2XL (24.4% a.i.) applied to conjunctiva.	Eye irritation evaluated according t0 Draize criteria at 1, 24, 48, and 72 hours and 7 days after dosing. No mortality or clinical signs of toxicity noted. Irritation of cornea and conjunctiva observed from 1 to 72 hours after application. At day 7, corneal effects were reversed in 5/6 rabbits and conjunctival effects were reversed in 6/6 rabbits.	Lutz and Parno 1993d MRID 43149805

Appendix 1: Acute toxicity of oxyfluorfen and oxyfluorfen formulations to experimental mammals.

Species	Exposure	Response	Reference
rabbits, New Zealand White, 6 males	Undiluted (0.1 ml) Goal 2XL (25.4%) applied to conjunctiva. Eyes were irrigated 24 hours after dosing.	Eye irritation evaluated according t0 Draize criteria at 1, 24, 48, and 72 hours and 7, 14, and 21 days after dosing. No mortality or clinical signs of toxicity noted. Corneal and conjunctival irritation observed through 72 hours, but resolved by day 7. Irritation of iris observed at 24 and 48 hours, but resolved at 72 hours	Lutz et al. 1995 MRID 43424203
rabbits, New Zealand White, 6 (3 males/3 females)	Single application of 0.1 ml test material (AG510, containing ~97% a.i.) to conjunctiva. No irrigation after administration	Eye irritation assessed at 1, 24, 48, and 72 hours after application according to Draize criteria. 1 hour: moderate conjunctival irritation 6/6 rabbits. 24 hours: minimal conjunctival irritation at 25 hours 6/6 rabbits. 48 hours: minimal conjunctival irritation at 25 hours 1/6 rabbits. 72 hours: no effects noted. No corneal effects at any time point. Based on these results, AG 510 is a mild irritant.	Dreher 1995a MRID 44712015

Appendix 1: Acute toxicity of oxyfluorfen and oxyfluorfen formulations to experimental mammals.

Species	Exposure	Response	Reference
rabbits, New Zealand White, 9 males	Single application of 0.1 g Goal Technical 95 Herbicide (97% a.i.) to corneal surface	Eye irritation assessed at 1, 24, 48, and 72 hours and 7 days after application according to Draize criteria. No treatment -related ocular effects were observed at a any observation time.	Lampe et al. 1988d MRID 44828906

Appendix 2: Developmental and Reproductive Toxicity of oxyfluorfen and oxyfluorfen formulations after repeated oral administrations.

Species	Exposure/Response	Reference
Teratology Studies		
rats, female, 25/group	RH-2915 Technical (71.4% a.i.) Administered by gavage to mated females at doses of 10, 100 and 1000 mg a.i./kg/day on days 6-15 of gestation. A vehicle control group received 0.5% methylcellulose. Maternal NOAEL: 100 mg a.i./kg/day Maternal LOAEL: 1000 mg a.i./kg/day; urine staining, significantly reduced mean body weight, slightly decreased food consumption Fetotoxic NOAEL: 100 mg a.i./kg/day Fetotoxic LOAEL: 1000 mg a.i./kg/day; statistically significant lower implantation efficiency, higher incidence of resorption, lower incidence of fetal viability No treatment-related teratogenic effects were observed.	Piccirillo 1977 MRID 00083444

Appendix 2: Developmental and Reproductive Toxicity of oxyfluorfen and oxyfluorfen formulations after repeated oral administrations.

Species	Exposure/Response	Reference
rats (27 per treatment group)	Goal Technical (71.4% a.i.) in corn oil administered by gavage to pregnant rats at 0, 15, 150, and 750 mg/kg on days 6-15 of gestation. No maternal or fetal toxicity at 15 mg/kg. No treatment related external, visceral or skeletal malformation in fetuses at this dose. No treatment-related effects on hematological variables or liver weight at any dose. Treatment related decrease in body weight and food consumption at does levels $\geq$150 mg/kg. Treatment related increase in fetal resorptions and decrease in fetal weight at does levels $\geq$150 mg/kg. Treatment-related increase in skeletal malformations (bending of scapula, forelimb and hindlimb bones) at does levels $\geq$150 mg/kg. Retarded development at does levels $\geq$150 mg/kg At 750 mg/kg dose level, 17/27 maternal deaths during treatment period. Ten survivors were pregnant, but all had completely resorbed litters. Signs of toxicity (hunched posture, ataxia, lethargy, alopecia, soft feces) observed. Gross pathological changes (reddened linings of stomach and intestines). No viable litters produced. Treatment-related increase in SGOT and alkaline phosphatase observed at this dose. NOAEL (maternal and fetal toxicity): 15 mg./kg LOAEL (maternal and fetal toxicity): 150 mg/kg	Rohm & Haas 1990 MRID 41678801 and Rohm & Haas 1991a MRID 4174401 (these are preliminary reports) Solomon and Ronnanello 1991 MRID 41806501 (final report)

Appendix 2: Developmental and Reproductive Toxicity of oxyfluorfen and oxyfluorfen formulations after repeated oral administrations.

Species	Exposure/Response	Reference
rats, CD strain,	Oxyfluorfen Technical (98 % a.i.) administered by gavage on days 6 to 15 of gestation at doses of 375, 750, and 1000 mg a.i./kg/day, plus a vehicle control group (methylcellulose, 1% w/v). On day 20 of gestation, females were killed and uterine contents examined. Maternal effects: No signs of maternal toxicity at any does level. Fetal effects: No effects at any dose level Oxyfluorfen at doses up to 1000 mg a.i./kg/day given to pregnant rats had no effects on females or on *in utero* development of fetuses.	Burns 1997b MRID 44933103
rabbits, 4 females/group	Range-finding study: Goal 25WP (26.9 % a.i.) administered by gavage to pregnant rabbits at doses of 0 (reverse osmosis purified water), 31, 62, 125, 250 and 500 mg a.i./kg/day. Mortality at doses of 125 mg/kg/day and higher; abortion at 125 mg/kg/day and reduced maternal weight gain at doses of 62 mg/kg/day and higher; increased resorptions and smaller average litter sizes at 250 and 500 mg/kg/day; decreased implantations at 500 mg/kg/day. NOAEL: 31 mg a.i./kg/day	Hoberman et al. 1981 MRID 00094051

Appendix 2: Developmental and Reproductive Toxicity of oxyfluorfen and oxyfluorfen formulations after repeated oral administrations.

Species	Exposure/Response	Reference
rabbits, New Zealand White, 19 inseminated females/group	Goal 25WP (26.9% a.i.) at 10, 30 and 90 mg a.i./kg/day on days 6-18 of gestation. Vehicle control and reverse osmosis water control groups were also used in the study. Maternal effects: mortality in 5/19 rabbits at 90 mg/kg/day, presumed associated with observed anorexia; anorexia and reduced body weight gain at 30 and 90 mg/kg/day; hematuria and decreased motor activity at 90 mg/kg/day; statistically significant increased incidence of abortion at 30 and 90 mg/kg/day. Fetal effects: No malformations at any dose, though the number of high-dose rabbits available for examination was small. No effects on implantation, litter size, fetal viability, fetal body weight or sex ratio at 10 or 30 mg/kg/day. The limited data available for high-dose rabbits (5 litters only) indicates decreased pregnancy, corpora lutea, implantation and litter size. **NOAEL for maternal and fetal effects: 10 mg a.i./kg/day**	Hoberman et al. 1982 MRID 00094052
rabbits, New Zealand White, 15 females/group	Oxyfluorfen Technical (98 % a.i.) administered by gavage on days 6 to 19 of gestation at doses of 10, 30 and 90 mg a.i./kg/day, plus a vehicle control group (methylcellulose, 1% w/v). On day 29 of gestation, females were killed and uterine contents examined. maternal effects: At highest dose level – reduced food intake and decreased fecal output. **NOAEL = 30 mg/kg/day** fetal effects: decreased mean litter weights, delayed skeletal ossification, delayed fetal head development . **NOAEL = 30 mg/kg/day**	Burns 1997a MRID 44933102

Reproduction Studies

Appendix 2: Developmental and Reproductive Toxicity of oxyfluorfen and oxyfluorfen formulations after repeated oral administrations.

Species	Exposure/Response	Reference
rats	2-generation reproduction study with Goal Technical Herbicide (71.4% a.i.) at dietary concentrations of 0, 100, 400, and 1600 ppm. P1 Adults/F1A Offspring: Treatment-related decrease in female body wt at 1600 ppm. No treatment-related effects in offspring. NOAEL = 400 ppm. P2 Adults/F2A Offspring: Treatment-related decrease in female body wt at 1600 ppm. Treatment-related decreases in mean number of offspring and mean number of live offspring and decreased fetal body weight. NOAEL = 400 ppm.	Rohm & Haas 1991b MRID 41768701 (This is a preliminary report)
rats, Crl:CDBR, 25 rats/sex/group,	2-generation reproduction study with Goal Technical Herbicide (71.4% a.i.) at dietary concentrations of 0, 100, 400, and 1600 ppm. Dose-related effects at dietary concentrations 400 ppm and greater. At 400 ppm, histological changes in kidneys (renal-pelvic mineralization, reactive hyperplasia, dilation of collecting ducts) of P1 and P2 males and P2 females. **For adult toxicity, NOAEC = 100 ppm.** Reproductive performance: No treatment-related effects on reproductive performance. Treatment-related decreased in fetal body weight at 1600 ppm. **Reproductive NOAEC = 400 ppm.**	Solomon et al. 1991 MRID 42014901 Note: This study appears to be the final report for the preliminary results described above.

Appendix 2: Developmental and Reproductive Toxicity of oxyfluorfen and oxyfluorfen formulations after repeated oral administrations.

Species	Exposure/Response	Reference
rat, Long-Evans, 20 female and 10 male/group	3-generation reproduction study with RH-2915 (82.2 - 85.7% a.i.) administered at 0, 2, 10 and 100 ppm at 85.7% a.i. for approximately 16 months followed by 0, 2, 10 and 100 ppm at 82.2% a.i. for approximately 1 month. This exposure period encompassed 1 mating of the parental generation and two matings of each of the F1 and F2 generations. No treatment-related effects on mortality, body weight or food consumption of males and non-pregnant females, mating, pregnancy or fertility; statistically significant decrease in body weight gain among high-dose Fo females between day 14 and 21 of lactation. This was not seen in F1 or F2 generations; statistically significant decrease in survival of high-dose offspring for days 0-4, 4-14 of lactation in F1a generations (correlated with weight loss in mothers). This was not seen in subsequent generations. No statistically significant treatment-related effects on fetal survival, size, sex, malformations, or gross pathology. No evidence of teratogenic or embryotoxic effects. **Maternal NOAEL/fetotoxic NOAEL = 10 ppm (From Table 4, Week 1, week 5 and week 10 dose for Fo females = 1.407, 0.992 and 0.721 mg a.i./kg/day)** **Maternal LOAEL/fetotoxic LOAEL = 100 ppm (from Table 4, Week 1, week 5 and week 10 dose for Fo females = 11.0, 10.080 and 7.390 mg a.i./kg/day)**	Killeen et al. 1977 MRID 00135073

Appendix 3: Subchronic and Chronic toxicity of oxyfluorfen and oxyfluorfen formulations to experimental mammals.

