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Fluridone

Human Health and Ecological Risk Assessment

Final Report

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Attachment I: Fluridone EXCEL Worksheets for Human Health and Ecological Risk Assessments. SERA EXWS 052-10-02a.

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
AEL	adverse-effect level
a.i.	active ingredient
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BLM	Bureau of Land Management
bw	body weight
calc	calculated value
CBI	confidential business information
CI	confidence interval
cm	centimeter
CNS	central nervous system
DAA	days after application
DAT	days after treatment
DER	data evaluation record
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
EFED	Environmental Fate and Effects Division (U.S. EPA/OPP)
ExToxNet	Extension Toxicology Network
F	female
FH	Forest Health
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FQPA	Food Quality Protection Act
g	gram
GLP	Good Laboratory Practices
ha	hectare
HDT	highest dose tested
HED	Health Effects Division (U.S. EPA/OPP)
HQ	hazard quotient
IARC	International Agency for Research on Cancer
IRED	Interim Reregistration Eligibility Decision
IRIS	Integrated Risk Information System
k_a	absorption coefficient
k_e	elimination coefficient
kg	kilogram
$K_{o/c}$	organic carbon partition coefficient
$K_{o/w}$	octanol-water partition coefficient
K_p	skin permeability coefficient
L	liter
lb	pound
LC_{50}	lethal concentration, 50% kill
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LOC	level of concern

LOD	limit of detection
m	meter
M	male
mg	milligram
mg/kg/day	milligrams of agent per kilogram of body weight per day
mL	milliliter
mM	millimole
mPa	millipascal, (0.001 Pa)
MOS	margin of safety
MRID	Master Record Identification Number
MSDS	material safety data sheet
MSMA	monosodium methanearsonate
MW	molecular weight
NAWQA	USGS National Water Quality Assessment
NCI	National Cancer Institute
NCOD	National Drinking Water Contaminant Occurrence Database
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
Pa	Pascal
PBPK	physiologically-based kinetic
ppm	parts per million
RBC	red blood cells
RED	re-registration eligibility decision
RfD	reference dose
SERA	Syracuse Environmental Research Associates
TEP	typical end-use product
T.G.I.A.	Technical grade active ingredient
TIPA	Triisopropanolamine
TRED	Tolerance Reassessment Eligibility Decision
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

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℃+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

Fluridone is an aquatic herbicide used to control aquatic macrophytes – i.e., large aquatic plants as opposed to microscopic aquatic algae. Unlike most terrestrial herbicides, application rates for fluridone are given as target concentrations of fluridone in water rather than as pounds per acre. Fluridone is an effective aquatic herbicide for some sensitive target species of aquatic macrophytes, like Eurasian watermilfoil and hydrilla. Over the range of labelled application rates—i.e., 10 to 150 ppb—adverse effects are likely in sensitive species of aquatic macrophytes. At application rates of up to about 20-30 ppb, which encompasses labelled rates recommended for treatment of target species in canals, effects on aquatic plants are likely to be limited to sensitive macrophytes, and perhaps some more tolerant species of macrophytes as well as some species of algae. Higher application rates are more likely to cause adverse effects in tolerant species of macrophytes and sensitive species of algae; whereas, the highest application rate of 150 ppb is likely to cause adverse effects in many if not all species of aquatic macrophytes as well as in some species of algae. Tolerant species of algae, however, are not likely to be affected even at the maximum application rate.

Under normal conditions of use, there is no basis for asserting that toxic effects are plausible in humans, terrestrial animals, or aquatic animals. In the case of an accidental spill using extreme exposure assumptions standard in all Forest Service risk assessments, fluridone concentration in water could exceed the level of concern for humans and aquatic animals. Whether or not the level of concern would be exceeded in the event of an actual spill depends on the amount of fluridone that is spilled and the size of the water body into which the spill occurs.

Program Description

Fluridone is currently supplied by SePRO as a liquid formulation (Sonar AS), a granular formulation (Sonar PR), and two pellet formulations (Sonar Q and Sonar SPR). Fluridone may be applied directly to standing (lentic) bodies of water—e.g., ponds or lakes—as well as to flowing (lotic) bodies of water—e.g., streams or canals. Either surface or subsurface applications may be made.

Application rates for fluridone are expressed as target concentrations in units of parts per billion (ppb or µg/L). The highest application rate is 150 ppb cumulative application per year, and this rate is intended for lakes or reservoirs. For smaller standing bodies of water (i.e., ponds), the maximum application rate is 90 ppb cumulative application per year. For canals or rivers, the recommended application rates range from 10 to 40 ppb, depending on the formulation and target vegetation. Fluridone is a slow acting herbicide, and its concentration in the water must be maintained at phytotoxic levels to effectively control target vegetation over a prolonged period of time. For all formulations, the product labels indicate that the effective concentrations of fluridone in water must be maintained for 30-90 days *under optimum conditions*. Auxiliary products are available from SePRO for monitoring fluridone concentrations in water as well as for conducting pretreatment bioassays to determine the susceptibility of target vegetation to

fluridone and post-treatment bioassay packages to assess the response of both target and nontarget vegetation to fluridone applications.

Human Health Risk Assessment

Hazard Identification

Although the mechanism of action of fluridone in plants is understood, the mechanism of action of fluridone in mammals is not well characterized. Fluridone is rapidly absorbed, metabolized, and excreted by mammals. While the metabolism of fluridone has not been studied extensively, it appears that fluridone is metabolized by hydroxylation, probably involving the cytochrome P450 enzyme system. In terms of acute toxicity, fluridone is classified as Category IV (the least toxic classification) for acute oral toxicity, skin irritation potential, and inhalation toxicity and as Category III (the second least toxic category) for eye irritation and dermal toxicity.

At sufficiently high doses, fluridone is associated primarily with changes in the liver, reduced body weight, and reduced food consumption. While there is no indication that fluridone causes birth defects, adverse effects in pregnant animals exposed to fluridone included reduced food consumption and reduced body weight, associated with an increased incidence of fetal mortality. Fluridone does not appear to be carcinogenic, based on standard life-time toxicity studies in rats and mice. Similarly, there is little indication that fluridone will cause specific neurotoxic effects or impairment of immune or endocrine function.

Relatively little information is available on the inerts in fluridone formulations but there is no basis for asserting that the inerts contribute substantially to hazard. The U.S. EPA raised concern for one environmental metabolite of fluridone, N-methylformamide. N-methylformamide can cause birth defects and can be generated from the aqueous photolysis of fluridone. Nonetheless, adequate field studies demonstrate that detectable concentrations of N-methylformamide are not found in water treated with fluridone at application rates equal to or greater than those used in Forest Service programs. While it is likely that some N-methylformamide is formed via the photolysis of fluridone, the failure to detect N-methylformamide in field studies is probably due to the rapid biodegradation of N-methylformamide in water.

Exposure Assessment for Human Health

The exposure assessments for workers and members of the general public are detailed in an EXCEL workbook that accompanies this risk assessment. This workbook contains a set of worksheets on fluridone that details each exposure scenario discussed in this risk assessment. In addition, the workbook includes summary worksheets for workers (Worksheet E01) and members of the general public (Worksheet E02).

Fluridone exposure for workers and members of the general public depends on the target concentration. For the current risk assessment, all exposure assessments are based on the application of a liquid formulation, Sonar AS, at a target concentration of 0.15 ppm, which is the maximum labeled target concentration. The consequences of using lower application rates are discussed in the risk characterization.

Data are not available on worker exposure rates for aquatic applications of fluridone. Consequently, the current risk assessment bases worker exposure rates on an aquatic application of 2,4-D—i.e., 0.0009 (0.0004-0.002) mg/kg body weight per lb handled. The U.S. EPA generally uses a different methodology for assessing worker exposure based on deposited dose rather than absorbed dose. This risk assessment does not consider the use of personal protective equipment because personal protective equipment is not required on the product labels and because the hazard quotients for workers, discussed in the risk characterization, do not suggest that personal protective equipment is necessary. For general exposures—i.e., those that might occur during normal applications of fluridone—the estimated absorbed doses are about 0.002 (0.0008-0.004) mg/kg body weight. For accidental exposures, the highest absorbed doses of about 0.1 (0.01-0.7) mg/kg bw are associated with wearing contaminated gloves for 1 hour.

Fluridone may be applied directly to surface water to which members of the general public may have access. Furthermore, restrictions are not imposed on public access to treated bodies of water. Thus, it is plausible that members of the general public could be exposed to fluridone, if the treated body of water is in an area that they frequent. Based on consumption of water treated at the target concentration of 0.15 mg/L (150 ppb), acute exposure levels of fluridone for members of the general public are about 0.01 (0.007-0.02) mg/kg bw/day. Accidental one-day or single event exposures associated with a sizeable spill of field solution into a small body of water result in absorbed dose estimates of 1.4 (0.2-8) mg/kg bw. Because fluridone is not persistent in water, longer-term exposure levels will be low for members of the general public, and the highest estimated longer-term absorbed dose is about 0.004 mg/kg bw/day.

Dose-Response Assessment for Human Health

The dose-response assessment for the human health risks associated with exposures to fluridone is relatively simple. Forest Service risk assessments typically adopt both acute and chronic RfD values from the U.S. EPA, unless there is a compelling basis to do otherwise. The U.S. EPA's Office of Pesticide Programs derived an acute RfD of 1.25 mg/kg bw for women of child-bearing age, based on a developmental study in rabbits. The EPA did not derive an acute RfD for other members of the general population. Accordingly, in the current Forest Service risk assessment, the acute RfD of 1.25 mg/kg bw is applied to all acute exposure scenarios. This approach, which is somewhat more conservative than that used by the U.S. EPA, reflects the generally conservative risk assessment methods used in all Forest Service risk assessments.

The U.S. EPA derived two chronic RfDs for fluridone: 0.08 mg/kg bw/day from the Office of Research and Development and 0.15 mg/kg bw/day from the Office of Pesticide Programs. The lower RfD is based on a life-time feeding study in rats. This study was reviewed by the Office of Pesticide Programs but was apparently not used because of reporting deficiencies. The Office of Research and Development also reviewed the rat feeding study as well as other supporting toxicity studies and judged that the feeding study using rats was suitable for deriving the lower chronic RfD of 0.08 mg/kg bw/day. Consistent with the conservative risk assessment methods used in all Forest Service risk assessments, the lower chronic RfD of 0.08 mg/kg bw/day is used

in the current risk assessment to characterize risks associated with longer-term exposures to fluridone.

Risk Characterization for Human Health Effects

The risk characterization for both workers and members of the general public is reasonably simple and unambiguous: based on a generally conservative and protective set of assumptions regarding both the toxicity of fluridone and potential exposures to fluridone, there is no basis for suggesting that adverse effects are likely in either workers or members of the general public, even at the maximum application rate that might be used in Forest Service programs.

For workers, no exposure scenarios, acute or chronic, exceed the RfD at the upper bound of the estimated dose associated with the highest application rate of 150 ppb (0.15 mg/L). The hazard quotients for general exposures associated with routine applications of fluridone to surface water are below the level of concern by factors of 20 to 100. Accidental exposure scenarios typically included in Forest Service risk assessments are also below the level of concern. The contaminated glove exposure scenario approaches the level of concern: wearing contaminated gloves for 1 hour results in a hazard quotient of 0.5.

For members of the general public, hazard quotients at the highest application rate are below a level of concern by factors of 20 to 20,000 for longer-term exposures. The upper bounds of acute exposure scenarios are below the level of concern by factors of at least 100. This risk characterization for members of the general public is consistent with the risk characterization presented by the U.S. EPA/OPP in their most recent risk assessment of fluridone.

Acute accidental exposure scenarios for members of the general public that involve the consumption of contaminated water after an accidental spill do exceed the level of concern with a maximum hazard quotient of 7. The accidental spill scenario is standard in all Forest Service risk assessments and is used to suggest the importance of mitigation measures in the event of an accidental spill.

Ecological Risk Assessment

Hazard Identification

Fluridone is an herbicide used to control unwanted aquatic macrophytes. In aquatic plants, as with terrestrial plants, fluridone acts by inhibiting phytoene desaturase, which leads to decreased levels of carotenes, which, in turn, leads to decreases in chlorophylls, photosynthesis, and carbohydrate stores. While these mechanisms of action appear to be relevant to all plants, the relationship of phytoene desaturase inhibition as well as other biochemical indicators of toxicity are not simply related to gross signs of toxicity, such as decreased biomass. Both laboratory toxicity bioassays as well as field studies indicate marked differences in species sensitivity within aquatic macrophytes. Common target macrophytes, such as watermilfoil and hydrilla, appear to be very sensitive to fluridone, based on measures of reduced biomass. Other species, like wild celery and some species of pondweed (*Potamogeton* sp.), are much more tolerant. The species differences and the apparent lack of a simple correlation between biochemical effects and

gross toxic effects appear to be related to the slow-acting nature of fluridone (in terms of progressing from biochemical effects to gross signs of toxicity) and differences in adaptation mechanisms among different species of aquatic macrophytes.

Field applications of fluridone will lead to relatively high peak or target concentrations of fluridone in water, followed by gradual to rapid decreases in fluridone concentrations. The available studies on aquatic macrophytes suggest that the declining pattern of concentrations does not markedly reduce the effects of fluridone on aquatic macrophytes, since the lower residual concentrations seem to impair the ability of aquatic macrophytes to recover from the effects of initially higher target concentrations.

While the laboratory and field data on algae are highly variable, algae appear to be less sensitive than many species of macrophytes to fluridone, and green algae appear to be more sensitive than blue-green algae. For both macrophytes and algae, immature organisms appear to be more sensitive to fluridone, relative to mature organisms of the same species.

While fluridone is an effective herbicide, no specific mechanism of action can be identified in terrestrial or aquatic animals. In both terrestrial and aquatic animals, the most frequently noted sign of short-term high-level exposures is some form of abnormal movement, typically characterized as ataxia or erratic movement. These general signs of toxicity are very often noted in animals after exposures to very large amounts (i.e., doses or concentrations) of pesticides and other compounds, and these signs of toxicity do not necessarily reflect a specific mechanism of action. Based on standard criteria used by the U.S. EPA for categorizing the inherent toxicity of pesticides, fluridone is classified as *Practically Nontoxic* to mammals and birds, and *Slightly Toxic* to *Moderately Toxic* in fish and aquatic invertebrates.

Exposure Assessment for Ecological Risk Assessment

The exposure assessments for the ecological risk assessment generally parallel those used for the general public in the human health risk assessment. In other words, the exposure scenarios are similar in the basic assumptions concerning the application of fluridone, and the differences in the estimated doses from those in the human health risk assessment are attributable to differences in body size and consumption rates for food or water. Also, as in the human health risk assessment, the exposure scenarios for terrestrial vertebrates are a subset of those used in most Forest Service risk assessments. Some exposure scenarios, such as the consumption of terrestrial vegetation, are not relevant to aquatic applications of fluridone.

The exposure scenarios for terrestrial wildlife are summarized in Worksheet G01 of the EXCEL workbook that accompanies this risk assessment. The highest exposure scenarios involve the accidental spill of 200 gallons of a field solution into a small pond. The estimated doses for birds and mammals cover a relatively narrow range: from about 0.5 to 20 mg/kg body weight. The expected non-accidental acute exposures are much lower, spanning a range from about 0.02 to 0.04 mg/kg body weight. Because fluridone degrades and dissipates in water with half lives of about 5 to 100 days, the range of the expected doses in the longer-term exposure scenarios is very low: from about 0.002 to about 0.25 mg/kg body weight/day.

Exposure of aquatic organisms to fluridone is taken as the nominal application rate or target concentration. In the EXCEL workbook that accompanies this risk assessment, the maximum application rate of 150 ppb is used. The consequences of using lower application rates are considered in the risk characterization.

Dose-Response Assessment for Ecological Risk Assessment

The available toxicity data on fluridone support separate dose-response assessments in seven groups of organisms: terrestrial mammals, birds, terrestrial invertebrates, fish, aquatic invertebrates, aquatic macrophytes, and aquatic algae. 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.

For terrestrial mammals, the toxicity endpoints correspond to the NOAEL values used in the human health risk assessment to derive the acute and chronic RfDs—i.e., an acute NOAEL of 125 mg/kg body weight and a chronic NOAEL of 8 mg/kg body weight/day. NOAEL values for birds, 1500 mg/kg bw for acute exposures and 68 mg/kg bw/day for longer-term exposures, are substantially higher than those for mammals. Although terrestrial invertebrates are not likely to be exposed to fluridone, and risks to this group are not quantified, the single available acute NOAEL of 3900 mg/kg bw suggests that terrestrial insects are less sensitive than mammals or birds to the effects of fluridone exposure.

As would be expected for an aquatic herbicide registered for the control of macrophytes, aquatic macrophytes are the most sensitive group of aquatic organisms with NOEC values ranging from 0.001 mg/L (1 ppb) in sensitive species to 0.024 mg/L (24 ppb) in tolerant species. All of these toxicity values correspond to target concentrations over periods of exposure ranging from 22 to 90 days. Generally, with respect to fluridone exposure, algae appear to be less sensitive than macrophytes, with NOEC values ranging from 0.02 mg/L (20 ppb) in sensitive species of algae to 0.5 mg/L (500 ppb) in tolerant species of algae. These NOEC values, however, all involve much shorter periods of exposure (from 4 to 6 days) than those for macrophytes. Some field studies indicate that mixed algal populations may be adversely affected after longer-term exposures associated with field applications of fluridone.

The data on fish and aquatic invertebrates are sparse, relative to the data on aquatic plants. The available acute toxicity data suggest that fish and invertebrates are about equally sensitive to fluridone, with acute NOEC values in sensitive species of 0.5 mg/L (fish) and 0.6 mg/L (invertebrates) and NOEC values in tolerant species of 2 mg/L (fish) and 3.35 mg/L (invertebrates). Longer-term NOEC values are similar for fish and aquatic invertebrates: NOEC values in sensitive species of 0.04 mg/L (fish) and 0.1 mg/L (invertebrates). Corresponding NOEC values for tolerant species are 0.48 mg/L (fish) and 0.6 mg/L (invertebrates).

Risk Characterization for Ecological Risk Assessment

The quantitative risk characterization for terrestrial species is given in Worksheet G02, and the corresponding risk characterization for aquatic species is given in Worksheet G03. Both of these

worksheets are in the EXCEL workbook that accompanies this risk assessment (Attachment 1). As in the human health risk assessment, the quantitative risk characterization is given as the hazard quotient—i.e., the level of exposure divided by a toxicity value. Unlike the human health risk assessment, however, the toxicity values used in the ecological risk assessment involve different endpoints and different durations of exposure for different groups of organisms. These differences are necessitated by the nature of the available data on the different groups of organisms.

Applications of fluridone to water are likely to cause adverse effects in at least some species of aquatic macrophytes. Except for accidental spills, there is no basis for asserting that toxic effects in any aquatic animals are plausible. For terrestrial animals, no exposure scenarios, including the accidental spill, result in hazard quotients that exceed the level of concern.

Fluridone is an effective aquatic herbicide for some sensitive target species of aquatic macrophytes, like Eurasian watermilfoil and hydrilla. Over the range of labelled application rates—i.e., 10 to 150 ppb—adverse effects are likely in sensitive species of aquatic macrophytes. The available data clearly indicate that the target species are sensitive aquatic macrophytes. At application rates of up to about 20-30 ppb, which encompasses labelled rates recommended for treatment of target species in canals, effects on aquatic plants are likely to be limited to sensitive macrophytes, and perhaps some more tolerant species of macrophytes as well as some species of algae. Higher application rates are more likely to cause adverse effects in tolerant species of macrophytes and sensitive species of algae; whereas, the highest application rate of 150 ppb is likely to cause adverse effects in many if not all species of aquatic macrophytes as well as in some species of algae. Tolerant species of algae, however, are not likely to be affected even at the maximum application rate.

Since applications of fluridone are likely to alter aquatic vegetation, secondary effects on fish, aquatic invertebrates, as well as some species of aquatic plants are likely. Secondary effects on terrestrial organisms associated with changes in water quality and perhaps the availability of some food items are also plausible. In that the application of fluridone is intended to alter the composition of aquatic macrophyte communities, these secondary effects must be considered in any site-specific application of fluridone to surface water. Implicit in the application of fluridone, however, is the assumption that changing the composition of aquatic vegetation is an intended and desirable management objective.

1. INTRODUCTION

This document provides risk assessments for human health effects and ecological effects to support an assessment of the environmental consequences of using fluridone in Forest Service programs. Fluridone is used only in aquatic weed control. The fluridone formulations covered in this risk assessment include liquid, granular, and pellet formulations of Sonar supplied by SePRO Corporation, and liquid, granular, and pellet formulations of Avast, supplied by Griffin LLC, until 2004, when SePRO Corporation acquired the assets of Griffin LLC. Thus, the only current *supplier* of fluridone formulations appears to be SePRO. Nevertheless, because the Griffin products are cited in the literature and existing supplies may still be in use, both the Griffin and SePRO formulations of fluridone are considered in this risk assessment.

Like other Forest Service risk assessments, this document has four chapters: 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 fluridone 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.

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 2007a).

The human health and ecological risk assessments prepared for the USDA Forest Service are not, and are not intended to be, comprehensive summaries of all of the available information. Nonetheless, the open literature on fluridone is modest, and an attempt was made to include a discussion of all studies in the open literature that may be useful in assessing the consequences of using fluridone in Forest Service programs. In addition to standard literature searches of TOXLINE and AGRICOLA, this risk assessment considers the available reviews on fluridone conducted for the U.S. Bureau of Land Management (ENSR 2005a,b), the Massachusetts Department of Agriculture (1997), as well as the fluridone reviews prepared by the U.S. EPA's Office of Pesticide Programs (U.S. EPA/OPP 2004a-g). ENSR (2005a,b) covers open literature and discusses unpublished studies submitted to the U.S. EPA. The U.S. EPA/OPP (2004a-g) reviews focus on the unpublished studies submitted to the agency by the registrant. These studies are treated by the U.S. EPA as confidential business information (CBI); accordingly, complete copies of these studies were not available for the current risk assessment. Nonetheless, the key information from these studies is summarized in the U.S. EPA/OPP citations noted above.

In addition to these documents, *cleared reviews* pertaining to fluridone were obtained from the U.S. EPA in response to a Freedom of Information Act (FOIA) request. Cleared reviews consist primarily of detailed summaries of registrant submitted studies (referred to as Data Evaluation Records or DERs), internal analyses and reviews conducted by the U.S. EPA, and correspondence between the U.S. EPA and the registrant. A total of 87 cleared reviews (as electronic files) were kindly provided by U.S. EPA/OPP.

In addition to reviews published in the open literature, there is a substantial amount of information on fluridone available on the Internet. For the most part, however, data obtained from the Internet are not used unless the information is well documented. The most useful database found on the Internet for this risk assessment is the ECOTOX database compiled and reviewed by the U.S. EPA (U.S. EPA/ORD 2008). ECOTOX is also the main ecotoxicity database used by the Pesticide Action Network (PAN 2007).

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

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 quite large. Because of the need to encompass many different types of exposure as well as the need to express the uncertainties in the assessment, this risk assessment involves numerous calculations, most of which are relatively simple. They are included in the body of the document. For the more cumbersome calculations, an EXCEL workbook, consisting of a set of worksheets, is included as an attachment to the risk assessment. The worksheets provide the detail for the estimates cited in the body of this document. Documentation on the use of EXCEL workbooks is provided in SERA (2007b).

2. PROGRAM DESCRIPTION

2.1. OVERVIEW

Fluridone is an aquatic herbicide used to control nuisance or invasive aquatic plants, which acts by inhibiting the synthesis of certain plant pigments (carotenoids). Fluridone is currently supplied by SePRO as a liquid formulation (Sonar AS), a granular formulation (Sonar PR), and two pellet formulations (Sonar Q and Sonar SPR). Fluridone may be applied directly to standing (lentic) bodies of water—e.g., ponds or lakes—as well as to flowing (lotic) bodies of water—e.g., streams or canals. Either surface or subsurface applications may be made.

Application rates for fluridone are expressed as target concentrations in units of parts per billion (ppb or µg/L). The highest application rate is 150 ppb, and this rate is intended for lakes or reservoirs. For smaller standing bodies of water (i.e., ponds), the maximum application rate is 90 ppb. For canals or rivers, the recommended application rates range from 10 to 40 ppb, depending on the formulation and target vegetation. Fluridone is a slow acting herbicide, and its concentration in the water must be maintained at phytotoxic levels to effectively control target vegetation over a prolonged period of time. For all formulations, the product labels indicate that the effective concentrations of fluridone in water must be maintained for 30-90 days *under optimum conditions*. Auxiliary products are available from SePRO for monitoring fluridone concentrations in water as well as for conducting pretreatment bioassays to determine the susceptibility of target vegetation to fluridone and post-treatment bioassay packages to assess the response of both target and nontarget vegetation to fluridone applications.

2.2. CHEMICAL DESCRIPTION AND COMMERCIAL FORMULATIONS

Fluridone is the common name for 1-methyl-3-phenyl-5-[3-(trifluoromethyl)phenyl]-4(1H)-pyridinone:

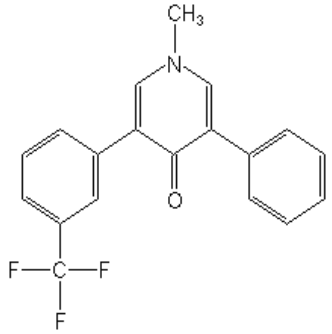

Table 1 summarizes the chemical and physical properties of fluridone. Additional information about the chemical and physical properties used in this risk assessment to model fluridone concentrations in the environment is discussed in Section 3.2 (Exposure Assessment for the human health risk assessment).

Although fluridone is labeled for the control of numerous aquatic plant species, the primary target species are Eurasian watermilfoil, *Myriophyllum spicatum* (northern U.S.), *Hydrilla verticillata* (southern U.S.), *Egeria densa* and hydrilla (western U.S.), as well as

common duckweed (*Lemna minor*) and other native and non-native nuisance aquatic plants throughout the United States (U.S. EPA/OPP 2004a).

Fluridone was developed in the mid-1970s and initially marketed in Syria by Eli Lilly (Arnold 1979; Tomlin 2004). At least until 1979, fluridone was classified as an experimental herbicide (West et al. 1979). The earliest U.S. registrant of fluridone appears to be Dow Elanco, which was given a registration for fluridone in 1986 (FANPP 2008). Subsequently, the registration of fluridone was transferred to Griffin LLC, and fluridone was marketed as various *Avast!* formulations, as specified in Table 2. In 2004, SePRO Corporation acquired the assets of Griffin LLC, including fluridone (SePRO 2004). Thus, the only current supplier of fluridone appears to be SePRO, even though U.S. EPA's Pesticide Product Label System (U.S. EPA/OPP 2008a) and the PAN database (PAN 2008) list SePRO and Griffin formulations as holding active registrations. Because the Griffin products are cited in the literature and because any existing supplies of the Griffin products may still be used, both the Griffin and SePRO formulations are considered in this risk assessment.

As summarized in Table 2, the products supplied by Griffin LLC included a liquid formulation (Avast! Aquatic Herbicide) and a granular formulation (Avast! SRP Aquatic Herbicide). Most of the fluridone formulations supplied by SePRO are designated as *Sonar* formulations and include a liquid formulation (Sonar AS), a granular formulation (Sonar PR), and two pellet formulations (Sonar Q and Sonar SPR). The two Sonar pellet formulations are assigned the same U.S. EPA registration number, 67690-3. On the basis of this information and a review of the material safety data sheets for these two formulations, Sonar Q and Sonar SPR appear to be the same product. SePRO also supplies a liquid formulation named Avast! SC. This product appears to be identical to the other two liquid formulations, Sonar AS (SePRO) and Avast! Aquatic Herbicide (Griffin).