Species	Exposure	Response	Reference
SUBCHRONIC ORAL EXPOSURE			
mice, Charles River CD-1, 15 animals/sex/group	Dietary exposure to Goal Technical Herbicide (72.5% a.i.) at concentrations of 0, 200, 800 and 3200 ppm a.i. for 13 weeks.	Dose-dependent increase in toxicity Clinical signs of toxicity: at 3200 dose only (lethargy, passiveness, arched backs. ataxia). Abnormal laboratory findings: at 200 ppm a.i. dose, decreased hemoglobin and hematocrit (males), increased platelet count, increased cholesterol (females) increased SGPT (females), ketonuria (females). Additional findings observed at higher exposure levels. abnormal gross pathology: at 200 ppm a.i. dose, increased liver weight, liver hypertrophy, necrosis and hemosiderosis, spleen hyperplasia (males), bone marrow hyperplasia (males), urinary bladder hyperplasia (females). Additional findings observed at higher exposure levels. **LOAEC = 200 ppm** a.i.	Nave and Longacre 1990a MRID 92136012 (this is a summary of MRID 00117602)

Appendix 3: Subchronic and Chronic toxicity of oxyfluorfen and oxyfluorfen formulations to experimental mammals.

Species	Exposure	Response	Reference
rats, 10/sex/group	Dietary exposure to oxyfluorfen technical (98 % a.i.) at 0, 500, 1500, 6000, and 10000 pm a.i. for 13 weeks	Findings after 13 weeks of treatment. 500 ppm: no treatment-related finding 1500 ppm: decreased mean cell volume and mean cell hemoglobin, some alterations of urine electrolytes. 6000 ppm: slightly decreased in body weight. Decreased packed cell volume, hemoglobin concentration, and mean cell volume. Elevated serum ALAT. creatinine, total cholesterol. High urine output and some changes in urine electrolytes. High lever and spleen weights (♂ and ♀) and high kidney weights (♀). Gross pathological changes to kidneys. 10000 ppm: decreased body weight and food consumption. Decreased packed cell volume, hemoglobin concentration, and mean cell volume. Elevated leukocyte counts. Hypochromic erythrocytes. Elevated serum alkaline phosphatase, ATAT. High urine output and some changes in urine electrolytes. High lever and spleen weights (♂ and ♀), high kidney weights (♀) and high thyroid weights (♂). Histopathologic changes to	Stewart 1997 MRID 44933101

Appendix 3: Subchronic and Chronic toxicity of oxyfluorfen and oxyfluorfen formulations to experimental mammals.

Species	Exposure	Response	Reference
rat, Japanese Charles River, CRF-CDF, 10/sex/group	13-week study; dietary exposure to RH 2915 (72.5% a.i.) at measured concentrations nominal concentrations of 0, 200, 1000 and 5000 ppm a.i. (Mean dose males: 0, 14, 71, and 361 mg a.i/kg/day; mean dose females: 0, 18, 75, and 396 mg a.i/kg/day). Note: Poor quality fiche and poor translation into English	5000 ppm: reduced body weight gain; increased food consumption; liver changes as for 1000 ppm (both sexes) and increased ALP (males); increased cholesterol (females) and increased plasma cholinesterase activity (females); vacuolar degeneration of distal tubuli of kidneys; hypertrophy and hyperplasia of transitional epithelia of kidney; deposition of calcium in renal pelvis; increased BUN; pigmentation of liver kupfer cells and kidney lumen and tubular epithelia; decreased adrenal weight and vacuolation of cells of the zona fasciculata; atrophy of thymus cortex; decreased RBCs, hematocrit; increased reticulocyte ratio, increased mean corpuscular volume and mean corpuscular hemoglobin 1000 ppm; increased food consumption; increased absolute liver weight (males) and increased incidence of swollen hepatic cells and fatty liver (males); vacuolar degeneration of distal tubuli of kidneys (females); hypertrophy and hyperplasia of transitional epithelia of kidney (females); deposition of calcium in renal pelvis (females); yellow pigmentation of tubular epithelia and lumen; decreased RBCs, hematocrit and hemoglobin concentration	Nomura Research Institute 1982 MRID 0117603

Appendix 3: Subchronic and Chronic toxicity of oxyfluorfen and oxyfluorfen formulations to experimental mammals.

Species	Exposure	Response	Reference
SUBCHRONIC INHALATION EXPOSURE			
rat, Charles River CD, 10/sex/group	aerosols of Goal 2E (% a.i. not stated)at average metered concentrations of 0.20 and 0.78 mg/L, 6 hr/day, 5 days/week for 20 or 11 exposure days in one month; untreated and vehicle (0.81 mg/L)controls; average aerodynamic mass median diameters were 3.2, 3.0 and 3.4 for the vehicle, low-dose and high-dose aerosols, respectively. For each sample, >90% by weight was considered respirable. Vehicle was not identified.	Vehicle controls had excessive salivation; no clinical signs in other groups. Statistically significant elevation in leukocytes and percentage of lymphocytes in Goal 2E exposed rats with respect to controls, but within range of normal for Charles River CD rats in experimenter's laboratory. Decreased adrenal weights with respect to vehicle controls in males at both concentrations Histopathologic respiratory system changes considered vehicle-related. Gross pathological respiratory changes considered vehicle-related	Goldenthal et al. 1978 MRID 00071916
SUBCHRONIC DERMAL EXPOSURE			

Appendix 3: Subchronic and Chronic toxicity of oxyfluorfen and oxyfluorfen formulations to experimental mammals.

Species	Exposure	Response	Reference
rabbit, New Zealand White, 4/sex/group, includes control and solvent controls	20 exposures (5 days/week for 4 weeks) to RH-2915 as either paste of technical grade in solvent/emulsifier or aqueous solution of emulsifiable concentrate (RH-2915 EC). Group I: untreated controls Group II: solvent/emulsifier (not specified) control. Group III: RH-2915 Technical at 2 g/kg (1500 mg a.i./kg) RH-2915 EC in aqueous solution applied to intact and abraded skin at Group IV: 0.1 ml/kg (24.2 mg a.i./kg); and Group V: 0.4 ml/kg (96.8 mg a.i./kg)	**mortality**: 1 Group II female **dermal**: all treatments, including solvent/emulsifier control caused erythema, edema, skin cracking, bleeding and dessication (least severe in Group V). **body weight**: significantly decreased in Group II and V males with respect to untreated controls. No difference between Group II and V male body weights (implicates solvent/emulsifier as causal agent). No effect on females. Transient decrease in body weight in Group III males and females with respect to untreated controls, with females rebounding more quickly than males **food consumption**: reduced (10-18%) in treated males (including Group II) throughout the test **hematology**: Increased mean white cell counts with respect to untreated controls in all females, Group II (67%), Group III (56%), Group IV(20%) and Group V(43%). Authors state that Group III and V values reached statistical significance with respect to controls. **Gross pathology:** pale or tan areas in liver of 1/4 males and 3/4 females in Group IV. Skin thickening and discoloration in all treated rabbits.	Cruzan et al. 1978 MRID 00071915

Appendix 3: Subchronic and Chronic toxicity of oxyfluorfen and oxyfluorfen formulations to experimental mammals.

Species	Exposure	Response	Reference
		CHRONIC EXPOSURE	
dog, 10/sex control, 6/sex, exposed	52-week dietary exposure to RH-2915 (71.4 - 73.8% a.i.)at 0, 100, 600 or 3600 ppm diet (males: 3.1, 18.5, 61.0 mg/kg/day; females: 0, 3.0, 18.8, 60.3 mg/kg/day).	NOAEL: 100 ppm LOAEL: 600 ppm based on decreased body weight gain, increased serum alkaline phosphatase; increased liver weight and increased bile-pigmented hepatocytes.	Piccirillo 1977 MRID 00071918 (26-week interim report) and Rohm and Haas 1981 MRID 00078767 (final report: not available; results as cited in U.S. EPA 2001a)

Appendix 3: Subchronic and Chronic toxicity of oxyfluorfen and oxyfluorfen formulations to experimental mammals.

Species	Exposure	Response	Reference
mice, Charles River CD-1, 60 mice/sex/group	20 month dietary exposure to RH-2915 technical (85.7% a.i.) at 0, 0 solvent control (ethanol), 2, 20 and 200 ppm a.i. Average doses: 0,0, 0.3, 3, 33 mg a.i./kg/day, males; 0,0, 0.4, 4, 42 mg a.i./kg/day, females.	No treatment-related changes for behavior, appearance, body wt, food consumption, and hematolgical or biochemical parameters. After 12 months: No gross pathological findings in 200 ppm a.i. group. Liver weights increased (♂) and microscopic moderate to severe liver changes (♂) characterized by hepatocyte vacuolization, hyaline bodies and hepatocyte necrosis in 200 ppm group. No positive findings at 2 or 20 ppm a.i. after 20 months: at 200 ppm a.i., no increase in liver weights. Slight increase (but not statistically significant) in liver masses, diagnosed histopathologically as hyperplastic nodules or hepatocellular carcinomas. Statistically significant increase hepatocellular regeneration lesion (characterized by variation in hepatocyte size and increase in mitotic activity). Statistically significant increase in combined hepatocellular carcinoma+adenoma+regeneration lesion at 200 ppm. No positive findings at 2 or 20 ppm a.i. NOAEC = 20 ppm a.i. (3 mg/kg/day) LOAEC = 200 ppm (33 and 42 mg/kg/day for M and F,	Goldenthal and Wazeter 1977 MRID 00037939

Appendix 3: Subchronic and Chronic toxicity of oxyfluorfen and oxyfluorfen formulations to experimental mammals.

Species	Exposure	Response	Reference

NOTE on Goldenthal and Wazeter 1977: U.S. EPA 2001a uses this study as the basis for deriving a Q1* of 7.3E-02 $(mg/kg/day)^{-1}$ based on combined liver adenoma/carcinoma. U.S. EPA 1987 (IRIS) says 2 ppm (0.3 mg a.i./kg/day) is the NOAEL and 20 ppm (3 mg/kg/day) is LOAEL (increased absolute liver weight, necrosis, regeneration and hyperplastic nodules, with increased incidences of effects at 200 ppm). U.S. EPA 2001a (HED) says 20 ppm is the NOAEL and 200 ppm is the LOAEL (increased SGPT, increased SAP and liver histopathology including hepatocyte necrosis). U.S. EPA 1987 derives an RfD of 0.003 mg/kg/day on the basis of a NOAEL of 0.3 mg/kg/day and an uncertainty factor of 100. U.S. EPA 2001a derives an RfD of 0.03 mg/kg/day on the basis of their NOAEL of 3 mg/kg/day and an uncertainty factor of 100.

Appendix 3: Subchronic and Chronic toxicity of oxyfluorfen and oxyfluorfen formulations to experimental mammals.