2.3. APPLICATION METHODS

Fluridone may be applied directly to standing (lentic) bodies of water—e.g., ponds or lakes—as well as to flowing (lotic) bodies of water—e.g., streams or canals. Either surface or subsurface applications may be made. The standard apparatus for making fluridone applications is not specified on the product labels; moreover, the equipment used to apply fluridone will vary according to the specific formulation and water body—i.e., lentic or lotic.

The fluridone formulations summarized in Table 2 are not specifically labeled for aerial application. The Use Closure Memorandum for fluridone (U.S. EPA/OPP 2004a) indicates that: *The aerial application of fluridone is limited to approximately 10 lakes throughout the U.S.* The USDA/Forest Service, however, does not anticipate using aerial applications of fluridone; accordingly, aerial applications receive no further consideration in this risk assessment.

For surface applications of liquid formulations (i.e., Sonar AS and Avast! SC), spray equipment will be used in which the formulation is mixed with water and sprayed over

the surface of the water. The product labels do not specify spray droplet sizes. It is likely that spray applications would be made with streams of water (rather than droplets) or with apparatus that yields very large droplet sizes. For subsurface applications, weighted trailing hoses can be used to apply fluridone near to or at the bottom of the water body—i.e., near the hydrosoil. Finally, liquid formulations of fluridone may be applied using metering devices in which a given amount of the formulation is released into the body of water each day. Metered applications are the only method for applying fluridone to flowing bodies of water such as streams or irrigation canals. SePRO recommends the liquid formulations of fluridone primarily for submergent (immersed) vegetation in standing bodies of water or waterbodies with minimum flow.

Granular formulations of fluridone such as Sonar PR and pellet formulations such as Sonar Q and Sonar SRP may be applied in essentially the same way as liquid formulations, except that the granular and pellet formulations are always applied directly to the surface of the water. Subsurface applications—e.g., weighted hoses—are not specified on the Sonar PR, Sonar SRP, or Sonar Q. Nonetheless, while the applications of granular and pellet formulations of fluridone are made to the surface of the water, both the granular and pellet formulations consist of fluridone in a clay matrix. The material safety data sheets for these formulations do not specify the density of the formulations. The average specific gravity of mineral sand, silt, and clay is about 2.65 g/cm^3 (SERA 2007c). Thus, after applications of granular or pellet formulations to the surface of the water, the formulated fluridone will most likely settle to the bottom of the water body where fluridone will be released to both the water column and sediment.

2.4. MIXING AND APPLICATION RATES

2.4.1. General Considerations

As summarized in Table 2, application rates for fluridone are expressed as target concentrations in units of parts per billion (ppb or µg/L). As discussed below, labeled application rates may be expressed in units of pounds of formulation per acre of treated water at a specified water depth. Functionally, this is equivalent to pounds per acre-feet of water (a three dimensional measure of the volume of water that is treated) than the more familiar lbs/acre which is a measure of pounds per treated surface area (a two dimensional measure of treatment area).

The product labels for fluridone provide directions for reaching the target concentration by applying an amount of the formulation per acre of surface area of the water body in a table which includes values for a variety of average depths of the water to be treated. For all formulations, the product labels indicate that the effective concentrations of fluridone in water must be maintained for 30-90 days *under optimum conditions*. The product labels do not further characterize or describe *optimum conditions*; nevertheless, it would seem that these conditions must relate to both the sensitivity of the target vegetation to fluridone and the characteristics of the water body in terms of maintaining the target concentrations of fluridone. In other words, fluridone is a slow acting herbicide, and the concentration of fluridone in the water must be maintained within a phytotoxic range for the effective control of the target vegetation over a prolonged period of time.

In interpreting the product labels, the distinction between *nominal concentrations* and *measured concentrations* is critical. The term ***nominal concentration*** refers to the calculated amount of fluridone in the water given the size and/or flow rate of the water body. Specific algorithms for calculating the nominal concentration are given below. The term ***measured concentration*** refers to the actual monitored concentration of fluridone in the water.

All fluridone product labels recommend using an enzyme-linked immunoassay (ELISA), referred to as the FasTEST, to measure the actual concentration of fluridone in water. In general, ELISA is a method for rapidly measuring concentrations of a compound or class of compounds by coupling an antibody specific to the compound or class of compounds with an enzyme that displays a detectable response in the presence of a compound or class of compounds. The FasTEST assay can be purchased from SePRO (http://www.sepro.com/default.php?page=sonar), and SePRO appears to be the only supplier of this ELISA. The FasTEST has been used in some recent field studies (Wersel et al. 2007), and Getsinger et al. (2002) demonstrated that the results from FasTEST were consistent with high-pressure liquid chromatography, a more labor-intensive and complex analytical method.

In addition to FasTEST, SePRO provides two other tools for use with Sonar formulations: PlanTEST and EffecTEST. PlanTEST is a package for conducting pretreatment bioassays to determine the susceptibility of target vegetation to fluridone. EffecTEST is another bioassay package designed to be employed during the application period to assess the response of both target and nontarget vegetation to the fluridone applications.

Standard analytical methods were developed for fluridone by West and coworkers with varying limits of detection (LOD). The methods for assaying fluridone in water include electron-capture gas chromatography (West 1978, LOD 10 to 30 ppb), high pressure liquid chromatography with ultraviolet detection at 254 nm (West and Day 1981, LOD 1ppb), and liquid chromatography with ultraviolet detection at 313 nm (West and Turner 1988). It is not clear, however, that these analytical methods from the 1980s are used to monitor field applications of fluridone.

2.4.2. Application Rates

The application rates for fluridone are summarized in Table 2 and are expressed as target nominal concentrations in units of ppb (µg/L) fluridone in water over the desired treatment period. As noted in Section 2.4.1, the recommended treatment period is 30-90 days. The application rates for all formulations are identical. As discussed in the following two subsections, the mixing and application methods differ between the liquid formulations and the granular or pellet formulations.

The maximum application rate for ponds is 90 ppb, and the maximum application rate for lakes and reservoirs is 150 ppb. The product labels define a pond as a static (as opposed to flowing) body of water that covers an area of 10 acres or less. Lentic bodies of water with larger surfaces areas are classified as lakes or reservoirs.

The maximum application rates for ponds, lakes, and reservoirs also represent the maximum cumulative application. Because measured fluridone concentrations will diminish over time, multiple applications may be necessary, and, following the approach on the product labels, these applications will be expressed in target concentrations in units of ppb. The total of all applications cannot exceed 90 ppb in ponds and 150 ppb in lakes or reservoirs. For example, a minimum concentration of 10 ppb is recommended to control Eurasian watermilfoil. Thus, if multiple applications are made to a pond at the nominal rate of 10 ppb in each application, no more than nine applications can be made—i.e., 10 ppb per application x 9 applications = 90 ppb cumulative application rate.

For flowing water bodies such as canals or streams, the product labels recommend a target concentration of 15-40 ppb for a minimum of 45 days. As with lakes and reservoirs, the maximum cumulative application rate for flowing water bodies is 150 ppb.

There are no restrictions on the use of treated water for fishing, swimming, or drinking by humans, livestock, or other domestic animals. Restrictions are placed on the use of treated water for crop irrigation. In addition, fluridone may not legally be applied at targeted rates of greater than 20 ppb within 1320 feet of a potable water source.

For the current risk assessment, application rates are expressed as the target or nominal application rates in units of ppb (μg/L), as specified on the product labels. The range of application rates is taken as 10-150 ppb, the range of application rates specified on the product label. As summarized in Table 2, the lower bound of the application rate is the lowest recommended rate to control Eurasian watermilfoil. The upper bound of the application rate is the highest labeled rate that can be applied to lakes or reservoirs. The central estimate of the application rate is taken as 90 ppb, the highest labeled rate for ponds.

As discussed in Section 2.4.1, the expression of the application rate in units of ppb is somewhat atypical. In terms of the application process, workers will apply a given amount of the formulation—e.g., quarts of formulation for liquids and pounds of formulation for granules or pellets—per acre of water surface area or stream flow rate. Details of these calculations are presented below in Section 2.4.3 for liquid formulations and Section 2.4.4 for granular and pellet formulations. These discussions are somewhat elaborate because of the need to clarify the rationale for the directions given on the product labels as well as some minor inconsistencies in the product labels.

2.4.3. Mixing and Applying Liquid Formulations

Like many liquid pesticide formulations, liquid formulations of fluridone (e.g., Sonar AS or Avast! As or Avast! Aquatic Herbicide) are typically diluted prior to application. In this risk assessment, this diluted solution is referred to as the field solution. Within the context of this risk assessment, the concentration in the field solution primarily influences dermal and direct spray scenarios, both of which depend on the fluridone concentration in the applied spray. As the concentration of fluridone increases, so does the risk of exposure.

Based on information in the product labels for the liquid formulations, spray volumes of 5-100 gallons per acre may be used. Dilutions of the formulation in applications involving metering systems may also be used; however, dilution volumes are not specified on the product labels. For the current risk assessment, the selected dilution volumes range from 5 to 100 gallons per acre with a central estimate of 20 gallons per acre—i.e., the approximate geometric mean of lower and upper bounds of the range.

The selection of application rates and dilution volumes in this risk assessment is intended simply to reflect typical or central estimates as well as plausible lower and upper bounds. In the assessment of specific program activities, the Forest Service may use program-specific application rates in the worksheets included with this report to refine assessments of any potential risks for a specific application.

2.4.3.1. Ponds and Reservoirs

For applying liquid formulations, the product labels provide tables that specify the number of gallons of formulation to apply per acre of standing water (pond or lake) of a specified depth for various target concentrations of fluridone in standing water. For example, the label for Sonar AS (bottom of p.4) indicates that 1.22 quarts of Sonar AS per acre of water surface area should be applied to a body of water that is, on average, 10 feet deep to achieve a target concentration of 45 ppb. To achieve a target concentration of 90 ppb, requires twice the amount—i.e., 2.44 gallons.

In addition to the tabular summaries of application rates in units of quarts of formulation/acre, the product labels provide the following algorithm:

$$\text{Quarts formulation/acre} = \text{Depth (ft.)} \times \text{Target Conc. } (\mu g/L) \times 0.0027 \qquad \text{(Eq. 1)}$$

Note that the algorithm given in Equation 1 may yield results that differ slightly from the application rates in quarts per acre provided in the tables on the product label. For example, for a 10-foot-deep water body and a target application concentration of 90 ppb, Equation 1 yields an application rate of 2.43 quarts of formulation per acre of water body surface area. As noted above, the table in the product label gives an application rate of 2.44 quarts per acre. These minor differences appear to be related to rounding the 0.0027 constant.

The constant of 0.0027 is not discussed in the label. In terms of the structure of Equation 1, the constant must have units of liter-quarts/acre-ft-µg. For this discussion, the composite conversion factor is referred to as ***cf1*** (to distinguish it from other conversion factors discussed below) and is derived as follows:

$$\textbf{\textit{cf1}} = 2.20462 \times 10^{-9} \text{ qt/µg} \times 43{,}560 \text{ ft}^2\text{/acre} \times 28.32 \text{ L/ft}^3$$
$$\textbf{\textit{cf1}} = 0.00271966 \text{ L qt/(acre ft µg)} \qquad \text{(Eq. 2)}$$

The individual conversion factors given in Equation 2 for ft^2/acre and L/ft^3 are standard factors that can be found in most reference texts (e.g., Budavari 1989). The qt/µg

conversion factor is based on the concentration of fluridone in the liquid formulations—i.e., 4 lbs/gallon or 1 lb/quart. Using a standard conversion factor of 453,592,370 µg/lb (e.g., Budavari 1989, 1 lb = 453,592.37 mg), the number of quarts of the formulation required to yield 1 µg a.i. can be calculated as:

$$qt/\mu g = 1/(1b/qt \times 453592370\ \mu g/lb) = 2.20462 \times 10^{-9}\ qt/\mu g \qquad \text{(Eq. 3)}$$

Taking the value of ***cf1*** with no rounding rather than the value of 0.0027 given on the product label, the calculated application rate for a 10-foot-deep pond and a target concentration of 90 ppb is 2.44766 quarts formulation per acre of surface area of the water body or, rounded to 2 significant places, 2.45 qt/acre.

Some application rates for fluridone are based only on the top 10 feet of lake water. Smith and Pullman (1997) indicate that this method is required by the Michigan Department of Environmental Quality. This statement is consistent with mixing directions given at the Michigan Department of Environmental Quality web site (MI/DEQ 2004). The 10-foot limit for calculating fluridone applications is not noted on the product labels or on materials from the U.S. EPA. As noted by Getsinger et al. (2004), thermal stratification can impact the mixing of fluridone in lakes, which can result in over- or under-dosing of a lake.

2.4.3.2. Canals, Rivers, and Streams

The calculation involved in the application of fluridone to flowing water bodies is based on the general point source dilution model (e.g., SERA 2007c, Section 7.5):

$$\textbf{\textit{Conc}}\ (\text{amount/L}) = \text{delta (amount/day)} \div \text{Flow(volume/day)}$$

or

$$\textbf{\textit{Conc}} = \boldsymbol{\delta} \div \boldsymbol{F} \qquad \text{(Eq. 4)}$$

where $\boldsymbol{\delta}$ (delta) is the daily load to the stream, $\boldsymbol{F}$ is the flow rate of the stream, and *Conc* is the concentration in the stream. Dividing the daily load to the stream by the flow rate yields an estimate of the concentration.

For applications to flowing water bodies, the product label provides a series of three equations to calculate the amount of liquid formulation to apply:

$$\boldsymbol{F}_{(\text{cu. ft/sec})} = \boldsymbol{V}_{\textbf{(ft/sec)}} \times \boldsymbol{D}_{(\text{ft})} \times \boldsymbol{W}_{(\text{ft})} \times 0.9 \qquad \text{(Eq. 5a)}$$

$$\boldsymbol{F}_{(\text{acre-ft/day})} = \boldsymbol{F}_{(\text{cu. ft/sec})} \times 1.98 \qquad \text{(Eq. 5b)}$$

$$\text{Quarts formulation/acre} = \boldsymbol{F}_{(\text{acre-ft/day})} \times \text{ppb}_{(\mu g/L)} \times 0.0027 \qquad \text{(Eq. 5c)}$$

As with the algorithm for lakes and ponds (Section 2.4.3.1), the product labels do not discuss or provide units for the constants given in Equations 5a, 5b, and 5c.