Species	Exposure	Response	Reference
rats, Long-Evans, 50/sex/group. Interim necropsy on 10/sex/high dose and 6/sex/control at 12 months. Interim laboratory studies on 6/sex/control and high dose at 1,3,6,10, 12, 18, 24 months	Combined carcinogenicity/chronic toxicity study. RH-2915 (85.7% a.i.) in the diet at 0, 2, 40.0 and 800/1600 (mean of 685) ppm a.i. for 24 months.	Although many statistically significant effects were randomly observed among the various control and treatment groups, no dose-response could be established for any effect. It is not possible to make meaningful qualitative or quantitative conclusions from this study. The histopathological results for the above study are presented in MRID 00135072. No treatment-related histopathologic changes were found in low-and mid-dose animals at either interim or final necropsy. Minimal hypertrophy of centrilobular hepatocytes (liver) was considered to be treatment-related and was seen in one male and 2 female high-dose rats. This effect was attributed to metabolic adaptation of the liver, and was not considered to be adverse due to the lack of any other treatment-related changes. There were no treatment-related or notable differences in the incidence of neoplastic changes between control and exposed rats. NOTE: this study was found to be unacceptable by OPP/HED (U.S. EPA 2001a), but was used by OPP/HED to establish a NOAEL of 800/1600 ppm	Auletta et al. 1978 MRID 00083445 Tornaben et al. 1977 MRID 00135072

Appendix 4: Mutagenicity studies on oxyfluorfen.

Organism	Exposure Level	Assay System	Effects	Reference
Mouse bone marrow cells	Single dose of Goal Technical Herbicide in corn oil administered by gavage at doses of 0, 0.5, 2.5, and 5.0 g a.i./kg	In vivo chromosome aberration assay	No increase in the number of aberrant cells. Goal Technical Herbicide was negative in the in vivo chromosome aberration assay.	Gudi 1990 MRID 41873801
Salmonella, strains TA98, TA100, TA 1535, and TA 1537	Goal Technical Herbicide (72.5% a.i.) at 0 (solvent control, DMSO), 1.0, 10, 100, 250, 500, 1000, 2500, 5000, 6000, 7600 µg formulation per plate.	Salmonella reverse mutation assay, with and without S-9 activation	Test substance produced a mutagenic response in this assay system in strains TA98 and TA100.	Nave and Longacre 1990b MRID 92136021 (this is a summary of MRID 00098420)
primary rat hepatocytes	Goal Technical Herbicide (73% a.i.) at concentrations of 0 (solvent control, DMSO), 0.10, 0.25, 0.5, 1.0, 2.5, 5.0, 10.0, and 25.0 µg/mL.	Unscheduled DNA synthesis assay	Test substance was inactive (non-genotoxic) in this assay system.	Nave and Longacre 1990c MRID 92136021
mouse lymphoma	Goal Technical Herbicide (72.7% a.i.) at concentrations of 0 (solvent control, DMSO), 62.5, 125, 250, 500, and 1000 µg/mL	mouse lymphoma forward mutation assay	Goal Technical Herbicide is weakly mutagenic in the presence of an activation system (S-9).	Nave and Longacre 1990d MRID 92136022

Appendix 4: Mutagenicity studies on oxyfluorfen.

Organism	Exposure Level	Assay System	Effects	Reference
Salmonella typhimurium (strains TA 1535, TA 1537, TA 98 and TA 100)	Ag 510 Technical (96% a.i.) in dimethyl sulfoxide – 50, 150, 500, and 1500 µg/plate	reverse mutation assay	AG 510 was not mutagenic in this test system.	Everich 1995a MRID 44933104
bone marrow cells of mice	1000 mg/kg AG 510 Technical (96% a.i.) in methyl cellulose administered by intraperitoneal injection	mouse micronucleus test	Test substance did not show any evidence of causing chromosome damage in this *in vivo* test.	Everich 1995b MRID 44933105
primary rat liver cells	Single oral dose (600 and 2000 mg/kg) of AG 510 Technical (96% a.i.) in methyl cellulose	*In vivo* unscheduled DNA synthesis assay	Test substance sis not elicit any evidence of inducing unscheduled DNA synthesis in rat liver in vivo.	Everich 1995c MRID 44922106
Salmonella typhimurium (strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100)	AG 510 (96% a.i.) at concentrations of 10 to 5000 µg/plate	mutagenic activity assay	AG 510 induced mutagenic activity in the TA 100 strain in the presence of S9 activation. No mutagenic activity was observed in any other strain	Willington 1999 MRID 44942801

Appendix 4: Mutagenicity studies on oxyfluorfen.

Organism	Exposure Level	Assay System	Effects	Reference
L5178Y TK+/- mouse lymphoma cells	Goal Technical 95 Herbicide (97.1% a.i.)	mouse lymphoma mutagenesis assay	Under test conditions, test substance did produced a negative response both in the presences and absence of S9 activation. Therefore, Goal Technical 95 herbicide is considered to be non-mutagenic in this system	Kirby 1987 MRID 44947202

Appendix 5: Toxicity of oxyfluorfen and oxyfluorfen formulations to birds

Species	Nature of Exposure	Effects	Reference
		Single Dose Gavage	
bobwhite quail, 5 males/5 females per exposure group	single dose of Goal Technical Herbicide (70.2% a.i.) in corn oil administered by gavage at does of 0 (corn oil control), 1470, and 2150 mg a.i./kg.	Birds observed for 21 days. One death at the highest dose. Signs of toxicity observed at both Goal doses (weakness, anorexia, piloerection, abnormal cage droppings, decreased food consumption). **LC_{50} >2150 mg a.i./kg**	Fletcher 1987a MRID 42142301
		Multiple Exposure Gavage	
bobwhite quail, 25-34 weeks old, 5/sex/group	21-day acute toxicity study; exposure to Goal Technical (70.2% a.i.) by gavage in corn oil at concentrations of 0, 1470 and 2150 mg a.i./kg body weight	LD_{50} >2150 mg a.i./kg LOAEC = 1470 mg a.i./kg on basis of transient anorexia and weakness Severely decreased food consumption days 0-3 (both groups) and 4-7 (high dose) in comparison with controls. No significant impact on body weight. Weakness and anorexia in treated birds but not in negative or vehicle controls. One death at 2150 mg/kg. Study was found to be acceptable in terms of fulfilling EPA test guidelines and requirements for testing	Godfrey and Longacre 1990d MRID 92136090 (Phase III summary of MRID 92136106)

Appendix 5: Toxicity of oxyfluorfen and oxyfluorfen formulations to birds

Species	Nature of Exposure	Effects	Reference
American kestrel (Falco sparvaricus), 4 nestlings	range finding part of study with multiple herbicides: dosing by gavage for 10 days with oxyfluorfen (98.5% a.i.) at 500 mg/kg in corn oil	No mortality. No definitive study on survival and growth was conducted with oxyfluorfen due to a lack of mortality in the range-finding study **NOAEL: 500 mg/kg**	Hoffman et al. 1991a,b
		Acute Dietary	

Appendix 5: Toxicity of oxyfluorfen and oxyfluorfen formulations to birds

Species	Nature of Exposure	Effects	Reference
bobwhite quail, 13 days old, 10 birds/group	5-day dietary exposure to Goal Technical Herbicide (70.2% a.i.) at concentrations of 0 (vehicle control, corn oil), 312, 625, 1250, 2500, and 5000 ppm a.i. (followed by 3-day observation period).	No mortalities or gross pathological changes in any treatment group. Effects observed at concentrations of 2500 and 5000: food avoidance, decreased body weight, decreased body weight gain. **LC_{50} >5000 ppm a.i.** For signs of toxicity – **NOAEC = 1250 ppm a.i.** **LOAEC = 2500 ppm a.i.**	Fletcher 1987b MRID 42142302 Godfrey and Longacre 1990e MRID 92136091 (Phase III summary
mallard ducks, 5 days old, 10 birds/group	5-day dietary exposure to Goal Technical Herbicide (70.2% a.i.) at concentrations of 0 (vehicle control, corn oil), 312, 625, 1250, 2500, and 5000 ppm a.i. (followed by 3-day observation period).	One mortality in the 5000 ppm a.i. group. No mortalities or gross pathological changes in any treatment group. Effects observed: decreased body weight in 5000 ppm a.i. group. **LC_{50} >5000 ppm a.i.** **NOAEC = 1250 ppm a.i.**	Fletcher 1987c MRID 42142303 Godfrey and Longacre 1990n MRID 92136092 (Phase III summary)

Fletcher 1987c Note: Food consumption during exposure averaged 22 g/bird, 19 g/bird, 18 g/bird, 17 g/bird, and 13 g/bird in the 312, 625, 1250, 2500, and 5000 ppm groups respectively (Table V). In the same order, mean body weights during exposure were 118 g, 115 g, 112 g, 120 g, and 93 g (Table IV). Thus, the fractional food consumption (g food/g bw) was 0.19, 0.17, 0.16, 0.14, and 0.14 and the corresponding doses were 59 mg/kg bw, 106 mg/kg bw, 200 mg/kg bw, 350 mg/kg bw, and 700 mg/kg bw.

Reproduction Studies

Appendix 5: Toxicity of oxyfluorfen and oxyfluorfen formulations to birds

Species	Nature of Exposure	Effects	Reference
mallard duck, 17 weeks. total number of animals in study: 80 males and 80 females	dietary exposure to Goal Technical purified (99.3% a.i.) at 0, 125, 250, 500, and 750 ppm a.i for 20 weeks. authors report overall calculated daily dose for 20 weeks based on food consumption: 0, 15.8, 31.0, 64.7, and 99.9 mg a.i./kg body wt/day.	Toxicity to adults: No treatment-related mortalities, signs of toxicity or gross pathological findings at any concentration tested. Reproductive parameters: No effect on reproductive parameters at 125, 250, or 500. At 750 ppm does level, decreased egg production, embryo development, and hatchability. NOAEC for reproductive effects = 500 ppm a.i.	Frey et al. 2003a MRID 46070101
mallard ducks, 1 male and 3 females per pen, 8 pens /group	RH-2915 Technical (% a.i.?) at 0 and 100 ppm diet	Experimental design and methodology only. No results given	Rohm and Haas 1981b MRID 00094057
mallard ducks, 5 male and 25 female per group	one generation study; dietary exposure to RH-2915 technical (% a.i. not stated) at 0, 20 and 100 ppm a.i.	Fiche is poor quality; cannot read tables; text states there was no mortality and no statistically significant differences in body weight between controls and exposed ducks. High-dose birds had significantly greater food consumption than controls at end of study. No treatment-related differences in number of eggs laid, eggshell thickness, embryo vitality or hatchling survival. **NOAEC = 100 ppm a.i.**	Piccirillo and Najarim 1978 MRID 00110734

Appendix 5: Toxicity of oxyfluorfen and oxyfluorfen formulations to birds

Species	Nature of Exposure	Effects	Reference
bobwhite quail,19 weeks old, total number of animals in study: 80 males and 80 females	dietary exposure to Goal Technical purified (99.3% a.i.) at 0, 125, 250, 500, and 750 ppm a.i for 20 weeks. authors report overall calculated daily dose for 20 weeks based on food consumption: 0, 11.3, 21.3, 43.5, and 69.2 mg a.i./kg body wt/day.	Toxicity to adults: No treatment-related mortalities, signs of toxicity or gross pathological findings at any concentration tested. Reproductive parameters: No effect on reproductive parameters at any concentration tested. **NOAEC for reproductive effects = 750 ppm a.i.**	Frey et al. 2003b MRID 46070102
bobwhite quail, 12 males and 24 females per concentration	one-generation study with Goal Technical (72.5% a.i.) at 0, 50 or 100 ppm a.i. diet (mean measured concentrations of not detected, 50.8 and 92.6 ppm a.i.)	No difference between controls and treated birds in percentage of eggs cracked, viable embryos, live 3-week embryos, normal hatchlings and 14-day old survivors. The percentage of cracked eggs was actually less in the treated groups than in controls. **NOAEC = 100 ppm a.i. diet (92.6 ppm a.i.)** Study was found "acceptable" in fulfilling EPA test guidelines and requirements	Godfrey and Longacre 1990c MRID 92136004 (Phase III summary of MRID 00117619)
bobwhite quail, 1 male and 2 females per pen, 12 pens/concentration	one-generation study, dietary administration of RH-2915 Technical (% a.i. not specified) at 0, 50 or 100 ppm.	No results given. This fiche contains only the study protocol	Rohm and Haas 1981a MRID 00094056

Appendix 5: Toxicity of oxyfluorfen and oxyfluorfen formulations to birds

Species	Nature of Exposure	Effects	Reference
bobwhite quail, 12 male and 24 females per group	one-generation study, dietary administration of RH-2915 (% a.i. not specified) at 0 20 or 100 ppm a.i.	Poor quality fiche. No treatment-related mortality. No statistically significant differences in body weight gain. Statistical analysis of food consumption was not conducted. No significant differences in number of eggs laid; eggshell thickness. No adverse effects on hatchling viability. **NOAEC = 100 ppm a.i.**	Piccirillo and Peterson 1978 MRID 00110735

Appendix 6: Effects of oxyfluorfen and oxyfluorfen formulations on terrestrial invertebrates and soil microorganisms

Species	Exposure	Observations	Reference
honey bees, adult worker, 100/group	Single exposure to Goal Technical Herbicide in a bell jar vacuum duster at approximate doses of 0, 33, 67, and 100 µg a.i./bee.	Acute dust exposure toxicity test. Bees evaluated for 96 hours No treatment-related mortality or signs of toxicity. **LD_{50} >100 µg a.i./bee** Author states that 100 µg a.i./bee is equivalent to 8.93 lb a.i./A.	Atkins 1992 MRID 4236801
Predacious mite (*Typhlodromus pyri Scheuten*), 5 replicates/treatment, 20 protonymphs/treatment	Exposure to plates sprayed with Goal 4F (also known as Goal 480C)(42.9% a.i.) at 1.44 kg a.i./ha (applied in a volume of 200 ml/ha); negative control (deionized water); positive control (Perfekthion at 12 ml/ha)	After 7days, differences in cumulative mortality between control and the Goal® 4F mites were statistically significant (Fisher's Exact test: $p < 0.001$). The mortality was 5, 98, 100% in the control, the Goal® 4F and positive control groups, respectively. From days 7 to 14, the reproduction was 5.5 eggs/ female in the control. In the Goal® 4F treatment, no reproduction was recorded since no females survived day 9 of the test. **LOAEC = 1.44 kg a.i./ha (1.28 lb a.i./acre)**	Milligan 2000 MRID 45271303
entomopathogenic nematodes; 2 species, 3rd instar juveniles	312 to 10,000 ppm of Goal formulation (% a.i. not specified)	NOAEC (immobility): 625 ppm LOAEC (immobility): 5000 ppm based on some limited immobility, although > 50% of the test organisms were mobile. NOAEC (ability to infect prey larvae): 10,000 ppm; i.e. no difference from controls at highest concentration tested	Rovesti and Desceo 1990

Appendix 6: Effects of oxyfluorfen and oxyfluorfen formulations on terrestrial invertebrates and soil microorganisms

Species	Exposure	Observations	Reference
soil microbes assessed: bacteria, fungi and actinomycetes	field test: pre-emergence application of oxyfluorfen (formulation and % a.i. not specified) to soil in which sesame is grown at 0.03 kg/ha	Initial reduction in bacterial, fungal and actinomycete populations at 25 post-treatment in comparison with hand-weeded controls. Populations equaled or exceeded controls at days 56 and 75 post-treatment.	Nayak et al. 1994
soil fungi	pre-emergence application of oxyfluorfen at 0.25 or 0.5 kg a.i./ha	Fungal population was not affected with respect to controls in medium black soil treated with 0.25 kg a.i./ha Fungal population was increased with respect to controls in sandy loam soil treated with 0.5 kg a.i./ha linseed oil seeds soaked in 50 ug/ml oxyfluorfen solution had fungal population similar to untreated controls. The fungal population was increased over controls in seeds soaked in 100 ul/ml oxyfluorfen	Ahmed and Vyas 1997
phosphate solubilizing microorganisms	field study; rice fields treated with post-emergence (10 days after transplanting seedlings) application of oxyfluorfen at 0.12 kg a.i./ha	oxyfluorfen increased the number of phosphate solubilizing microorganisms in the rhizosphere of the soil (sampling mean of 75.8 cfu x 10^4 per gram of soil) with respect to controls (61.2 cfu x 10^4 per gram of soil); increased the phosphate solubilizing capacities in the rhizosphere soil; and increased the available phosphate content in the rhizosphere soil.	Das et al. 2003

Appendix 6: Effects of oxyfluorfen and oxyfluorfen formulations on terrestrial invertebrates and soil microorganisms

Species	Exposure	Observations	Reference

Appendix 7: Toxicity of oxyfluorfen to terrestrial plants

Plant	Exposure	Response	Reference
Standard EPA-required studies; unpublished			
10 plant species: cabbage, carrot , corn, cucumber, lettuce, oats, onion, ryegrass, soybean, tomato	Goal Technical (71.5% a.i.) applied at 0, 0 (solvent control, acetone), 0.0060, 0.060, 0.6 lb, and 1.5 a.i./A.	Seedling germination study. Endpoint examined – % emergence No morphological abnormalities observed for any species. Most sensitive species: Tomato **NOAEC: 0.050 lb a.i/A** Most tolerant species: cabbage, corn, cucumber, lettuce, oats, ryegrass, and soybean **NOAEC: 1.5 lb a.i/A**	Hoberg 1990 MRID 41644001
10 plant species: cabbage, carrot , corn, cucumber, lettuce, oats, onion, ryegrass, soybean, tomato	Goal Technical (71.5% a.i.) applied at 0, 0 (solvent control, acetone), 0.00020, 0.0020, 0.020, 0.20 lb, and 2.0 a.i./A. Range varied according to species.	Seedling emergence study. Emergence observed 10 and 14 days post-application. Most sensitive species: cabbage, lettuce, onion, ryegrass **NOAEC: 0.0024 lb a.i/A** Most tolerant species: soybean **NOAEC: 0.31 lb a.i/A**	Hoberg 1990 MRID 41644001
10 plant species: cabbage, carrot , corn, cucumber, lettuce, oats, onion, ryegrass, soybean, tomato	Goal Technical (71.5% a.i.) applied at 0, 0 (solvent control, methanol), 0.00020, 0.0020, 0.020 and 2.0 lb a.i./A. Range varied according to species.	Vegetative vigor study. Plants examined 14 days after application. Most sensitive species: tomato **NOAEC: 0.00066 lb a.i/A** Most tolerant species: corn **NOAEC: 0.034 lb a.i/A**	Hoberg 1990 MRID 41644001

Appendix 7: Toxicity of oxyfluorfen to terrestrial plants

Plant	Exposure	Response	Reference
Lettuce transplants at 6-8 inches in height	Greenhouse study. Goal 1.6E Herbicide applied at rates of 0.5, 0.25, 0.125, 0.062, 0.031, 0.016 0.008, 0.004, and 0 lb a.i./A with addition of TRITON AG-98 low foam spray adjuvant (0.25% v/v/). Single spray application.	Vegetative vigor assessed 3days after spraying. on a scale with addition of TRITON AG-98 low foam spray adjuvant (0.25% v/v/). Dose-response increase in damaged observed. Results (application rate/score): 0/0 0.004/3.7 0.008/5.2 0.016/5.7 0.031/7.0 0.062/6.7 0.125/9.0 0.25/9.5 0.50/9.5	Holmdal 1984a MRID 00141610
Lettuce transplants at 4-8 inches in height	Field drift loss study. Aerial application of Goal 1.6E Herbicide at 0.5 lg a.i./A with addition of TRITON AG-98 low foam spray adjuvant (0.25% v/v/).	Examined relationship of spray drift to plant damage by placing plants at various distances from the aerial application site (35 to 800 m). Phytotoxicity assessed at 3 days after application. on a scale with addition of TRITON AG-98 low foam spray adjuvant (0.25% v/v/). Based on visual damage to plants, crop injury results from spray drift.	Holmdal 1984b MRID 00144894 (same information presented in MRID 92136058)
Relevant studies published in the open literature			
Gladiolus, 10 cultivars, 2 replicates each of treated and 4 replicates of non-treated rows	Field study: Pre-emergence treatment via hand-sprayer with oxyfluorfen (% a.i. not specified) at either 2 or 4 lb a.i./acre	"Oxyfluorfen caused leaf burn and greatly reduced the production of gladiolus corms and cormels." LOAEC: 2 lb a.i./acre on the basis of average corm yield in grams from 1000 cormels.	Bing 1979

Appendix 7: Toxicity of oxyfluorfen to terrestrial plants

Plant	Exposure	Response	Reference
broccoli, 4 cultivars	post-emergence greenhouse study: seedlings (4-5-leaf stage) sprayed with emulsifiable concentrate formulation of oxyfluorfen (no other specific details given) at rates of 0.1, 0.2, 0.4, 0.8 and 1.6 kg/ha. Spring 1993 and Fall 1993 post-transplant field studies: oxyfluorfen sprayed at concentrations of control 0.25, 0.5 and 1.0 kg/ha, with and without surfactant (0.25% v/v) in Spring 1993; oxyfluorfen at concentrations of control, 0.125, 0.25, 0.5 and 1.0 kg/ha, with surfactant in Fall 1993	No effect of surfactant. Regardless of the study, all cultivars exposed to oxyfluorfen at rates of 0.25 kg/ha or less recovered from injury sufficiently to have yields similar to controls. At higher application rates, cultivars varied in terms of sensitivity and yield. Cultivars which mature later (e.g. Pinnacle) recovered more readily from injury to yield broccoli heads similar to controls in terms of number and size. Early-maturing cultivars (e.g. Green Goliath) were more likely to have yield losses with respect to controls. Bottom line: Appropriate choice of cultivar is important if oxyfluorfen is to be used as a post-emergence treatment for weed control. NOAEC: 0. 25 kg/ha LOAEC: 0.5 kg/ha (injury leading to reduction in crop yield with respect to controls)	Farnham and Harrison 1995