Equation 5a calculates the flow rate ($\boldsymbol{F}$) in ft^3/sec with a unitless adjustment factor of 0.9. The calculation of the gross flow rate as the product of the flow velocity ($\boldsymbol{V}$), average depth ($\boldsymbol{D}$), and average width ($\boldsymbol{W}$) is straightforward. While somewhat speculative, the

adjustment factor of 0.9 appears to be taken from an algorithm for calculating stream flow volume based on stream flow velocity measured as the time it takes a float to traverse a given length of a stream (Robins and Crawford 1954). Float measurements provide a reasonable approximation for the rate of flow at the stream surface. Due, however, to flow resistance at the banks and the bottom of a stream (i.e., laminar flow), float measurements overestimate the true velocity of stream flow. Accordingly, Equation 5a without a correction factor will overestimate the true rate of stream flow. The empirical correction factor of 0.9 was developed by Embody (1927) for application to streams with smooth bottom surfaces. A factor of 0.8 was proposed for streams with rough bottom surfaces; nonetheless, the only factor discussed on the product label is 0.9.

The factor of 1.98 in Equation 5b is simply a two decimal place rounding of the composite conversion factor (***cf2***), for cubic feet/second to acre-feet per day in units of acre-feet sec/ft^3 day where an acre-foot (the volume encompassed by a 1-acre area that is 1-foot deep) is equivalent to 43,560 ft^3:

$$\textbf{\textit{cf2}} = \text{acre-feet}/43{,}560\ ft^3 \times 60\ \text{sec/min} \times 60\ \text{min/hr} \times 24\ \text{hr/day} \qquad \text{(Eq. 6)}$$
$$\textbf{\textit{cf2}} = 1.98347\ \text{acre-feet sec}/ft^3\ \text{day}$$

The constant of 0.0027 is identical to ***cf1*** derived in Equation 2 and discussed in Section 2.4.3.1, and it has the same units of measure—i.e., L qt/(acre ft µg).

The constant of 0.0027 in Equation 5c is identical to the constant derived in Equation 2 and has units of liter-quarts/acre-ft-µg where quarts refers to the required number of quarts of a 4 lb a.i./gallon formulation.

2.4.4. Mixing and Applying Granular and Pellet Formulations

Because of the need to maintain fluridone concentrations in treated waters, granular or pellet formulations may provide an advantage in terms of efficacy. Both the granular formulations (Sonar PR) and pellet formulations (Sonar Q and Sonar SRP) contain 5% (w/w) fluridone. Consequently, calculating the amount of formulation to apply per unit of water body—i.e., water volume for ponds or lakes and flow rate for streams and rivers—is the same for both formulations. Neither granular nor pellet formulations are mixed prior to application.

2.4.4.1. Ponds and Reservoirs

Similar to the product labels for liquid formulations, the product labels for granular and pellet formulations provide tables that specify the number of pounds of formulation (rather than quarts) to apply per acre of standing water of a specified depth for various target concentrations of fluridone. For example, the labels for Sonar Q and Sonar SRP pellet formulations indicate that 24.5 pounds of the formulation should be applied per acre of water surface area to a body of water with an average depth of 10 feet in order to achieve a target concentration of 45 ppb. To achieve a target concentration of 90 ppb, twice the amount—i.e., 49 pounds of the formulation—is required (see table in the first column of p.4 of the product label). Since both the granular and pellet formulations

contain fluridone at a concentration of 5%, the label for the granular formulation, Sonar PR, includes the same table included on the labels for Sonar Q and Sonar SRP.

All of the labels for granular and pellet formulations also provide the same equation for calculating the amount of formulation in units of pounds to achieve a specified target concentration in a pond or lake with a specified average depth:

$$\text{Pounds formulation/acre} = \text{Depth (ft.)} \times \text{Target Conc. } (\mu g/L) \times 0.054 \qquad \text{(Eq. 7)}$$

As with the algorithm for liquid formulations (Eq. 1), the algorithm for the granular and pellet formulations yields results that differ somewhat from the tables on the labels. For example, Equation 7 yields an application rate of 48.6 lbs/acre of water surface area for a body of water with an average depth of 10 feet and a target concentration of 90 ppb rather than the 49 lb/acre value given in the table. Again, these minor differences between the tables and the algorithm appear to be related to rounding of the 0.054 constant.

The constant of 0.054 can be derived in a manner similar to the conversion factor for liquid formulations (***cf1*** in Equation 2). In terms of the structure of Equation 7, the conversion factor must have units of lb formulation/acre-ft-µg. Designating this conversion factor as ***cf3***, the factor is derived as:

$$\textbf{\textit{cf3}} = 20 \text{ lb formulation/lb a.i.} \times 43{,}560 \text{ ft}^2\text{/acre} \times 28.32 \text{ L/ft}^3 \text{ /}453{,}592{,}370 \text{ µg a.i./lb a.i.}$$
$$\textbf{\textit{cf3}} = 0.0543933 \text{ lb formulation/(acre ft µg a.i.)} \qquad \text{(Eq. 8)}$$

Using ***cf3*** rather than the rounded conversion factor of 0.054, to achieve a target concentration of 90 µg/L in a 10-foot-deep body of water requires 48.954 lbs formulation.

2.4.4.2. Canals, Rivers, and Streams

The algorithm for calculating the amount of a granular or pellet formulation to apply to a flowing canal, river, or stream is analogous to the algorithm for liquid formulations and is given on the product label in three steps:

$$\boldsymbol{F}_{(\text{cu. ft/sec})} = \boldsymbol{V}_{(\text{ft/sec})} \times \boldsymbol{D}_{(\text{ft})} \times \boldsymbol{W}_{(\text{ft})} \times 0.9 \qquad \text{(Eq. 9a)}$$
$$\boldsymbol{F}_{(\text{acre-ft/day})} = \boldsymbol{F}_{(\text{cu. ft/sec})} \times 1.98 \qquad \text{(Eq. 9b)}$$
$$\text{Pounds formulation/acre} = \boldsymbol{F}_{(\text{acre-ft/day})} \times \text{ppb}_{(\mu g/L)} \times 0.054 \qquad \text{(Eq. 9c)}$$

Equations 9a and 9b are identical to the equations for the liquid formulation (Eq. 5a and Eq. 5b), as discussed in Section 2.4.3.2. The constant of 0.054 is identical to cf3, as derived in Equation 8, Section 2.4.4.1 with units of lb formulation/acre-ft-µg.

2.5. USE STATISTICS

Most Forest Service risk assessments attempt to characterize the use of an herbicide or other pesticide in Forest Service programs relative to the use of the herbicide or other pesticide in agricultural applications. The information on Forest Service use is typically taken from Forest Service pesticide use reports (http://www.fs.fed.us/

foresthealth/pesticide/reports.shtml), and information on agricultural use is typically taken from use statistics compiled by the U.S. Geologic Survey (http://ca.water.usgs.gov/pnsp/ pesticide_use_maps/) and/or detailed pesticide use statistics compiled by the state of California (http://www.calepa.ca.gov/).

This kind of comparison cannot be made for fluridone. Based on the records of Forest Service applications, fluridone has not been used extensively in Forest Service programs. Only a single fluridone application has been reported in the Forest Service records: an application of 2 lbs to 5 acres in Forest 10 in Region 8 – i.e., the Ozark St. Francis National Forest in Arkansas. No target concentration is specified.

Because fluridone is not registered for use on crops, information regarding agricultural use is not available from the U.S. Geologic Survey. The most recent use report from California indicates that total fluridone use in California during 2004 was about 2659 pounds, of which about 2.9 pounds (≈0.11%) was applied to water, presumably as an aquatic herbicide (CDPR 2007, p. 168). The remaining applications in California are classified as landscape maintenance, regulatory pest control, rights of way, and structural pest control.

3. HUMAN HEALTH RISK ASSESSMENT

3.1. HAZARD IDENTIFICATION

3.1.1. Overview

Although the mechanism of action of fluridone in plants is understood, the mechanism of action of fluridone in mammals is not well characterized. Fluridone is rapidly absorbed, metabolized, and excreted by mammals. While the metabolism of fluridone has not been studied extensively, it appears that fluridone is metabolized by hydroxylation, probably involving the cytochrome P450 enzyme system. In terms of acute toxicity, fluridone is classified as Category IV (the least toxic classification) for acute oral toxicity, skin irritation potential, and inhalation toxicity and as Category III (the second least toxic category) for eye irritation and dermal toxicity.

At sufficiently high doses, fluridone is associated primarily with changes in the liver, reduced body weight, and reduced food consumption. While there is no indication that fluridone causes birth defects, adverse effects in pregnant animals exposed to fluridone included reduced food consumption and reduced body weight, associated with an increased incidence of fetal mortality. Fluridone does not appear to be carcinogenic, based on standard life-time toxicity studies in rats and mice. Similarly, there is little indication that fluridone will cause specific neurotoxic effects or impairment of immune or endocrine function.

Relatively little information is available on the inerts in fluridone formulations but there is no basis for asserting that the inerts contribute substantially to hazard. The U.S. EPA raised concern for one environmental metabolite of fluridone, N-methylformamide. N-methylformamide can cause birth defects and can be generated from the aqueous photolysis of fluridone. Nonetheless, adequate field studies demonstrate that detectable concentrations of N-methylformamide are not found in water treated with fluridone at application rates equal to or greater than those used in Forest Service programs. While it is likely that some N-methylformamide is formed via the photolysis of fluridone, the failure to detect N-methylformamide in field studies is probably due to the rapid biodegradation of N-methylformamide in water.

3.1.2. Mechanism of Action

Considerations about the mechanism of action generally focus on the molecular, biochemical, and/or physiological interactions of a toxic agent with an organism. Understanding mechanisms of action is important to interpreting the available toxicity data. Furthermore, the extent to which the mechanism of action is understood, affects the extent to which the toxicity data can be used to extrapolate from effects in experimental animals to potential effects in humans or potential interactions of the pesticide with other chemicals.

Fluridone is an herbicide, and its mechanism of action in plants (i.e., the inhibition of carotene synthesis) is relatively well characterized, as discussed further in Section 4.1.2.4. Clearly this mechanism of action is not directly relevant to the human health,

and although fluridone may cause grossly adverse effects in mammals, as further discussed in this hazard identification, the mechanism(s) of toxicity have not been identified. Furthermore, the U.S. EPA (2004b,d) has not identified a mechanism of action for fluridone that can be used in considering the cumulative effects or its potential for interacting with other pesticides.

3.1.3. Pharmacokinetics and Metabolism

3.1.3.1. General Considerations

Pharmacokinetics involves the quantitative study of the absorption, distribution, and excretion of a compound. Pharmacokinetics is important to this risk assessment because several of the most plausible exposure assessments (Section 3.2) involve dermal exposure, while most of the dose-response assessments (Section 3.3) used to interpret the consequences of dermal exposure involve oral exposure levels. Accordingly, it is necessary to understand the kinetics of both oral and dermal absorption so that dermal exposure assessments can be appropriately compared with oral dose-response assessments.

A rat metabolism study, conducted by Berard and Rainey (1981) and submitted to the U.S. EPA/OPP in support of the registration on fluridone, reports that fluridone is rapidly metabolized and excreted by rats— i.e., 80% of the dose was excreted in the urine within 72 hours. In this study, rats were administered ^{14}C-labeled fluridone at 100 mg/kg. At 24 hours after dosing, an average of 43.5% (with a range of 21.1-71.4%) of the dose was recovered in the bile and 65.6% (47.8-85.1%) was recovered in the bile by 48 hours after dosing. Fluridone appeared to be extensively metabolized by hydroxylation and then conjugated, with only about 12% of the excreted radioactivity recovered as unmetabolized fluridone.

U.S. EPA/OPP (2004d, p. 29) summarizes the Berard and Rainey (1981) study as well as another metabolism study referenced as MRID 103261 and 103262. The other study involved doses of 10, 100, 250, 500 or 1000 mg/kg bw. In terms of the kinetics of elimination, the results presented in U.S. EPA/OPP (2004d, p. 29) are similar to the results presented by Berard and Rainey (1981): rapid absorption after oral dosing with most of the compound (78-90%) excreted within 3 days, primarily in the feces (68-85%) with lesser amounts in the urine (4-19%). As detailed further in Section 3.1.3.3, this rapid rate of excretion suggests that fluridone is not likely to accumulate substantially in mammals over long periods of exposure.

In terms of the mechanism of elimination, however, these two studies are not consistent. The study by Berard and Rainey (1981) indicates that most of the compound is excreted in the urine but the other metabolism study summarized in U.S. EPA/OPP (2004d) indicates that most of the compound is excreted in the feces. The basis for this discrepancy is not apparent.

A very brief summary of a more recent metabolism study is also given in U.S. EPA/OPP (2004d, p. 30, MRID 44265101) confirming the rapid metabolism of fluridone via ring hydroxylation and N-demethylation. While somewhat speculative, the available

information on the metabolism of fluridone suggests that the cytochrome P450 enzyme system (i.e., liver mixed function oxidase) mediates the rapid metabolism of fluridone.

3.1.3.2. Dermal Absorption

Most of the occupational exposure scenarios and many of the exposure scenarios for the general public involve dermal exposure to fluridone. For these exposure scenarios, dermal absorption is estimated and compared with an estimated acceptable level of oral exposure based on subchronic or chronic toxicity studies in animals. Thus, it is necessary to assess the consequences of dermal exposure relative to oral exposure and the extent to which fluridone is likely to be absorbed from the surface of the skin.

Two types of dermal exposure scenarios are considered: immersion and accidental spills. As documented in SERA (2007a), the calculations of absorbed dose for dermal exposure scenarios involving immersion or prolonged contact with chemical solutions use Fick's first law and require an estimate of the permeability coefficient, K_p, expressed in cm/hour. For direct spray or accidental spill scenarios, which involve deposition of the compound on the surface of the skin, dermal absorption rates (proportion of the deposited dose that is absorbed per unit time) rather than dermal permeability rates are used in the exposure assessment.

Kinetic studies involving the dermal absorption of fluridone are not available. In the absence of experimental data, quantitative structure activity relationships are employed to estimate dermal absorption rates (SERA 2006a). Using the method recommended by U.S. EPA/ORD (1992), the estimated dermal permeability coefficient for fluridone is 0.00037 cm/hour with a 95% confidence interval of 0.00024-0.00058 cm/hour. These estimates are used in all exposure assessments based on Fick's first law, and the calculations for these estimates are presented in Worksheet B05. The central estimate of the K_p—i.e., 0.00037 cm/hour —is essentially identical to the value of 0.0004 cm/hour used in the EPA exposure assessment for swimmers (U.S. EPA/OPP 2004d). As documented in U.S. EPA/OPP (2003), the EPA swimmer model also uses the algorithm from U.S. EPA/ORD (1992) but does not derive confidence intervals. The estimated first-order dermal absorption rate coefficient is 0.0012 $hour^{-1}$ with a 95% confidence interval of 0.00053-0.0027 $hour^{-1}$. The calculations for these estimates are presented in Worksheet B06.

Notably, the above approach to assessing dermal absorption differs from that used by the U.S. EPA. U.S. EPA/OPP (2004d) uses a *dermal absorption factor* of 39% based on ratios of LOAELs from a 21-day dermal toxicity study and a developmental toxicity study in rabbits. The reference for the dermal toxicity study appears to be Probst et al. (1981b), summarized in Appendix 3, in which a daily dermal dose of 786 mg/kg/day was associated with a decrease in kidney weight but no pathological changes in kidney tissues. The reference for the developmental study in rabbits appears to be MRID 159963 summarized in U.S. EPA/OPP (2004d) in which decreased body weight was observed in dams treated at 300 mg/kg bw/day for 12 days (Days 6-15 of gestation) [300 mg/kg bw divided by 786 mg/kg bw/day = 0.381].

Because the duration of the oral and dermal studies are different, the approach used by the U.S. EPA is not readily comparable to the first-order absorption coefficient used in the current risk assessment. Under the assumption of first-order absorption, the proportion absorbed (P_{Abs}) for a given absorption rate (***k***) after time ***t*** is equal to:

$$P_{Abs} = 1 - e^{-kt}.$$

Taking the absorption rates [0.0012 (0.00053-0.0027) $hour^{-1}$] and the 12-day duration of the reproduction study in rabbits, the estimated proportion absorbed would be 0.29 (0.14-0.54). Taking the same approach but using the 21 day exposure period from the dermal study, the estimated proportion absorbed would be 0.45 (0.23-0.74). Thus, the first-order assumption used for dermal exposures in the current risk assessment appears to be comparable to the ratio approach used by the U.S. EPA.

3.1.3.3. Excretion

While excretion rates are not used directly in either the dose-response assessment or risk characterization, excretion half-lives can be used to infer the effect of longer-term exposures on body burden based on the *plateau principle* (e.g., Goldstein et al. 1974). The concentration of the chemical in the body after a series of doses (X_{Inf}) over an infinite period time can be estimated based on the body burden immediately after a single dose, X_0, by the relationship:

$$X_{Inf}/X_0 = 1 / (1 - e^{-ke\ t^*)})$$

where t* is the interval between dosing.

As noted in Section 3.1.3.1, the whole body excretion of fluridone is about 78-90% over a 72-hour (3-day) period after dosing (U.S. EPA/OPP 2004d, p. 29). Using a first-order approximation, these excretion patterns correspond to elimination rates (k_e) of about 0.50 day^{-1} [k_e = -ln(1-*P*)/*t* = -ln(1-0.78)/3 days] to 0.77 day^{-1} [k_e = -ln(1-0.90)/3 days]. Using these estimates of k_e and setting the interval between doses to 1 day (i.e., daily dosing), the increased body burden with infinite exposure relative to the body burden after a single dose would be about 1.9-2.5. While perhaps coincidental, the estimated chronic-to-acute body burden ratios of 1.9-2.5 are quite similar to reported bioconcentration factors for fluridone in fish—i.e., most reported BCF values range from about 1.3 to 6, as summarized in Table 1.

The range of increased body burden over time – i.e., 1.9 to 2.5 – suggests that fluridone has a modest potential to accumulate in mammals after repeated dosing. While this range is relatively low compared to highly lipophilic pesticides (e.g., U.S. EPA/OPP 2008b), the estimated increase in body burden is modestly higher than some other terrestrial herbicides such as aminopyralid (SERA 2007c).

3.1.4. Acute Oral Toxicity

One type of acute toxicity information involves time-specific LD_{50} or LC_{50} values (i.e., doses or concentrations of a toxicant that result in or are estimated to result in 50%

mortality of the test species during a specified exposure or observation period). These values can be viewed as an index of acute lethal potency. In addition, acute oral LD_{50} values are often available on both the active ingredient (a.i.) as well as formulations of the active ingredient, and a comparison of LD_{50} values for the a.i. to the formulation can sometimes be used to at least indirectly assess the role, if any, of inerts in the toxicity of formulations (Section 3.1.14).

The human health risk assessment of fluridone conducted by the U.S. EPA/OPP (2004d) cites the oral LD_{50} of fluridone for rats as >10,000 mg/kg bw, which is used to classify fluridone as having low acute oral toxicity—i.e., Category IV (U.S. EPA/OPP 2004d, p. 10). As documented in SERA (2007a, Table 3-2), the toxicity classifications used by U.S. EPA/OPP impact the labeling requirements of pesticides, with progressively less severe warning notices (referred to as signal words) going from Category I (*Danger*) to Category IV (no signal word required).

As summarized in Appendix 2, the rat LD_{50} study used by the U.S. EPA/OPP (2004d) appears to be that summarized by (Flick 1979b) in which 10 male and 10 female rats were given a single gavage dose of 10,000 mg/kg bw technical grade fluridone and the animals were observed for 14-days. Mortality occurred in 3/10 males, and signs of toxicity (characterized as hypoactivity, leg weakness, ataxia, and increased urine output) were observed 1-4 hours after dosing.

It is not clear, however, that these signs of toxicity were caused by fluridone or were secondary to stress associated with the very high gavage dose. This type of high, single dose study is generally referred as a *limit test*— a single-dose screening study to determine if more elaborate testing is needed. Currently, the limit test for mammals involves a maximum dose of 2000 mg/kg bw (SERA 2007a, Section 3.1.4). The toxicity studies on fluridone, however, are very old, and some of the older studies, such as the study summarized by Flick (1979b) used doses substantially higher than 2000 mg/kg bw. Subcutaneous studies were also conducted in rats, and no signs of toxicity were observed at doses up to 5000 mg/kg bw (Appendix 2, Frick 1979a).

Acute oral doses of fluridone formulations at 500 mg/kg bw resulted in no signs of toxicity in rats (Ansley and Arthur 1980a). Owing to the low toxicity of technical grade fluridone, the failure to observe toxic effects at lower doses of the formulations is not particularly useful information.

As also summarized in Appendix 2, acute oral limit tests were conducted in mice (gavage LD_{50} > 10,000 mg/kg bw), dogs (capsule LD_{50} > 500 mg/kg bw), and cats (capsule LD_{50} > 250 mg/kg bw). In the high-dose mouse study, signs of toxicity similar to those seen in rats were observed for 48 hours after dosing, and mortality occurred in 2/10 females and 3/10 males. The relatively longer duration of the adverse effects in mice suggests that the effects could be attributed to fluridone. This assessment is also consistent with subcutaneous toxicity studies in mice in which the signs of toxicity were quite similar to those seen after oral dosing (Appendix 2, Frick 1979a,b). In both dogs and cats, no frank

signs of toxicity were observed; however, vomiting was seen in 1of 4 dogs 5 hours after dosing and 1 of 4 cats 1 day after dosing.

3.1.5. Subchronic or Chronic Systemic Toxic Effects

Systemic toxicity encompasses virtually any effects that a chemical has once it is absorbed. As discussed in SERA (2006a, Section 3.1.5), *subchronic* and c*hronic* are somewhat general terms that refer to studies involving repeated dosing. Certain types of effects, however, are of particular concern to this risk assessment, including effects on the nervous system (Section 3.1.6), effects on the immune system (Section 3.1.7), developmental or reproductive effects (Section 3.1.8), and carcinogenicity or mutagenicity (Section 3.1.9). This section discusses the remaining studies on systemic toxic effects.

Information on the subchronic and chronic toxicity of fluridone is summarized in Appendix 3. All of the studies summarized in this appendix are from unpublished studies submitted to U.S. EPA/OPP in support of the registration of fluridone. The information in Appendix 3 is taken from the Tolerance Reassessment Eligibility Decision (TRED) for fluridone (U.S. EPA/OPP 2004b) as well as several data evaluation records (DERs) prepared by the EPA (Frick 1979b; Probst 1980a; Probst 1981c,d,e). As documented in Appendix 3, there are a few minor differences in the study summaries provided in the DERs, compared with the study summaries provided in the TRED. This is not an unusual circumstance, particularly for compounds like fluridone for which the DERs are rather old. Nonetheless, the differences between the TRED and DERs are insubstantial.

Chronic toxicity studies are available in mice, rats and dogs. The chronic study in mice involved fluridone dietary concentrations of 0, 0, 33, 100, or 300 ppm for 2 years (Probst 1981d,e). The EPA/OPP (2004d) estimated the daily doses as 0, 5, 15, or 50 mg/kg bw/day. No treatment related effects were observed at the two lower doses, and the NOAEL for this study was determined to be 15 mg/kg bw/day. This NOAEL is the basis for the chronic RfD derived by the EPA (U.S. EPA/OPP 2004b) in the TRED (Section 3.3.2). The dose of 50 mg/kg bw/day was classified as a LOAEL based on an increased incidence of hyperplasia of the liver as well as a 209% increase in serum alkaline phosphatase activity relative, to the control group. Both the increase in liver hyperplasia and the increase in serum alkaline phosphatase are consistent with liver damage.

The chronic study in rats (Probst 1980b) yielded a somewhat lower NOAEL of about 8 mg/kg bw/day with a corresponding LOAEL of about 25 mg/kg bw/day. The LOAEL is based on decreased body weight and an increase in liver and kidney weights. As discussed further in Section 3.3.2 (Chronic RfD), EPA used the NOAEL of 8 mg/kg bw/day (U.S. EPA/ORD 1987) to derive the RfD that is currently on the EPA's Integrated Risk Information System (IRIS) database.

A chronic toxicity study is also available in dogs (Probst 1981c). Qualitatively, this study is consistent with the studies in mice and rats indicating that the liver is the most sensitive target organ—i.e., the endpoints observed included increased liver weight and increases in serum alkaline phosphatase. Quantitatively, however, the chronic study in dogs

yielded an NOAEL of 75 mg/kg bw/day and a corresponding LOAEL of 150 mg/kg bw/day, suggesting that dogs are substantially less sensitive than mice or rats.

A difference in sensitivity between dogs and small rodents is supported by subchronic (90-day) studies in mice, rats, and dogs. As summarized in Frick (1979b), the subchronic NOAEL for dogs is 200 mg/kg bw/day. The subchronic NOAEL values for rats and mice are 25 and 15 mg/kg bw/day, respectively. As in the chronic studies, the most sensitive target organ appears to be the liver.

Remarkably, the differences between the subchronic and chronic NOAEL values are not substantial. The subchronic and chronic NOAELs in mice are identical—i.e., 15 mg/kg bw/day—and the ratios of subchronic to chronic NOAELs is about 3 in rats (25 mg/kg bw/day divided by 8 mg/kg bw/day) and 2.7 in dogs (200 mg/kg bw/day divided by 75 mg/kg bw/day). These relatively modest differences are consistent with limited pharmacokinetic data on fluridone (Section 3.1.3.3), suggesting that fluridone has a very limited potential (factors of about 1.9-2.5) to accumulate in mammals.

3.1.6. Effects on Nervous System

As discussed in Section 3.1.4 (Acute Oral Toxicity), fluridone doses associated with lethality are also associated with weakness in the limbs and ataxia or an unsteady gait. Although these effects might be characterized as indirect neurotoxic effects, they are probably simple secondary effects associated with severe intoxication rather than direct damage to nerve tissue or function. In the toxicity studies involving repeated exposures (Appendix 3), no signs of neurotoxicity were reported in subchronic or chronic toxicity studies, teratology studies, or in the one multigeneration reproduction study (Probst et al. 1980a). Accordingly, there is no indication that fluridone is a direct neurotoxin and only limited information suggesting that fluridone may be an indirect neurotoxin.

3.1.7. Effects on Immune System

Various tests were developed to assess the effects of chemical exposures on a range 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 (Durkin and Diamond 2002). Except for studies on skin sensitization (Section 3.1.11.2), specific studies concerning the effects of pesticides on immune function are not required for pesticide registration, and no such studies are available on fluridone. In the EPA human health risk assessment of fluridone (U.S. EPA/OPP 2004d), potential effects on immune function are not addressed specifically.

While there are no studies concerning the immunological effects of fluridone, limited information is available from the standard subchronic and chronic studies (Section 3.1.5). Typical subchronic or chronic animal bioassays involve morphological assessments of the major lymphoid tissues, including bone marrow, major lymph nodes, spleen and thymus (organ weights are sometimes measured as well), and blood leukocyte counts. These assessments can detect signs of inflammation or injury indicative of a direct toxic effect of the chemical on the lymphoid tissue. Changes in morphology/cellularity of

lymphoid tissue and blood, indicative of a possible immune system stimulation or suppression, can also be detected.