Appendix 7: Toxicity of oxyfluorfen to terrestrial plants

Plant	Exposure	Response	Reference
broccoli, 10 cultivars	greenhouse experiment with potted seeds; pre-emergence application of oxyfluorfen via conveyor belt sprayer 2 weeks after planting at 0.13, 0.25, 0.5, 1.0, and 1.5 kg/ha (formulation and % a.i. not specified)	LOAEC: 0.13 kg/ha. All application rates injured broccoli (cotyledon crinkling and slight growth retardation at lower rates, to severe growth reduction and cotyledon necrosis and seedling death at highest rates.	Harrison and Farnham 1998
	field study: pre-emergence application of oxyfluorfen (formulation and % a.i. not specified); three different studies (Fall 1993, Spring 1994 and Fall 1994) with pre-emergence application	"Broccoli seedling weights and stand counts averaged across 10 cultivars and oxyfluorfen application rates of 0.125, 0.25 and 0.5 kg/ha were 70% and 81% of control respectively, for the two fall-planted experiments and 39 and 50% of control, respectively, for the spring-planted experiment	
Tomato, 6 cultivars	field studies; post-transplant spraying (via backpack sprayer, no adjuvant) with oxyfluorfen (formulation and % a.i. not specified) at rates of 0.28 and 0.56 kg a.i/ha.	LOAEC: 0.28 kg a.i./ha based on significantly less yields than hand-weeded controls	Masiunas 1989

Appendix 7: Toxicity of oxyfluorfen to terrestrial plants

Plant	Exposure	Response	Reference
18 species (9 families) of native Australian plants	greenhouse study with plants in containers; pre-emergence treatment with Goal 24EC at 1 kg a.i./ha	Early phytotoxicity observed in most species, especially in the Proteaceae and Gramineae families. Most species outgrew the treatment-related injuries incurred by day 85 after treatment.	Jusaitis et al. 1993
Roses, dormant potted plants with 1 cm shoots	pre-emergence application of oxyfluorfen (no details on formulation or % a.i.) to tops of roses at label application rate.	No effects	Karlik and Gonzalez 1997
soybeans	field study in India; pre-emergence application of oxyfluorfen (Goal 23.5 EC) at 0.2 and 0.3 kg/ha	LOAEC: 0.2 kg/ha, With respect to hand-weeded controls: reduction in nitrogenase activity 90 days after treatment; significantly lower uptake of nitrogen; significantly less dry matter accumulation; significantly reduced seed yield	Singh et al. 1995

Appendix 8: Toxicity of oxyfluorfen and its formulations to fish

Species	Exposure	Effects	Reference
Sheepshead minnow, juveniles, 10 per concentration, 2 replicates	96-hour static acute toxicity with Goal technical (71.4 % a.i.) at nominal concentrations of negative control, solvent control (acetone: 0.34 mg/L), 13, 22, 36, 60 and 100 mg a.i./L	96-hour LC_{50}: > 100 mg a.i./L NOAEC: 100 mg a.i./L No mortality or treatment-related toxicity at any concentration. EFED core study	Graves and Peters 1990 MRID 41698801
Fathead minnow, eggs and fry, 2 replicates each concentration, 40 fry/concentration after hatching	Early life stage flow-through test with Goal Technical (71% a.i.) at mean measured RH-2915 concentrations of 0, solvent control, 10, 20, 38, 74 and 160 ug/L (don't know whether this is a.i.), eggs exposed within 48 hours of fertilization until completion of hatching, then fry were exposed for 30 days post-hatch	NOAEC = 38 ug/L (0.038 mg/L) LOAEC = 74 ug/L (0.074 mg/L) on basis of reduced survival, total length and average weight of fry in comparison with controls. 160 ug/L fry were extremely lethargic and fry in 74 ug/L group were less vigorous than controls EFED core study	Godfrey and Longacre 1990f MRID 92136057(Phase III summary of MRID 00099270)
Bluegill	96-hour flow-through acute toxicity with oxyfluorfen technical (94% a.i.)	96-hour LC_{50} = 200 mg a.i./L NOAEC = 56 ug/L EFED core study	MRID 95585 as cited by U.S. EPA 2001b

Appendix 8: Toxicity of oxyfluorfen and its formulations to fish

Species	Exposure	Effects	Reference
Bluegill, juveniles, 10 per concentration, 2 replicates	96-hour static acute toxicity with Goal technical (71.4% a.i.) at mean measured test concentrations of negative control, solvent control (acetone), 0.029, 0.054, 0.093, 0.175, and 0.346 mg a.i./L NOTE: the two highest concentrations were greater than the water solubility of the test substance and were 47 - 73% of the nominal concentrations	96-hour LC_{50} = 0.21 mg a.i./L NOAEC = 0.093 mg a.i./L LOAEC = 0.175 mg a.i./L At 0.175 mg/L, 5/20 fish died in 48 hours. At 0.346 mg/L, 14/20 fish were moribund or died within 24 hours. All were dead by 72 hours. EFED core study	Graves and Smith 1991a MRID 42129801
Rainbow trout	96-hour flow-through acute toxicity test with oxyfluorfen technical (94% a.i.)	96-hour LC_{50} = 410 mg a.i./L NOAEC = 180 ug/L EFED core study	MRID 95585 as cited by U.S. EPA 2001b
Rainbow trout, juveniles, 10 per concentration, 2 replicates	96-hour static acute toxicity with Goal technical (71.4% a.i.) at mean measured concentrations of negative control, solvent control (acetone) , 0.037, 0.083, 0.175, 0.398 and 1.09 mg a.i./L	96-hour LC_{50} = 0.25 mg a.i./L NOAEC = 0.037 mg a.i./L LOAEC = 0.083 mg a.i./L 24% and 20% of the fish in the 0.083 and 0.175 mg/L groups died within 96 hours. 70% of the fish at 0.398 mg/L were dead within 96 hours. 15% of the fish in the 1.09 mg/L group died within 24 hours and 19/20 were dead by 96 hours. EFED core study	Graves and Smith 1991b MRID 42129802

Appendix 8: Toxicity of oxyfluorfen and its formulations to fish

Species	Exposure	Effects	Reference
Channel catfish	96-hour static acute toxicity test with oxyfluorfen technical (74% a.i.)	96-hour LC_{50} = 400 mg a.i./L NOAEC = 180 ug/L EFED core study	MRID 96881 as cited by U.S. EPA 2001b
Oreochromis niloticus and *Gambusia affinis* (freshwater fish found in Egypt)	study of brain acetylcholinesterase inhibition: exposure to Goal (23.6 mg oxyfluorfen/L) at previously measured LC50 concentrations of 3 mg a.i./L (O niloticus) and 4.3 mg a.i./L (G affinis) for 6 days; 0.33 LC_{50} values for 15 days; and 0.1 LC_{50} values for 30 days.	Statistically significant reductions in brain acetylcholinesterase activity (AChE) with respect to pre-test control values in both species and all doses (all in mg a.i./L) and durations of exposure: ***Oreochromis niloticus*** 6-day LOAEC: 3 mg/L 15-day LOAEC: 1 mg/L **30-day LOAEC: 0.3 mg/L** ***Gambusia affinis*** 6-day LOAEC: 4.3 mg/L 15-day LOAEC: 1.43 mg/L 30-day LOAEC: 0.43 mg/L	Hassanein 2002
Oreochromis niloticus (freshwater Egyptian fish)	measure of the bio-marker hsp70 (heat shock protein 70: a protein produced in response to environmental and chemical stressors) in the liver and kidney as a measure of exposure: exposure to Goal at concentrations of 3.0, 1.5 and 0.75 mg a.i./L for 6, 15 and 24 days, respectively.	Induction of heat shock proteins in both kidney and liver; Statistically increased percentage of heat shock protein with respect to controls was observed as follows: **3 mg a.i./L**: at 2,4 and 6 days exposure **1.5 mg a.i./L**: at 5, 10 and 15 days exposure **0.75 mg a.i./L** at 8, 16 and 24 days exposure **LOAEC: 0.75 mg a.i./L**	Hassanein et al. 1999

Appendix 9: Toxicity of oxyfluorfen and its formulations to aquatic invertebrates

Species	Exposure	Effects[a]	Reference
		Freshwater species	
Daphnia magna	48-hour flow through test. Goal 2XL(P) at measured concentrations of 0, 0.085, 0.25, 0.66, 1.4 and 3.3 mg Goal2XL(P)/L	48-hour immobilization EC_{50}: 0.33 mg formula/L 48-hour NOAEC: 0.085 mg formula/L (0.020 mg a.i./L)	Sutherland et al 2000a MRID 45271301
Daphnia magna	48-hour static test. Oxyfluorfen technical (82.2% a.i.)	48-hour EC_{50}: 1500 ug a.i./L NOAEC: 100 ug a.i. /L EFED core study	MRID 96881 as cited by U.S. EPA 2001b
Daphnia magna	21-day life cycle study. Exposure to Goal Technical (71.8% a.i.) At measured concentrations (as RH-2915) of control, solvent control, 1.8, 4.3, 7.4, 13 and 28 ug/L based on results of 2 range-finding studies	NOAEC: 13 ug a.i./L LOAEC: 28 ug a.i./L on basis of adult mean length, survival of young, and young/adult/reproduction day The study is classified as "supplemental" by EFED.	Godfrey and Longacre 1990g MRID 92136094 (Phase III summary of MRID 92136106) NOTE: this appears to be the same study reported below by Forbis 1986

Appendix 9: Toxicity of oxyfluorfen and its formulations to aquatic invertebrates

Species	Exposure	Effects[a]	Reference
Daphnia magna	21-day life cycle study under flow-through conditions. Exposure to RH-2915 at concentrations (measured) of 0, 1.8, 4.3, 7.4, 13, and 28 µg/L [does not indicate if this is formulation or a.i.].	adult length NOAEC: 13 µg /L LOAEC: 28 µg/L adult survival NOAEC: 28 µg/L LOAEC: >28 µg/L #young/adult/reproductive day NOAEC: 13 µg/L LOAEC: 28 µg/L	Forbis 1986 MRID 42142305
freshwater clam (**Elliptio complanata**)	96-hour exposure to Goal Technical Herbicide (74% a.i.) at concentrations of 0, 0 (solvent control, acetone), 3.2, 5.6, 10.0, 18.0, and 32.0 µg formulation/L.	Endpoint assessed: percent mortality Dose-related increased in mortality (70% at highest dose). 24-hour EC_{50} = >32.0 µg formulation/L 48-hour EC_{50} = >32.0 µg formulation/L **96-hour EC_{50} = 9.57 µg formulation/L** **96-hour LOAEC = 3.2 µg formulation/L** Note: EFED does not convert values to on basis of % formulation for other studies it cites based on 71-74% technical grade herbicide, therefore for purposes of comparison, these values are considered ug a.i./L	Godfrey and Longacre 1990b MRID 92136009 (this is a summary of MRID 00134452)

Appendix 9: Toxicity of oxyfluorfen and its formulations to aquatic invertebrates

Species	Exposure	Effects[a]	Reference
Mayfly	48-hour static mayfly toxicity study with Goal 1.6E at concentrations of 0, 0 (solvent blank, (formulation without a.i.) 0.01, 0.022, 0.046, 0.10, 0.22, 0.46 and 1.0 mg/L [does not indicate if this is formulation or a.i.].	For lethality: Dose-response lethality at concentrations of 0.22mg/L and greater. 15% mortality observed in solvent control () group. **48-hour LC_{50} = 0.42 mg /L** (95% CL, 0.24 - 1.0 mg/L) For sub-lethal effects: loss of equilibrium and quiescence observed at concentrations of 0.22mg/L and greater 48-hour EC_{50} = 0.19 mg /L (95% CL, 0.1 - 0.46 mg/L) NOTE: authors state that due to solvent toxicity, LD50 and EC50 values reported here may not accurately reflect the toxicity of GOAL. The solvent control is the formulation without the a.i. NOTE: there appear to be problems with this study. It is not clear if it is properly controlled. Fiche is very difficult to read	Swigert 1986 MRID 42048003
		Estuarine/marine Species	
Eastern oyster	48-hour static test, oxyfluorfen technical (74.0% a.i.)	48-hour LC50 > 32 ug a.i./L NOAEC = 3.2 ug a.i./L EFED supplemental study	MRID 96881 as cited by U.S. EPA 2001b
Eastern oyster	96-hour flow through test of shell deposition, oxyfluorfen technical (71.4% a.i.)	96-hour EC50 = 69.3 ug a.i./L NOAEC = 37.5 ug a.i./L EFED core study	MRID 423789-01 as cited by U.S. EPA 2001b

Appendix 9: Toxicity of oxyfluorfen and its formulations to aquatic invertebrates

Species	Exposure	Effects[a]	Reference
Eastern oyster embryo larvae (*Crassostrea virginica*)	48-hour exposure to Goal Technical Herbicide (74% a.i.) at concentrations of 0, 0 (solvent control, acetone), 3.2, 5.6, 10.0, 18.0, and 32.0 µg formulation/L.	Endpoint assessed: percent abnormal development Dose-related increase in abnormal development (23.0% at highest concentration). **48-hour EC_{50} = 95.0 µg formulation/L** (95% CL: 20.6 - 437.7) **NOAEC <3.2 µg formulation/L**	Godfrey and Longacre 1990a MRID 92136008 (this is a summary of MRID 00134453)
Grass shrimp	96-hour static test. Oxyfluorfen technical (74.0% a.i.)	96-hour LC50 = 32 ug a.i./L NOAEC = 18 ug a.i./L EFED supplemental study	MRID 309701-17 as cited by U.S. EPA 2001b
Fiddler crab	96-hour static test. Oxyfluorfen technical (74.0% a.i.)	96-hour LC50 > 1000 mg a.i./L NOAEC = 320 mg a.i./L EFED supplemental study	MRID 96811 as cited by U.S. EPA 2001b
sea urchin (Lytechinus variegatus), fertilized eggs	effect on egg development following exposure to Goal (240 g a.i./L) at a concentration of 2.7 x 10^{-4} M within 3 minutes of egg fertilization.	Microscopic study revealed that oxyfluorfen delays early egg development by interfering with development of the mitotic apparatus and subsequent formation of the equatorial plate and asters.	Medina et al. 1994

Appendix 10: Toxicity of oxyfluorfen to aquatic algae and macrophytes

Species	Exposure	Effects [a]	Reference
AQUATIC ALGAE and DIATOMS			
Selenastrum capricornutum	120-hour exposure to Goal Technical (71.5% a.i.) at concentrations (measured) of 0.32, 0.39, 0.78, 1.7, and 3.6 µg a.i./L	Endpoint assessed: reduction in cell density All units = µg a.i./L EC_{50}: 0.35 95% CL: 0.33-0.37 NOAEC: 0.32	Giddings 1990 MRID 41618401
Selenastrum capricornutum	96-hour exposure to Goal 2XL(P) at measured concentrations of 0, 0.076, 0.15, 0.25, 0.43 and 1.9 ug formulation/L	EC_{50} for cell density and area under the growth curve = 1.2 ug Goal 2XL(P)/L NOAEC for cell density, growth rate and area under the growth curve = 0.43 ug Goal2XL(P)/L	Sutherland et al 2000b MRID 45271302
Anabaena flos-aquae	120-hour exposure to Goal Technical (71.5% a.i.) at concentrations (measured) of 0.17, 0.25, 0.44, 1.2, and 2.0 mg a.i./L (170, 250, 440, 1200, and 2000 µg a.i./L)	Endpoint assessed: reduction in cell density All units = µg a.i./L EC_{50}: >2000 95% CL: – NOAEC: 2000	Giddings 1990 MRID 41618401
Navicula pelliculosa	120-hour exposure to Goal Technical (71.5% a.i.) at (measured) concentrations of 0.10, 0.18, 0.40, 0.62, and 1.4 µg a.i./L	Endpoint assessed: reduction in cell density All units = µg a.i./L EC_{50}: 0.24 95% CL: 0.066-0.82 NOAEC: 0.10	Giddings 1990 MRID 41618401

Appendix 10: Toxicity of oxyfluorfen to aquatic algae and macrophytes

Species	Exposure	Effects [a]	Reference
Skeletonema costatum	120-hour exposure to Goal Technical (71.5% a.i.) at concentrations (nominal) of 0.30, 0.60, 1.3, 2.5, and 5.0 µg a.i./L	Endpoint assessed: reduction in cell density All units = µg a.i./L EC_{50}: 9.3 95% CL: 1.1-5.8 NOAEC: 2.5	Giddings 1990 MRID 41618401
Pseudokirchneriella subcaptica (formerly *Selenastrum capricornutum*)	Goal Technical Purified Herbicide (99.19% a.i.). Nominal concentrations tested 0.30, 1.5, 3.0 µg a.i./L in the sediment/humic acid system (measured concentrations 0.26, 1.4, and 2.9 µga.i./L)	10-day toxicity test with freshwater green algae, **with artificial sediment and humic acid added to the test system**. **for inhibition of biomass**: **10-day NOAEC = 2.9 µg a.i./L** (the highest dose tested) **10-day EC_{50} >2.9 µg a.i./L** **For growth rate**: **10-day NOAEC = 2.9 µg a.i./L** (the highest dose tested) **10-day EC_{50} >2.9 µg a.i./L**	Hoberg 1999 MRID 45581601

Appendix 10: Toxicity of oxyfluorfen to aquatic algae and macrophytes

Species	Exposure	Effects [a]	Reference
Seven species of algae tested: 6 green algae, 1 blue-green alga *(Synechoccus leopoliensis)*	72-96-hour biomass and growth assay of Goal 2E (240 g/L a.i.)	**Species: EC_{50} (ug formulation/L)** *Scenedesmus subspicatus*: 0.676 *Scenedesmus quadricauda*: 2.19 *Raphidocelis subcapitata*: 26.3 *Chlamydomonas reinhardii*: 274.3 *Stichococcus bacillaris*: 11159.2 *Chorella kesleri*: 38368.5 *Synechoccus leopoliensis*: 49676.1	Rojickova-Padrtova and Marsalek 1999.

Appendix 10: Toxicity of oxyfluorfen to aquatic algae and macrophytes

Species	Exposure	Effects [a]	Reference
Green algae, *Scenedesmus obliquus*	48-hour exposure to oxyfluorfen at 0, 7.5, 15 or 22.5 ug/l	Thirteen measures of growth rate, chlorophyll content and indicators of photosynthetic and antioxidant enzyme activities were measured. **LOAEC: 7.5 ug/L** Statistical difference from controls in growth rate (↓); chlorophyll synthesis (↓); catalase activity (↑); glutathione reductase activity (↑); glutathione-S-transferase activity (↑); and several measures of photosynthetic activity, with the most sensitive variables indicating adverse impacts on photosystem II. Variables with statistical significance at the low dose showed dose-related changes (increases or decreases, as appropriate).	Geoffroy et al. 2003

Appendix 10: Toxicity of oxyfluorfen to aquatic algae and macrophytes

Species	Exposure	Effects [a]	Reference
Green algae, *Scenedesmus acutus*	10uM oxyfluorfen for 6 hours in the light; controls	oxyfluorfen damages proteins which are integral components of photosynthetic electron transport (cytochromes and chlorophyll). This study analyzes spectrophotometric changes and protein components. Results show damage to various forms of cytochromes c, f, and chlorophyll, specifically, with loss of the amino acids of water soluble proteins as follows: methionine (60%), histidine (30%), arginine (25%), tyrosine (20%) and glutamic acid (4%)with respect to untreated controls.	Kunert et al 1985; Kunert and Boeger 1984
AQUATIC MACROPHYTES			
duckweed *(Lemna gibba*)	7-day exposure to Goal Technical (71.5% a.i.) at concentrations of 0.72, 1.2, 2.2, 4.3, and 6.2 µg a.i./L	Endpoint assessed: reduction in frond growth All units = µg a.i./L EC_{50}: 1.4 95% CL: 0.87-2.4 Reported NOAEC: <0.55 (note: reported value lower than lowest concentration tested) LOAEC: 0.55	Giddings 1990 MRID 41618401

Appendix 11: Laboratory and field simulation studies on the environmental fate of oxyfluorfen

Data Summary	Reference
Aquatic Sediment Halftimes	
Shake flask assay: biotic halftime of 412 days and abiotic halftime of 2200 days.	Walker et al. 1988
Dislodgeable Residues	
Investigation of dislodgeable residue dissipation from pine foliage under nursery conditions. Goal herbicide applied at 0.15 kg a.i./ha [approximately 1.5 µg/cm^2] to loblolly pine and ponderosa pine. 24-hours after application, oxyfluorfen residues dissipated to <20% of initial foliar deposits. Maximum amount of oxyfluorfen dislodgeable residues: 0.04 to 0.11 µg/cm^2. Based on the application rate of 1.5 µg/cm^2, the fraction residue is 0.027 to 0.07. **Foliar half-life = 9.91 hr (range 7.5 to 12.5 hr)**	Massey 1990 MRID 42098301
Hydrolysis	
In buffered aqueous solution, no hydrolysis of oxyfluorfen (^{14}C-RH-2915) occurred during exposure to ambient light at pH 4, 7, and 10 both 25◦C and 45◦C during a 30-day incubation period. Oxyfluorfen appears resistant to hydrolysis.	Reibach 1990a MRID 92136023
Hydrolysis study of two concentrations (0.05 and 0.5 ppm) of ^{14}C-RH-2915 at pH 4, 7, and 10 in darkness at ambient 25 and 45◦C. Samples tested at 0, 3, 21,and 30 days. Oxyfluorfen appears resistant to hydrolysis.	Garstka 1990 MRID 92136063
Halftime in non-sterile water of 660 days. Halftime in sterile water of 1315 days.	Walker et al. 1988
Reference aerobic aquatic degradation rate used by EFED: 1741 days based on one-half of the aerobic soil degradation rate	U.S. EPA/OPP 2001b
Reference anaerobic aquatic degradation rate used by EFED: 1308 days based on one-half of the aerobic soil degradation rate	U.S. EPA/OPP 2001b
Octanol/Water Partition Coefficient	

Appendix 11: Laboratory and field simulation studies on the environmental fate of oxyfluorfen