As noted in Section 3.1.5 and Appendix 3, remarkable effects in lymphoid tissue were not noted in these standard toxicity studies on fluridone. In the supplemental chronic toxicity study in rats, a decrease in lymphocytes (a general group of white blood cells involved in mediating immune responses) was observed along with a numerous other effects on blood cells. This effect, however, was statistically significant only in the high-dose males at month 22 of the study—i.e., 25% less than control values. At the time of study termination (month 24), the lymphocyte count was reduced (16% less than control values) in the high-dose males; however, the effect was not statistically significant (see Table 9 in Probst 1980a). The only other reported statistically significant effect on lymphocyte count was an increase in lymphocytes (11% greater than controls) at 12 months in low-dose female rats (Probst 1980a). Although these variations in lymphocyte counts were statistically significant with respect to the control groups, it is not clear that they suggest a biologically significant impact on immune function. No effects on lymphocytes are reported in the chronic toxicity studies in mice (Probst 1981d,e) or dogs (Probst 1981c); yet, each of these studies involved differential leukocyte counts.

3.1.8. Effects on Endocrine System

Assessments 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). In addition, changes in the structure of major endocrine glands—i.e., the adrenal, hypothalamus, pancreas, parathyroid, pituitary, thyroid, ovary, and testis—may also be indicative of effects on the endocrine system. Disruption of the endocrine system during development may give rise to effects on the reproductive system, which might be expressed only after maturation. Consequently, multigeneration exposures are recommended for toxicological assessment of suspected endocrine disruptors (Durkin and Diamond 2002). The one available multigeneration reproduction study on fluridone is discussed in Section 3.1.9.2, and the effects of fluridone on gonadal tissue are discussed in Section 3.1.9.3.

Some toxicity studies on fluridone report decreases in body weight: the developmental study in rabbits (Probst and Adams 1980b), the 3-generation reproduction study in rats (Probst et al. 1980a), and the chronic toxicity study in rats (Probst 1980b). In all three of these studies, significant decreases in body weight were noted only at the highest dose tested. In the chronic toxicity study in rats, Probst et al. (1980a) report a significant decrease in food conversion after 18 months among high-dose males and females. Following standard protocols, the chronic toxicity study conducted terminal histopathology on a number of organs associated with the endocrine system: adrenal, pancreas, thyroid, parathyroid, pituitary, ovary, and testis tissue. Sporadic changes, characteristic of aging rats, were noted, including parathyroid hyperplasia, focal atrophy of the pancreas, and pituitary nodules. Based on the DER prepared by the EPA, there is no indication that these changes were attributable to fluridone. While changes (increases or decreases) in body weights could be associated with effects on endocrine function,

body weight loss is a very common observation in toxicity studies and could be due to a variety of other factors secondary to aging or other toxic adverse effects. In the absence of any clear or consistent indication of effects on endocrine tissue, there is no basis for asserting that decreases in body weights observed in some studies are associated with changes in endocrine function. This analysis is consistent with the interpretations provided in the EPA risk assessment (U.S. EPA/OPP 2004d, p. 16): *In the available toxicity studies on fluridone, there were no estrogen, androgen and/or thyroid mediated toxicity*.

3.1.9. Reproductive and Teratogenic Effects

3.1.9.1. Teratology Studies

Developmental studies are used to assess whether a compound has the potential to cause birth defects as well as other effects during development or immediately after birth. 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 generally required for the registration of pesticides. Very specific protocols for developmental studies are established by U.S. EPA/OPPTS and are available at http://www.epa.gov/opptsfrs/publications/OPPTS_Harmonized.

As summarized in Appendix 3, two developmental studies are available in rats (MRID 159963 as summarized by U.S. EPA/OPP 2004d; Probst and Adams 1980a) and one developmental study is available in rabbits (Probst and Adams 1980b). The study in rats by Probst and Adams (1980a) is not discussed in the EPA risk assessment (U.S. EPA/OPP 2004d). The DER for Probst and Adams (1980a) indicates that this study was classified as *Supplemental* rather than *Acceptable* due to the lack of maternal toxicity at any dose level. As also noted in Appendix 3, no cleared DER is available on the other developmental study—i.e., MRID 159963, as summarized by U.S. EPA/OPP (2004d). While somewhat speculative, it appears that MRID 159963 was conducted after Probst and Adams (1980a) and in response to the Agency's classification of Probst and Adams (1980a) as only *Supplemental*. In any event, the more recent study in rats did identify a clear maternal LOAEL (300 mg/kg bw/day), and this dose is associated with decreased fetal body weight and delayed ossification.

More severe effects were observed in the study in rabbits (Probst and Adams 1980b). Although no effects were noted at a dose of 125 mg/kg bw/day, a dose of 300 mg/kg bw/day was associated with several adverse effects, most notably an increase in abortions and a decrease in maternal body weight and food consumption. As discussed further in Section 3.3.3 (Acute RfD), the EPA uses this study as the basis for the acute RfD for fluridone (U.S. EPA/OPP 2004d).

3.1.9.2. Reproduction Studies

Reproduction studies involve exposing one or more generations of the test animal to the test substance. The general experimental method involves dosing the parental (P or F_0) generation (i.e., the male and female animals used at the start of the study) to the test substance prior to mating, during mating, after mating, and through weaning of the

offspring (F_1). In a 2-generation reproduction study, this procedure is repeated with male and female offspring from the F_1 generation to produce another set of offspring (F_2). In a 3-generation reproduction study, the F_2 is mated one or more times to produce offspring typically referenced as F_{3a}, F_{3b} and so on, depending on the number of times the F_2 generation is mated. 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.

The U.S. EPA requires only one acceptable multigenerational reproduction study, and the registrant submitted a single study (Probst et al. 1980a). This 3-generation reproduction study involved dietary exposures of 0, 200, 650, or 2000 ppm for 2 months during the growth (pre-mating) phase as well as a continuing dietary exposure for at least 10 weeks prior to and throughout mating, gestation, lactation, and until necropsy in the F_1 and F_2 generations and through gestation and lactation in the F_3 generation. The only effect noted in this study was a decrease in body weight in the F_2 pups (90.7% of controls; $p<0.05$) on Day 21 of lactation at the dietary concentration of 2000 ppm. This dietary level corresponds to doses of about 112 mg/kg bw/day. No effects were noted at the dietary level of 650 ppm, which corresponds to an average dose of about 36 mg/kg bw/day.

3.1.9.3. Target Organ Toxicity

As noted in Section 3.1.8 (Effects on Endocrine System), damage to gonadal tissue (ovaries or testes) can suggest an effect on endocrine function; moreover, damage to these organs would clearly suggest a potential for adverse reproductive effects. With the exception of the chronic study in rats (Probst 1980a), there is no indication that fluridone will damage gonadal tissue. As summarized in Appendix 3, an increased incidence of small testes was observed in the high-dose group—i.e., a dietary concentration of 2000 ppm, corresponding to a daily dose of about 80.8 mg/kg bw/day. As detailed in Probst 1980a, small testes were noted in all groups of male rats: 7/60 in the control group, 6/60 in the low-dose group, 9/60 in the mid-dose group, and 23/60 in the high-dose group. With respect to the control group, the high-dose males do evidence a response that is statistically significant using the Fisher Exact test (p=0.000657). The slight increase in the mid-dose group is not statistically significant (p=0.291).

3.1.10. Carcinogenicity and Mutagenicity

The potential carcinogenicity of fluridone is assessed primarily using the chronic toxicity studies in rats (Probst 1980a,b) and mice (Probst 1981d,e). As detailed in Appendix 3 and also noted in U.S. EPA/OPP (2004d), no statistically significant increases in tumor incidence, with respect to the control groups, were noted in any of the chronic toxicity studies.

In addition to chronic toxicity studies, the U.S. EPA requires mutagenicity testing for most pesticides. A relative standard battery of mutagenicity studies was conducted on fluridone: *in vitro* assays with specialized strains for *Salmonella typhimurium* and *Escherichia coli* with technical grade fluridone (Frick 1979b), an *in vitro* assay in

Salmonella typhimurium with a Sonar formulation (Mauer 1984b), a dominant lethal assay with technical grade fluridone in Fischer 334 rats (Probst et al. 1979), and a sister chromatid exchange assay using bone marrow from Chinese Hamsters (Probst 1981b). No positive mutagenic activity was noted in any of these standard test systems.

During the initial EPA review on fluridone, the chronic toxicity studies and mutagenicity studies were reviewed by the Toxicology Branch of OPP, and this review concludes that *… the available data did not provide evidence for the carcinogenicity of fluridone in either rats or mice* (Quest 1985, p. 14). This conclusion is maintained in the more recent EPA risk assessment (U.S. EPA/OPP 2004d, p. 11).

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

3.1.11.1. Skin Irritation

As summarized in Appendix 2, a number of acute toxicity/skin irritation studies were conducted on technical grade fluridone (Frick 1979a), Sonar SRP (Pohland et al. 1989a), Sonar 5P (Ansley and Arthur 1980c; Ansley and Levitt 1981c), and another formulation characterized as a 50% wettable powder (Frick 1979a). These studies are all relatively old; furthermore, ingredients in formulations may change over time. Nonetheless, all but the last formulation appear to correspond to formulations currently in use (Table 2). No skin irritation was noted in any of these studies. Based on these acute studies, U.S. EPA/OPP (2004d) classifies the skin irritant potential of fluridone as Category IV, the lowest or least hazardous ranking, indicating that no irritant effects to the skin would be anticipated with acute exposures.

As discussed in Section 3.1.3.2 (Dermal Absorption), there is a 3-week subchronic dermal toxicity study involving a preparation of fluridone characterized as *Fluridone 4AS*, a 44.5% aqueous suspension of fluridone (Probst et al. 1981b). Although the preparation is characterized as a formulation in the DER for Probst et al. (1981b), it does not appear to correspond to any of the formulations covered in the current risk assessment. Nonetheless, the study notes slight to severe erythema over the 3-week exposure period.

3.1.11.2. Skin Sensitization

Two dermal sensitization studies are available, one on technical grade fluridone (Probst and Pierson 1981) and the other on a Sonar SRP/5P formulation (Pohland and St. Clair 1989). These studies follow a standardized protocol and both studies are classified by the EPA as *Guideline,* a term, essentially synonymous with *Acceptable*, which indicates that the studies followed the proscribed protocols. Both studies yielded the same result, no evidence of dermal sensitization.

3.1.11.3. Ocular Effects

Two studies are also available on the ocular effects of Sonar 5P, a 5% granular formulation of fluridone. From the available DERs (Ansley and Arthur 1980b; Ansley and Levitt 1981b), it is not clear whether the test material used in the study corresponds directly to one of the 5% formulations covered in this risk assessment (Sonar PR, Sonar

Q, and Sonar SRP, as summarized in Table 2). Both of these studies are classified as *minimum data*. Although, the designation is not currently used by the EPA, the discussions in the DERs suggest that these studies would be classified as *Supplemental*. A set of DERs prepared by the EPA (Moats 1990) provides a brief summary of an eye irritation study conducted with Sonar SRP. This study is explicitly classified as *Supplemental* because of reporting deficiencies. In the two studies on the *Sonar P* formulations, moderate eye irritation was noted with slight corneal effects characterized as *dullness* which was reversible by 3 days after exposure. No eye irritation was noted in the brief summary of the eye irritation study with Sonar SRP. In that all of these studies involved instillations of ground granular formulations directly into the eyes of rabbits, the failure to note any eye irritation in the study with Sonar SRP seems somewhat unusual. Although the human health risk assessment prepared by the EPA (U.S. EPA/OPP 2004d) cites fluridone as a Category III eye irritation, none of these studies is discussed in the EPA assessment.

There are no studies in the available data concerning the ocular effects of the liquid formulations of fluridone—i.e., Sonar AS or Sonar SC. The MSDS for Sonar AS indicates that the formulation may cause *...slight transient (temporary) eye irritation. Corneal injury is unlikely.* This statement is consistent with the information summarized above on granular Sonar formulations.

3.1.12. Systemic Toxic Effects from Dermal Exposure

As with most of the acute oral toxicity studies (Section 3.1.4), all acute dermal toxicity studies are limit tests in which only a single dose of the test material was used. Acute dermal toxicity studies using a limit dose of 2000 mg/kg bw are available on Sonar SRP (Pohland et al.1989a), Sonar P (Ansley and Arthur 1980c; Ansley and Levitt 1981c), and a 50% wettable powder formulation (Frick 1979a). An additional acute oral toxicity study is available on technical grade fluridone at a dose of 500 mg/kg bw (Frick 1979a). No mortality or signs of toxicity were noted in any of these studies. Using the categorization scheme adopted by the EPA, these dermal toxicity values are the basis for designating fluridone as Category III for dermal toxicity (U.S. EPA/OPP 2004d, p. 10), which requires the signal word *Caution* on product labels (SERA 2007a, Table 3-2).

One subchronic dermal toxicity study is available on fluridone (Probst et al. 1981b). In this study (detailed in Appendix 3), fluridone was applied to the clipped dorsal skin of rabbits at doses of 192, 384, and 786 mg/kg bw/day. The study produced no signs of overt toxicity; however, a decrease in relative kidney weights was noted in the high-dose group. As discussed in Section 3.1.3.2, the EPA used this study to derive a conversion factor of 38% for adjusting oral doses to equivalent dermal doses (U.S. EPA/OPP 2004d).

3.1.13. Inhalation Exposure

As summarized in Appendix 2, the available literature includes four acute inhalation toxicity studies: two on technical grade fluridone (Frick 1979a), one on Sonar SRP/5P (Pohland et al. 1989b), and one on a 50% wettable powder formulation (Frick 1979a). As with the acute oral and acute dermal toxicity studies, all of the acute inhalation studies involved only a single concentration (ranging from 2.13 to 9.6 mg/L), and no mortality

was noted in any study. The study by Pohland et al. (1989b) used a 4-hour exposure period; each of the other studies used a 1-hour exposure period. Signs of toxicity, including hypoactivity and ataxia, are noted only in the 4-hour exposures reported by Pohland et al. (1989b). In the EPA human health risk assessment (U.S. EPA/OPP 2004b), fluridone is classified as Category IV for inhalation toxicity, which indicates minimal concern, based on the Frick (1979) study involving exposure to 2.13 mg/L technical grade fluridone (Frick 1979a).

3.1.14. Inerts and Adjuvants

The EPA is responsible for regulating inerts and adjuvants in pesticide formulations. As implemented, these regulations affect only pesticide labeling and testing requirements. The term *inert* has been used to designate compounds that do not have a direct toxic effect on the target species. While the term *inert* is codified in FIFRA, some inerts can be toxic, and the U.S. EPA now uses the term *Other Ingredients* rather than *inerts*. The term *inerts* is used in this section for brevity and because it is the term still commonly used.

The U.S. EPA classifies inerts into one of four lists based on the available toxicity information: toxic (List 1), potentially toxic (List 2), unclassifiable (List 3), and non-toxic (List 4). List 4 is subdivided into two categories, 4A and 4B. List 4A constitutes inerts for which there is adequate information to indicate a minimal concern. List 4B constitutes inerts for which the use patterns and toxicity data indicate that use of the compound as an inert is not likely to pose a risk. These lists as well as other updated information regarding pesticide inerts are maintained by the U.S. EPA at the following web site: http://www.epa.gov/opprd001/inerts/.

As summarized in Table 3, very little information is available on the specific inerts in fluridone formulations. Both liquid formulations, Avast! SC and Sonar A.S., contain propylene glycol. Propylene glycol is permitted for use in pesticide products (U.S. EPA/OPP 2007). Propylene glycol is also exempt from tolerances as a food-use inert ingredient under the Code of Federal Regulations (40 CFR part 180), and propylene glycol was categorized as a List 4B inert. As also summarized in Table 3, the granular formulations of fluridone all contain clay. Clay is listed by Pennsylvania and New Jersey as a hazardous substance if clay constitutes more than 1% of a chemical formulation. The bases for these listings are unclear but may reflect a general concern for inhalation exposures to particulate matter. When used as a pesticide inert, clay has been categorized at List 4A—i.e., an inert of minimal concern.

A major problem in evaluating many inert ingredients is the limited toxicity data available on these compounds. The U.S. EPA's Agency-wide database on RfDs and similar values is IRIS—Integrated Risk Information System. Propylene glycol was reviewed in IRIS, but no toxicity values were derived because sufficient information is not available on this compound (U.S. EPA/ORD 1991).

Another major limitation in assessing the hazards associated with pesticide inerts is that the amounts of the inerts in the formulations is not always specified, and this is the case

with formulations of fluridone. Thus, even if toxicity values were readily available on inerts such as propylene glycol, a quantitative analysis of the potential contribution of the inerts relative to the active ingredient could not be made.

The only remaining approach to assessing the contribution of inerts to the toxicity of the formulation is to compare toxicity values for the formulation, expressed in units of active ingredient, to corresponding toxicity values for the unformulated active ingredient. As discussed previously in the hazard identification for human health, mammalian toxicity data are not available for the liquid formulations and quantitative comparisons of mammalian LD_{50} and LC_{50} values are not useful because the available mammalian toxicity values are based on limit tests that use only one dose. As discussed further in Section 4.1.3 (Hazard Identification for Aquatic Organisms), paired toxicity studies in aquatic organisms were conducted on a Sonar AS formulation as well as technical grade fluridone (Hamelink et al. 1986) and there is no indication that the inerts/other ingredients in fluridone formulations contribute substantially to the toxicity of the formulations.

This current Forest Service risk assessment adopts the same approach implicit in the U.S. EPA/OPP (2004d) human health risk assessment—i.e., fluridone is considered the toxic agent of concern, and risks are quantified based on exposures to fluridone.

3.1.15. Impurities and Metabolites

3.1.15.1. Metabolites

As discussed in SERA (2007, Sections 3.1.3.1), two types of metabolites may be considered in a risk assessment, *in vivo* metabolites and environmental metabolites. *In vivo* metabolites refer to the compounds formed within the animal after the pesticide has been absorbed. Environmental metabolites refer to compounds that may be formed in the environment by a number of different biological or chemical processes, including breakdown in soil or water or breakdown by sunlight (photolysis).

As summarized in Section 3.1.3.1, fluridone is rapidly metabolized *in vivo* by rats, and the major metabolic routes appear to be hydroxylation and N-demethylation which may be mediated by cytochrome P450 enzyme system. As with many other pesticides, it seems reasonable to assert that the available *in vivo* toxicity studies will encompass the concerns with *in vivo* metabolites in both the human health and ecological risk assessments.

The occurrence and potential significance of the environmental metabolites of fluridone is a somewhat more complex issue. In a drinking water assessment for fluridone, the U.S. EPA/OPP (2004f) identifies N-methylformamide (NMF) as an environmental metabolite of concern. In terms of potential health effects, NMF is a concern based on developmental effects seen in both rabbits and rats in the study by Kelich et al. (1995). In this study, pregnant rats were dosed at 0, 1, 5, 10 or 75 mg/kg bw/day on days 6 through 15 of gestation and pregnant rabbits were dosed at 0, 5, 10 or 50 mg/kg bw/day on day 6 through 18 of gestation. In both species, no adverse effects were observed at the dose of 10 mg/kg bw/day. At the next higher dose—i.e., 75 mg/kg bw/day for rats and

50 mg/kg bw/day for rabbits—maternal effects included decreased food consumption accompanied by a decrease in body weight. Effects on offspring included decreased fetal survival, decreased fetal weight, as well as increases in the incidence of developmental malformations. Thus, the developmental NOAEL for NMF (10 mg/kg bw/day) is over a factor of 10 below the developmental NOAEL for fluridone—i.e., 125 mg/kg bw/day (Probst and Adams 1980b) as discussed in Section 3.1.91. George et al. (2000) noted that formamide, a metabolite of NMF, also causes developmental effects in rats, albeit at somewhat higher doses—i.e., a NOAEL of 50 mg/kg bw/day with a corresponding LOAEL for developmental effects of 100 mg/kg bw/day.

U.S. EPA/OPP (2004f, pp. 2-3) expressed concern that NMF would be formed as a result of aqueous photolysis, assuming a maximum conversion efficiency of 74%. This information is referenced to MRID 41940104, which is not otherwise identified in U.S. EPA/OPP (2004f). This study, however, appears to be the photolysis study conducted by Saunders and Mosier (1983) in which the photolysis of fluridone was studied in both distilled and natural water. As summarized in Figure 1, Saunders and Mosier (1983) noted that NMF, along with a number of other breakdown products, is formed in the photolysis of fluridone at a light intensity of 500 $\mu W/cm^2$. Over a 27-day treatment period, 74% of the theoretical amount of NMF was formed in distilled water and 36% was formed in natural water.

U.S. EPA/OPP (2004f, Table 1) indicates that the peak expected concentration of NMF would be 2.64 µg/L from the photolysis of 20 µg/L fluridone. This calculation is not detailed in U.S. EPA/OPP (2004f) but appears to be a reflection of the assumed photolysis rate of 0.74 day^{-1} corrected for the molecular weight differences. As summarized in Table 4, the molar conversion factor for NMF, relative to fluridone, is 0.179 [MW of NMF 59.07 / MW of fluridone 329.3]:

$$20\ \mu g/L \times 0.74\ day^{-1} \times 0.179 \times 1\ day = 2.6492\ \mu g/L$$

U.S. EPA/OPP (2004f) notes that the peak expected concentration of NMF based on the above algorithm is not consistent with a monitoring study in which no NMF was detected (at a limit of detection of 2 ppb) after the application of fluridone (as both Sonar AS and Sonar SRP) at a nominal rate of 150 ppb. While the study is not explicitly referenced in the EPA document, the summary corresponds to the study by West et al. (1990) in which fluridone was applied to two ponds in Florida at a nominal rate of 0.15 ppm (150 ppb) using Sonar AS in one pond and Sonar SRP in the other pond with monitoring of fluridone and NMF conducted over a period of 324 days after application. Consistent with the summary in U.S. EPA/OPP (2004f), no NMF was detected in any of 192 water samples. Using the EPA algorithm, an application rate of 150 ppb would be expected to lead to a concentration of about 20 ppb [150 ppb x 0.74 x 0.179 = 19.869 ppb].

One potential reason for the failure to detect NMF in water could be the difference between nominal and actual concentrations, which might be particularly important for the granular formulations, especially Sonar SRP which is a slow release formulation. West et al. (1990, Table IV, p. 316) provide detailed concentration-time data on fluridone after

applications of Sonar AS and SRP, and these data are illustrated in Figure 2 of the current risk assessment. Note that the last monitoring event at Day 324 after treatment is not included because the fluridone concentration was below the limit of detection (1 ppb) in both ponds.

As would be expected from the differences in Sonar AS (a liquid formulation) and Sonar SRP (a slow-release granular formulation), the patterns in fluridone concentrations are substantially different. For Sonar AS, the mean concentration reached a maximum of 116 ppb on Day 6 after treatment, about 77% of the nominal application rate of 150 ppb. While not illustrated in Figure 2, the maximum monitored concentration of fluridone in the pond treated with Sonar AS was 122 ppb on Day 4 after treatment. In the pond treated with Sonar SRP, the highest average concentration was only 29 ppb, and this concentration did not occur until 43 days after treatment.

Using the algorithm from U.S. EPA/OPP (2004f) with the average daily fluridone concentrations reported by West et al. (1990), the expected maximum concentrations of NMF would be about 15.4 ppb [116 ppb x 0.74 x 0.179] in the pond treated with Sonar AS and 3.84 ppb [29 ppb x 0.74 x 0.179] in the pond treated with Sonar SRP. While 3.84 ppb is near the limit of detection for NMF, 15.4 ppb is substantially above the limit of detection. Thus, differences in the nominal and actual concentrations of fluridone in water do not appear to account for the failure of West et al. (1990) to detect NMF in pond water after the application of fluridone.

The potential formation of NMF from fluridone under field conditions was also examined by Osborne et al. (1989). In this study, fluridone was applied to two man-made ponds in Florida at rates of 150 ppb in one pond and 466 ppb in the other, using a 41.7% formulation of fluridone. While the formulation is not otherwise specified, the 41.7% formulation is consistent with Sonar AS, a liquid formulation of fluridone. Osborne et al. (1989) sampled water in each pond for up to 168 days after treatment and assayed for both fluridone (LOD 1 ppb) and NMF (LOD 2 ppb). The average monitored values of fluridone in the two ponds up to 80 days after treatment are illustrated in Figure 3. Concentrations of fluridone in both ponds after 80 days gradually declined from about 10 ppb to below the limit of detection. While not illustrated in Figure 3, Osborne et al. (1989) report individual measures of fluridone in water at peak values of about 375 ppb for Pond 1 (nominal rate of 150 ppb) and about 700 ppb for Pond 2 (nominal rate of 466 ppb). These high peak values occurred in the upper 0.5 meters of pond water and probably reflect incomplete mixing.

No NMF was detected in either Pond 1 or Pond 2 in the study by Osborne et al. (1989). Again using the algorithm from U.S. EPA/OPP (2004f) with the nominal application rates, the expected concentrations of NMF would be about 20 ppb [150 ppb x 0.74 day^{-1} x 0.179 x 1 day = 19.87 ppb] and 62 ppb [466 ppb x 0.74 day^{-1} x 0.179 x 1 day = 61.73 ppb].

In discussing the failure to detect NMF, West et al. (1990, p. 319) conclude that: *Fluridone degraded in all of the studies* [their study as well as the study by Osborne et al.

1989]*, but it did not degrade to NMF*. A similar statement is made by Osborne et al. (1989, p. 76). While neither study found NMF in a reasonably aggressive monitoring program, the conclusion that fluridone did not degrade to NMF seems tenuous. The data by Saunders and Mosier (1983) clearly indicate that NMF will form from the photolysis of fluridone; furthermore, West et al. (1990) indicate that the surface of the ponds allowed for photolysis.

A more plausible explanation for the failure to detect NMF in ponds treated with fluridone may involve the kinetics of the formation and degradation of NMF. The conversion factor of 0.74 day^{-1} used in U.S. EPA/OPP (2004f) may be implausibly conservative. As detailed in Saunders and Mosier (1983), a proportion of 0.74 of the theoretical maximum amount of fluridone—i.e., correcting for differences in molecular weight—formed over a 27-day treatment period. Assuming first-order kinetics, the formation rate, k, may be calculated as -Ln(1-P)/t, where P is the proportion converted and t is the duration required for the conversion. Thus, based on the study by Saunders and Mosier (1983) data, the formation rate of NMF is about 0.05 day^{-1} [-Ln(1-0.74)/27 days]. This is the rate in distilled water. As summarized in Table 4, the formation rate in natural water was about 0.017 day^{-1} [-Ln(1-0.36)/27 days], a factor of about 3 lower than the rate in distilled water.

Based on the Saunders and Mosier (1983), NMF appears to be chemically stable in water and is not subject to significant hydrolysis or photolysis. While U.S. EPA/OPP (2004f) indicates that no data on the degradation of NMF were available for their analysis, EPA estimation software (Meylan and Howard 2007b) suggests that NMF is chemically stable but readily biodegradable. While relatively little data are available on the environmental fate of NMF, U.S. EPA/HPVIS (2004) indicates that NMF was readily degraded—i.e., 98% in 3 days—using an industrial activated sludge inoculum. Again using first-order kinetics as an approximation, this would correspond to a degradation rate of about 1.3 day^{-1} [-Ln(1-0.98)/3 days] or a half-life of about 0.5 days, which is similar to the lower bound biodegradation half-life of 18 hours (0.75 days) reported by Health Canada (2007) for dimethylformamide.

While these degradation rates for NMF are not based on the type of detailed studies typically available on pesticides, they are consistent with the field data from West et al. (1990) as well as Osborne et al. (1989) indicating that NMF is not found in natural water after fluridone applications. This information is consistent with the supposition that NMF is formed by the photolysis of fluridone but is much more rapidly biodegraded in water. Thus, there is no basis for asserting that NMF exposures will be toxicologically significant, relative to those of fluridone. As discussed further in Section 3.4.3 (Risk Characterization for members of the general public), the hazard quotients for fluridone are far below any level of concern, and any incidental exposure to NMF would not substantially impact the characterization of risk.