Data Summary	Reference
125,900 (log Ko/w = 5.2) This is based on QSAR and is consistent with the output of EPI-Suite.	Brudenell et al. 1995
29,512 (Log Ko/w 4.47)	Tomlin 2004; USDA/ARS 1995

Photolysis, Aqueous

At pH 7, 14C-oxyfluorfen undergoes rapid photolysis results in several degradates. Degradates were not identified. Degradation scheme depicted in Figure 3, p. 32.	Reibach 1991b MRID 42129101
Half-life: 2.34 to 3.00 days (varied according to where parent compound was labeled)	
Aqueous photolysis study of oxyfluorfen labeled in 2 positions – chlorophenyl ring and nitrophenyl ring. For chlorophenyl ring: At pH 7, samples were irradiated for 20 days in natural sunlight or placed in dark. Half-life in dark = 70.9 days. Half-life in sunlight = 3.7 days. Photodegradation produced multiple polar prducts (all <10% of total radioactivity). For nitrophenyl ring: At pH 7, samples were irradiated for 20 days in natural sunlight or placed in dark. Half-life in dark = 81.9 days. Half-life in sunlight = 5.4 days. Photodegradation produced multiple polar products (all <10% of total radioactivity).	Reibach 1990e MRID 92136064
Reference value used by EFED based on Reibach 1991b: 7.5 days	U.S. EPA/OPP 2001b
5 hr	Ying and Williams 1999

Photolysis, Soil

Appendix 11: Laboratory and field simulation studies on the environmental fate of oxyfluorfen

Data Summary	Reference
Investigated fate of ^{14}C-oxyfluorfen on moist soil (sandy loam) surface following irradiation by natural sunlight. Samples evaluated at 0, 8, 15, and 30 days.	Reibach 1991 MRID 41999901
Half-life = 28 days Due to low levels of individual degradates, degradation products were not identified. Most degradates were polar in nature. Two volatile degradates were formed. A proposed degradation scheme is depicted in Figure 22 of this report.	
5.19 days	Ying and Williams 1999

Soil Degradation/Dissipation

Metabolism of ^{14}C-RH-2915 (Goal) in aerated and non-aerated clay loam soil. 14C in soil measured 1, 3, 6, and 12 weeks for aerated soil and 3 and 12 weeks for non-aerated soil. RH-2915 "applied" to achieve 1 lb a.i./acre. Soil characteristics: CEC 9.9 meq/100 g; OM 1.5%; pH 5.25; sand 0.8%; silt 69.4%; clay 29.8%	Peirson and Fisher 1978 MRID 00149203
RH-2915 rapidly became associated with the soil fraction and was not appreciably degraded in soil. A slight increase in degradation products and polar material was observed over time. RH-2915 shows a slow, but measurable decline over 12 weeks in both aerated and non-aerated soil. Aeration had no apparent effect on soil metabolism.	

Appendix 11: Laboratory and field simulation studies on the environmental fate of oxyfluorfen

Data Summary	Reference
Aerobic soil metabolism of oxyfluorfen in sandy loam and clay loam soils for 1 year (25◦C, in the dark). No significant levels of metabolites were detected. Trace amounts of ^{14}C-CO_2 detected. On clay soil, half-life = 291 to 294 days (varied with location of ^{14}C-label) On sandy soil, half-life = 556 to 596 days (varied with location of ^{14}C-label)	Korsch and Doran 1988a MRID 42142309 (same information reported in MRID 92136098)
Anaerobic metabolism of Oxyfluorfen in sandy loam soil evaluated for 60 days after being under aerobic conditions for 30 days. No significant levels of metabolites were detected. Bound ^{14}C increased fro 7 to 12 5 during anaerobic period. Trace amounts of ^{14}C-CO_2 detected. anaerobic Half-life = 554 to 603 days (varied with location of ^{14}C-label)	Korsch and Doran 1988b MRID 42142310 (same information presented in MRID 92136098)
Filed study to determine the persistence and mobility of Goal Herbicide 2E. Test material applied at 2.0 lb a.i./A to bare soil at 2 sites in CA. Soil cores examined for up to 18 months post-application. Soil types – loamy sand (coast site) and clay loam (valley site) half-life clay loam– 32.8 to 52.7 days half-life loamy sand: 34.0 to 58.1 days Residues found only in the top six inches of soil, no significant downward movement observed.	Reibach 1995 MRID 43840101

Appendix 11: Laboratory and field simulation studies on the environmental fate of oxyfluorfen

Data Summary	Reference
Field study to determine half-life of oxyfluorfen. Goal Herbicide 1.6E applied at 2.0 lb a.i./A to bare soil at 2 sites in CA – a valley site (loamy sand) and a coastal site (loam soil). Soils sampled 8 times during the first month and then at months 1, 2, 3, 4, 5, 6, 9, 12, 15, and 18 after application at depths up to 48 inches. Soil composition (top 0-12 inches): Valley site: sand 736, silt 13%, clay 9%, OM 0.5%, pH 7.1, CEC 2.8 mEg/100g Coastal site: sand 78%, silt 40%, clay 24%, OM 1.5%, pH 6.9, CEC 14.5 mEg/100g Residue levels immediately after application (top 0-3 inches of soil): Valley site: 0.680 ppm Coastal site: 1.555 ppm No residues were found below 12 inches at any site for any sampling time. Oxyfluorfen was not mobile. However, residues were only sporadically detected at the 6-12 inch depth. Half-life: Coast site: Half-life in top 0-3 inches of soil = 262 days; Half-life in top 0-12 inches of soil = 254 days. Valley site: Half-life in top 0-3 inches of soil = 117 days; Half-life in top 0-12 inches of soil = 118 days.	Riebach 1990i MRID 92136122
Reference aerobic soil halftime used by EFED: 870.5 days (upper 90th percentile)	Reibach 1990f cited in U.S. EPA/OPP 2001b
Reference anaerobic soil halftime used by EFED: 653.9 days (upper 90th percentile)	Reibach 1990e cited in U.S. EPA/OPP 2001b
Half-life = 35 d	Ahrens 1994, as cited in Futch and Singh 1999 Beach et al. 1995

Appendix 11: Laboratory and field simulation studies on the environmental fate of oxyfluorfen

Data Summary	Reference
Half-life = 86 d: 0-15 cm; single treatment of 120 kg/ha 103 d: 0-15 cm; single treatment of 240 kg/ha 30 d: 0 - 5 cm; single treatment of 60 kg/ha 33 d: 0 - 5 cm; single treatment of 120 kg/ha 78 d: 0-15 cm; four treatments of 60 kg/ha 69 d: 0-15 cm; four treatments of 120 kg/ha 70 d: 0-15 cm; single treatment of 720 g[sic]/ha	Frank et al. 1991
Under different temperatures and moisture regimes, Half-life range = 101-242 d; clay loam = 59-142 d; silty clay = 106-169d; silty clay = 38-128 d; sandy clay loam = 43-81 d; loam = 15-171 d; silty clay	Yen et al. 2003
Very little movement in sandy clay loam soil columns. Retained in top 5-cm of soil.	Milanova and Grigorov 1996

Appendix 11: Laboratory and field simulation studies on the environmental fate of oxyfluorfen

Data Summary	Reference

Soil Binding (Kd, Ko/c)

Adsorption of oxyfluorfen evaluated at 4 concentrations (0.024, 0.059, 0.087, 0.117) in 4 soil types (sandy loam, clay loam, silty clay loam, and sand). Soil characteristics: sandy loam: 56.6% sand, 33.2% silt, 10% clay; %OM 1.3; CEC 6.1; pH 6.5; %OC 0.765 clay loam: 26.0% sand, 46.0% silt, 28.0% clay; %OM 3.0; CEC 16.9; pH 6.9; %OC 1.765 sand: 93.2% sand, 0.8% silt, 6.0% clay; %OM 0.5; CEC 2.1; pH 7.3; %OC 0.294 silty clay loam: 8.8% sand, 62.0% silt, 29.2% clay; %OM 1.2; CEC 6.6; pH 7.0; %OC 0.706 Kd values: sandy loam 88.12 clay loam 125.37 sand 9.44 silty clay loam 30.28 Koc (adsorption) values: sandy loam 8076 clay loam 5886 sand 2991 silty clay loam 32381	Reibach 1988 MRID 42142311
$K_{o/c}$ = 100,000	Ahrens 1994, as cited in Futch and Singh 1999

Appendix 11: Laboratory and field simulation studies on the environmental fate of oxyfluorfen

Data Summary	Reference
K_d at 25°C = 613; clay loam = 463; silty clay = 421; silty clay = 151; sandy clay loam = 52; loam = 755; silty clay	Yen et al. 2003
K_d at 37°C = 763; clay loam = 668; silty clay = 484; silty clay = 172; sandy clay loam = 111; loam = 829; silty clay	
Reference value for Koc used by EFED based on Reibach 1990j: 5585 (lowest non sand value) and 6831 (median value).	U.S. EPA/OPP 2001b

Appendix 11: Laboratory and field simulation studies on the environmental fate of oxyfluorfen

Data Summary	Reference
Translocation	
Study objective: To determine if Goal Herbicide applied to soil surrounding bearing apple trees is absorbed by the roots and translocated to twig, leag and fruit. Plant material examined from 7 to 126 days after application. Application: ^{14}C-NPR Goal Herbicide at 2, 4, and 8 lb a.i./A and ^{14}C-CF_3 Goal Herbicide at 2 lb a.i./A. Results: No 14C detected in any twig, leaf or fruit. Conclusions: Goal Herbicide is not absorbed through the root system and translocated into aerial portions of the tree.	Zogotski and Lafferty 1986 MRID 00160143 (data also reported in MRID 921306027
Bioconcentration in Fish	

Appendix 11: Laboratory and field simulation studies on the environmental fate of oxyfluorfen

Data Summary	Reference
Bluegill sunfish exposed to ^{14}C-oxyfluorfen, labeled in either the CF_3 position or the nitrophenyl (NPR) position, at a nominal concentration 10 µg/L for 40 days, followed by 14 days of depuration. Bioconcentration for CF_3-labeled position: muscle: Concentration of ^{14}C increased up to exposure day 14, when an apparent equilibrium was reached. **BCF Mean equilibrium= 605, 1 day=0.24**. whole fish: Concentration of ^{14}C continued to increase over the 40day exposure period. **Maximum BCF at 40 days = 2200, 1 day=0.5.** viscera: Concentration of ^{14}C increased up to exposure day 10, when an apparent equilibrium was reached. **BCF Mean equilibrium = 3265, 1 day = 1.8**. Bioconcentration for NPR-labeled position: muscle: Concentration of ^{14}C increased up to exposure day 14, when an apparent equilibrium was reached. **Mean equilibrium BCF = 450, 1 day = 0.14**. whole fish: Concentration of ^{14}C increased up to exposure day 14, when an apparent equilibrium was reached. **Mean equilibrium BCF = 450, 1 day = 0.42**. viscera: Concentration of ^{14}C increased up to exposure day 10, when an apparent equilibrium was reached. **Mean equilibrium BCF = 4360, 1 day = 1.7**. Elimination: For oxyfluorfen labeled in the CF_3 positions, >80% ^{14}C was eliminated from muscle, whole fish and viscera at the end of the 14-day depuration period. For oxyfluorfen labeled in the NPR position, >90% ^{14}C was eliminated from muscle, whole fish and viscera.	Reibach 1990b MRID 92136026 (same information reported in MRID 42098303 and MRID 92136064)

Appendix 12: Field or field simulation studies on the environmental fate of oxyfluorfen.

Application	Observations	Reference
Monthly broadcast application (for 1 year) of granular Rout and OH-2 to bed areas in a container production nursery in the Piedmont region of South Carolina. Amount applied not given. Open beds on sloped terrains, with containment ponds receiving runoff. Water and sediment samples monthly for 1 year.	Oxyfluorfen never detected at levels greater than 0.009 µg/ml in pond water. Highest sediment concentrations were in Dec. 1991 (2.75 µg/g) and April 1992 (>3.0 µg/g). Authors report that levels detected were low compared to amount applied. A "rigorous digestion" of the sediments to release bound residues was not conducted.	Camper et al. 1994
General survey of farm ponds in Ontario, Canada	No oxyfluorfen detected.	Frank et al. 1990

Appendix 12: Field or field simulation studies on the environmental fate of oxyfluorfen.

Application	Observations	Reference
Treatment 1: Oxyfluorfen formulated as Goal (192 g a.i./L) was applied at 120 and 240 g a.i./ha (0.1 and 0.2 lb/acre) to plots of six-leaf stage onions growing in organic soil at the research station on Holland Marsh near Toronto, Canada. Application was with a boom-type sprayer on July 12, 1985.	Onion and soil (0-15cm) samples were taken on 0, 10 and 70(normal harvest time) days after treatment. At Day 0, oxyfluorfen residue on onions was 0.63 mg/kg and 1.10 mg/kg for the 120 and 240 g/ha application rates, respectively. At Days 10 and 70, residues were <0.05 mg/kg (the limit of detection) for both application rates. Half-life of residues in soil was 86 days and 103 days for the 120 and 240 g/ha application rates, respectively.	Frank et al. 1991
Treatment 2: Oxyfluorfen formulated as Goal (192 g a.i./L) was applied at 60 and 120 g a.i./ha to plots of six-leaf stage onions growing in organic soil at the research station on Holland Marsh near Toronto, Canada. Application was with a boom-type sprayer on July 12, 1986.	Onion and soil (0-5cm) samples were taken on 0, 11, 40, and 70 days after treatment. At Day 0, oxyfluorfen residue on onions was 0.33 mg/kg and 0.38 mg/kg for the 60 and 120 g/ha application rates, respectively. At Days 11, 40, and 70, residues were <0.05 mg/kg (the limit of detection) for both application rates. Half-life of residues in soil was 30 days and 33 days for the 60 and 120 g/ha application rates, respectively.	
Treatment 3: Oxyfluorfen formulated as Goal was applied at 120 g a.i./ha to plots of 1st-4th leaf stage onions growing on four separate farms on Holland Marsh near Toronto, Canada. Application was with a boom-type sprayer on May 29 or June 9, 1987.	Onion samples were taken on 0, 1,2,4,6,8, and 10 days after treatment. At Day 0, residue of oxyfluorfen on onions was 1.22 mg/kg, and decreased to <0.05 mg/kg (the detection limit) by Day 6. A half life disappearance was calculated to be 1.6 days, with a first order regression equation. According to the authors, residue decline did not appear to be correlated to rainfall.	
Treatment 4: Oxyfluorfen formulated as Goal was applied at 60 and 120 g a.i./ha to plots of 2nd and 4th-5th leaf stage onions growing in organic soil	Onion samples were taken following the fourth application and then on 0,	

Appendix 12: Field or field simulation studies on the environmental fate of oxyfluorfen.

Application	Observations	Reference
Treatment 5: Oxyfluorfen formulated as Goal was applied at 240 g a.i./ha to plots of 3-4 true leaf stage onions growing in organic soil at a research station on Holland Marsh near Toronto, Canada. Application was with a boom-type sprayer on June 21, 1988.	Onion samples were taken on Days 0-6 after treatment. At Day 0, residue of oxyfluorfen on onions was 0.19 mg/kg, and decreased to <0.01 mg/kg (below the detection limit) by Day 6. A half life disappearance was calculated to be 1.7 days, with a first order regression equation. Accumulated rainfall changed from 0 mm to 11 mm at Day 1, and then remained unchanged.	*Frank et al. 1991, cont.*
Treatment 6: Oxyfluorfen was applied at 720 g [*sic*]a.i./ha to organic soil at a research station on Holland Marsh near Toronto, Canada. Application was with a boom-type sprayer on June 21, 1988.	Soil samples collected prior to treatment showed residues <0.05 mg/kg (below detection limit). Soil samples were collected at three depths: 0-5, 5-10, and 10-15 cm. Authors give the theoretical concentration in the upper 15 cm as 0.30, or 1.20 mg/kg in the upper 5 cm from a 120 g/ha application. Initial concentrations indicated little or no loss during application. Half-life of residues in soil was 70 days. Regression analysis showed a best fit for disappearance of oxyfluorfen was a Log y = a + bx equation.	

Appendix 12: Field or field simulation studies on the environmental fate of oxyfluorfen.

Application	Observations	Reference
Oxyfluorfen (Goal 1.6E®) was applied at 4.03 kg/ha to Candler sand soil from Central Florida. The soil had been uniformly packed into leaching columns to simulate the soil profile as collected in the field, then saturated with water and allowed to drain prior to application. Oxyfluorfen was applied with a small dropper to the soil surface, then allowed to equilibrate for several hours. 3.2, 6.4, 9.6, or 12.8 cm of water was allowed to drip onto the column, and columns were again allowed to drain. The columns were then split in half, and seeds of bioindicator plants (winter rye grass, *Lolium perenne*) were planted along their lengths.	Visual ratings as to the depth in cm of toxic levels of herbicide movement were made 28 d after planting as indicated by plant death or lack of seed germination. Interaction between oxyfluorfen leaching depth and water application rate was significant at the 5% level; leaching of oxyfluorfen increased as the amount of water applied increased. Oxyfluorfen moved from 5.41 cm to 8.89 cm; the authors rated it as an herbicide with low mobility. Chemical characteristics of oxyfluorfen cited from other studies were given.	Futch and Singh 1999
General survey of Arno River in Italy.	Detected in one of four years in survey. In that year, detected in 4% of samples with a maximum concentration of 0.00011 mg/L.	Griffini et al. 1997
Oxyfluorfen (Goal 1.6E®) was applied to rooted cuttings of Euonymus grown in pots of peat/sand. Oxyfluorfen was applied into the potting media (2, 7, or 14 cm deep) when cuttings were planted (at 10, 100, or 1000 ppm as Goal 1.6E®, or 1.92, 19.2, or 192.0 mg/kg Goal), or as surface spray (1.6, 16.0, or 160.0 L/ha as Goal 1.6E®, or 0.31, 3.1, or 31.0 kg/ha Goal) immediately after planting.	Presence of oxyfluorfen in effluent was determined 1 and 8 wks after application by bentgrass bioassay. At 1 week, no herbicide was detected in effluents from surface spray up to 3 kg/ha or from rates up to 19 mg/kg incorporated in the upper 2 or 7 cm layer. At 8 wks, no herbicide was detected in effluent except at the 192 mg/kg rate.	Horowitz et al. 1989

Appendix 12: Field or field simulation studies on the environmental fate of oxyfluorfen.

Application	Observations	Reference
Oxyfluorfen was applied at 20 ppm and 200 ppm to a 2- to 3- cm surface layer in columns packed with a potting media (HF mix , 3:1redwood bark and sand) and UCD mix (1:1 peat and sand); and columns of agricultural soils, Stockton clay and Yolo fine sandy loam.	Movement of oxyfluorfen was determined by bioassays with bentgrass. Depth of leaching was 1 cm in UCD mix, 3 cm with Stockton clay, 5 cm with Yolo fine sandy loam, and 6 cm with HF mix. The authors report depth of leaching was not related to soil organic matter content. Raising dose from 20 to 200 ppm increased the depth of leaching.	Horowitz and Elmore 1991
Granular formulation Rout (a mix of oryzalin and oxyfluorfen), equivalent to oxyfluorfen at 2.2 kg a.i./ha (2 lb/ac), was applied to beds of container plants in a nursery in Chesnee, SC. The beds were sloped 5%, and drained into a single storm drain.	Runoff collected at the storm drain showed oxyfluorfen residues consistently below 1 mg/L water. Cumulative oxyfluorfen loss was calculated by multiplying volume of water runoff at each sampling time by the detected herbicide concentration; losses totaled 11.8 g a.i., 0.44% applied. Oxyfluorfen residues in a containment pond receiving the runoff were determined and showed a decrease over time, with the highest concentration of 0.147 mg/L at 1 day after treatment followed by a decrease to <0.04 mg/L at approximately 3 days after treatment.	Keese et al. 1994

Appendix 12: Field or field simulation studies on the environmental fate of oxyfluorfen.

Application	Observations	Reference
Granular formulations of OH-2 (2% oxyfluorfen, 1% mendimethalin) or Rout (2%oxyfluorfen, 1% oryzalin), equivalent to oxyfluorfen rate of 2.2 kg a.i./ha, was applied to trays of containers of azaleas with plastic, woven fabric, or gravel bedcovers on a 5% slope at the South Carolina Botanical Garden. Applications were broadcast with a hand-held shaker can, with overhead sprinkler irrigation begun within 30 min. This microplot study was conducted in June and September, 1991.	Water runoff samples were collected immediately after application and on 1, 2, 5, 9, and 19 days after application. Cumulative oxyfluorfen loss in runoff water showed significant differences among all three bedcovers; after Day 2, loss was greatest from plastic and least from gravel. This pattern remained until the end of the study. Plastic bedcover lost >160 µg oxyfluorfen after 19 days.	Keese et al. 1994
Sediment and pond water at a commercial nursery in the coastal region of SC were monitored for two years (Feb 1991-Jan 1993) during normal nursery operations. Granular applications of OH-2 at the standard rate equivalent to 2 kg a.i. /ha (1.8 lb/acre) were made periodically to bed areas for weed control by nursery operators, and then followed by overhead irrigation.	The highest concentration of oxyfluorfen found in pond water and sediment was 0.04 µg/ml and 4.0 µg/g, respectively. In irrigation water, the highest concentration found was 0.005 µg/ml. Oxyfluorfen did not accumulate in water or sediment over the 2 yr period.	Riley et al. 1994
Oxyfluorfen (as Goal 23.%EC) was sprayed at 0.1, 0.2, and 0.4 kg a.i./ha onto cabbage, potato, and groundnut crops following sowing and planting, during 1986-1988 (Location and physical details not given).	The crops and soil samples (0-15 cm) were analyzed for oxyfluorfen residues at 3 months after application. Residues were not detectable in edible parts of cabbage or potato except in the 2nd and 3rd season, when traces were detected in cabbage only at the highest applied dose of 0.4 kg a.i./ha; only traces were detected in groundnut-kernel and soil samples.	Sundararaja n et al. 1993