3.1.15.2. Impurities

Virtually no chemical synthesis yields a totally pure product. Technical grade fluridone, like other technical grade products, undoubtedly contains some impurities. To some

extent, concern for impurities in technical grade fluridone is reduced by the fact that the toxicity studies on fluridone were conducted with the technical grade product or a formulated end-use product. Thus, if toxic impurities are present in the technical grade product, they are likely to be encompassed by the available toxicity studies on the technical grade product.

3.1.16. Toxicological Interaction

There is no information available on the interactions of fluridone with other compounds, and most inferences that could be made are speculative. As discussed in Section 3.1.3.1, fluridone may be metabolized and detoxified by the cytochrome P450 enzyme system. Thus, other compounds that are also metabolized by cytochrome P450 enzymes or compounds that bind tightly to cytochrome P450 enzymes may compete with fluridone, and this competition could enhance the toxicity of fluridone by inhibiting detoxification. The quantitative significance of interactions with other compounds metabolized by cytochrome P450 depends on many factors including the binding affinity of the different compounds to cytochrome P450. In addition, many compounds that are metabolized by cytochrome P450 will also induce cytochrome P450 (e.g., Lewis et al. 1998). In other words, exposure to a compound that serves as a substrate for cytochrome P450 will often result in a series of processes that lead to increased amounts of cytochrome P450 in the organism. Thus, while concurrent exposures to fluridone and other substances that are metabolized by cytochrome P450 may enhance the toxicity of fluridone, sequential exposures may have the opposite effect. If cytochrome P450 is induced in an organism by a compound prior to exposure to fluridone, the higher levels of cytochrome P450 could result in the more rapid detoxification of fluridone.

3.2. EXPOSURE ASSESSMENT

3.2.1. Overview

The exposure assessments for workers and members of the general public are detailed in an EXCEL workbook that accompanies this risk assessment (Attachment 1). This workbook contains a set of worksheets on fluridone that details each exposure scenario discussed in this risk assessment. In addition, the workbook includes summary worksheets for workers (Worksheet E01) and members of the general public (Worksheet E02). The documentation for these worksheets is provided in SERA (2007b).

Fluridone exposure for workers and members of the general public depends on the target concentration. For the current risk assessment, all exposure assessments are based on the application of a liquid formulation, Sonar AS, at a target concentration of 0.15 ppm, which is the maximum labeled target concentration. The consequences of using lower application rates are discussed in the risk characterization (Section 3.4).

Since data are not available on worker exposure rates for aquatic applications of fluridone, the current risk assessment bases worker exposure rates on an aquatic application of 2,4-D—i.e., 0.0009 (0.0004-0.002) mg/kg body weight per lb handled. The U.S. EPA generally uses a different methodology for assessing worker exposure based on deposited dose rather than absorbed dose. This general method is used in a recent BLM risk assessment, and it leads to exposure estimates that are lower (by factors of about 6 to 30) than those used in the current Forest Service risk assessment. This risk assessment does not consider the use of personal protective equipment because it is not required on the product labels and because the hazard quotients for workers, discussed in the risk characterization, do not suggest that personal protective equipment is necessary. For general exposures—i.e., those that might occur during normal applications of fluridone—the estimated absorbed doses are about 0.002 (0.0008-0.004) mg/kg body weight. For accidental exposures, the highest absorbed doses of about 0.1 (0.01-0.7) mg/kg bw are associated with wearing contaminated gloves for 1 hour.

Fluridone may be applied directly to surface water to which members of the general public may have access. Furthermore, restrictions are not imposed on public access to treated bodies of water, meaning that members of the general public are likely to be exposed to fluridone, if the treated body of water is in an area that they frequent. Based on consumption of water treated at the target concentration of 0.15 mg/L (150 ppb), acute exposure levels of fluridone for members of the general public could be much higher than non-accidental exposures for workers—i.e., absorbed doses of about 0.01 (0.007-0.02) mg/kg bw/day. Accidental exposures associated with a sizeable spill of field solution into a small body of water result in absorbed dose estimates of 1.4 (0.2-8) mg/kg bw/day for members of the general public. Again, these estimates are much higher than estimated accidental exposure levels for workers. Because fluridone is not persistent in water, longer-term exposure levels will be low for members of the general public, and the highest estimated longer-term absorbed dose is about 0.004 mg/kg bw/day.

3.2.2. Workers

3.2.2.1. General Exposures

In most Forest Service risk assessments, the exposure assessments for workers are based on a standard set of exposure scenarios involving applications of terrestrial herbicides and insecticides. Although these exposure assessments vary according to the available data for each chemical, the organization and assumptions used in the exposure assessments are standard and consistent. As documented in SERA (2007a), worker exposure rates are expressed in units of mg of absorbed dose per kilogram of body weight per pound of chemical handled. Based on analyses of several different pesticides using various application methods, default exposure rates are typically estimated for three different types of applications: directed foliar (backpack), boom spray (hydraulic ground spray), and aerial. The application of fluridone to ponds or lakes as well as to streams or rivers involves application methods that are quite different from the application methods considered in most Forest Service risk assessments. The specific types of application methods are discussed in Section 2.4 of this Forest Service risk assessment. Accordingly, the standard methods used in most Forest Service risk assessments do not apply to aquatic applications of fluridone.

The literature on fluridone does not include data regarding workers exposed to aquatic applications of fluridone. Nonetheless, a study on worker exposure rates associated with aquatic applications of 2,4-D (Nigg and Stamper 1983) is available (SERA 2006a). The study involved the application of a liquid formulation of 2,4-D by airboat handguns to control water hyacinths. The absorbed doses of 2,4-D were assayed in four workers as total urinary elimination over a 24-hour period. The estimated occupational exposure rates for the 2,4-D workers were 0.0009 (0.0004-0.002) mg/kg body weight per lb handled.

To estimate worker exposure rates for fluridone applications, the estimated occupational exposure rates for the 2,4-D workers are used with the estimated amount of fluridone handled, as specified in Worksheets C01. Accordingly, the estimated worker exposure rates for fluridone are about 0.0018 (0.0008–0.004) mg/kg bw/day. As shown in Worksheet A01, the amount handled is calculated as the product of the target application rate and the volume of water to be treated. For the current risk assessment, the target application rate is taken as the highest labeled rate, 150 ppb (equivalent to 0.15 mg/L). The volume of water is taken as 6,000,000 liters. The water volume is based on assumptions used by the U.S. EPA in a recent occupational exposure assessment for rotenone, another aquatic pesticide (U.S. EPA/OPP 2006).

Using 2,4-D data to estimate worker exposures to fluridone adds uncertainty to the risk assessment; yet, there are no further data to support the worker exposure assessment based on absorbed dose. The U.S. EPA typically uses a deposition-based approach with data from the Pesticide Handlers Exposure Database (e.g., PHED Task Force 1995), but the occupational exposure assessments for fluridone are not included in the recent TRED on fluridone (EPA/OPP 2004b). ENSR International prepared a recent risk assessment on fluridone for the Bureau of Land Management (BLM) (ENSR 2005a), using a

deposition-based approach analogous to PHED estimates. In that risk assessment, the occupational exposure rate is taken as 0.0069 mg/lb a.i. handled for dermal exposure and 0.0017 mg/lb a.i. handled for inhalation exposure (ENSR 2005a, Table 4-2, p. 4-37). In addition, ENSR (2005a, Table 4-16, p. 4-57) used a dermal absorption factor of 0.4, which is very close to the factor of 0.39 used in U.S. EPA/OPP (2004d), as discussed in Section 3.1.3.2 of the current risk assessment. For inhalation exposures, ENSR (2005a, Table 4-16, p. 4-57) used an absorption factor of 1, a standard assumption used by the U.S. EPA. Thus, the combined dermal and inhalation absorbed dose rate based on the deposition approach is about 0.0045 mg/worker [(0.0069 mg x 0.4) + 0.0017 mg] or 0.000064 mg/kg bw per lb a.i. handled, using a standard 70 kg body weight.

The absorbed dose estimated of 0.000064 mg/kg bw per lb a.i. handled based on the PHED/deposition approach used by the U.S. EPA is about a factor of 14 (6.25-31) below the absorbed dose rate of 0.0009 (0.0004-0.002) mg/kg body weight per lb handled (detailed above), based on the methods typically used in Forest Service risk assessments.

While there are substantial uncertainties in worker exposure estimates based on either method, the higher absorbed dose rates are used in the current risk assessment both for consistency with other Forest Service risk assessments and because the exposure estimates based on absorbed dose rates are more conservative—i.e., lead to higher exposure estimates—by factors of about 6-30. As discussed in Section 3.4.2 (Risk Characterization for Workers), this more conservative approach has little impact on the risk assessment. Using the more conservative absorbed-dose approach, risks to workers are substantially below the level of concern.

While careful handling and application practices should be used when handling any pesticides, the product labels for fluridone formulations do not require the use of specific personal protective equipment. Given the very low hazard quotients for workers (Section 3.4.2), the use of and need for personal protective equipment is not further considered in the current risk assessment.

3.2.2.2. Accidental Exposures

Typical occupational exposures may involve multiple routes of exposure (i.e., oral, dermal, and inhalation); nonetheless, dermal exposure is generally the predominant route of exposure for pesticide applicators (Ecobichon 1998; van Hemmen 1992). Typical multi-route exposures are encompassed by the absorbed-dose method 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 the pesticide into the eyes or contaminating the surface of the skin.

There are various methods for estimating absorbed doses associated with accidental dermal exposure (SERA 2007a). Two general types of exposures are modeled in this risk assessment: those involving direct contact with a solution of the pesticide and those associated with accidental spills of the pesticide 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 altering the surface area of the skin that is contaminated.

For this risk assessment, two exposure scenarios are developed for each of the two types of dermal exposure, and the estimated absorbed dose for each scenario is expressed in units of mg chemical/kg body weight. Both sets of exposure scenarios are summarized in Worksheet E01, which references other worksheets in which the specific calculations are illustrated.

Exposure scenarios involving direct contact with chemical solutions are characterized by immersion of the hands for 1 minute in a field solution of the pesticide or wearing contaminated gloves for 1 hour. Generally, it is unreasonable to assume or postulate that the hands or any other part of a worker will be immersed in a chemical solution for a defined period of time. Nevertheless, contamination of gloves or other clothing is quite plausible. For these exposure scenarios, the key assumption is that wearing gloves grossly contaminated with a chemical solution is analogous to immersing the hands in a chemical solution. In both cases, the concentration of the chemical solution in contact with the skin and the resulting dermal absorption rate are basically constant.

For both scenarios (hand immersion and contaminated gloves), the assumption of zero-order absorption kinetics is appropriate. Following the general recommendations of U.S. EPA/ORD (1992), Fick's first law is used to estimate dermal exposure. As discussed in Section 3.1.3.2, an experimental dermal permeability coefficient (k_p) for fluridone is not available. In the absence of experimental data, the K_p for a pesticide is estimated using the algorithm from U.S. EPA/ORD (1992b), which is documented in Worksheet B05.

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 chemical solution 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 (Section 3.1.3.2), and the duration of exposure. For both scenarios, it is assumed that the contaminated skin is cleaned effectively after 1 hour.

3.2.3. General Public

3.2.3.1. General Considerations

Fluridone may be used to control unwanted vegetation in water bodies used by the general public for recreational activities, like fishing or swimming, and as a source of drinking water. As indicated on the product labels for fluridone, there are very few restrictions on public access to treated water bodies, with the exception that fluridone may not be applied at application rates of 20 ppb or greater within ¼ mile of potable water intakes. As detailed further in Section 3.4.3 (Risk Characterization for members of the general public), these restrictions have no impact on the current risk assessment because all non-accidental exposures for members of the general public are far below

levels of concern. Consequently, the restrictions on fluridone applications are not explicitly considered in exposure assessments for members of the general public. The assumption is made that the standard exposure scenarios discussed below are likely to occur.

Because of the conservative exposure assumptions used in the current risk assessment, the number of individuals who might be exposed to fluridone does not have a substantial impact on the characterization of risk presented in Section 3.4. As detailed in SERA (2007a, Section 1.2.2.2), the exposure assessments developed in this risk assessment are based on ***Extreme Values*** rather than a single value. Extreme value exposure assessments, as the name implies, bracket the most plausible estimate of exposure (referred to generally as the central estimate) with extreme lower and upper bounds of plausible exposure estimates.

This Extreme Value approach is essentially an elaboration on the concept of the *Most Exposed Individual* (MEI), sometime referred to as the *Maximum Exposed Individual* (MEI). As these terms also imply, exposure assessments that use the MEI approach attempt to characterize the extreme but still plausible upper limit on exposure. This approach to exposure assessment is commonly used by government agencies, including the U.S. EPA, and other organizations. In the current risk assessment, the upper bounds on exposure are all based on the MEI.

In addition to this upper bound MEI value, the Extreme Value approach used in this risk assessment also provides central and lower bound estimates of exposure. While not germane to the assessment of upper bound risk, it is worth noting that the use of the central estimate and especially the lower bound estimate is not intended to lessen concern. To the contrary, the central and lower estimates of exposure are used to assess the feasibility of mitigation—e.g., measures taken to limit exposure. The implementation of the Extreme Value approach in the exposure assessment is part of an integrated approach designed to encompass plausible upper limits of risk for the most exposed and most sensitive individuals, regardless of the specific probabilities or number of exposures, as well as more likely and lower estimates that could occur by happenstance or as the result of mitigation measures.

3.2.3.1.1. Summary of Assessments

The two types of exposure scenarios developed for the general public include acute exposure and longer-term or chronic exposure. As summarized in Worksheet E03, acute exposure scenarios are classified as either accidental or non-accidental. Specific accidental scenarios are developed for the consumption of contaminated water or fish after an accidental spill. The longer-term or chronic exposure scenarios parallel the acute exposure scenarios for the consumption of contaminated water and fish.

Most Forest Service risk assessments also include scenarios for the consumption of contaminated vegetation or fruit as well as the direct spray of a small child and a woman. These scenarios are not included in the current risk assessment which only considers aquatic applications of fluridone. Section designations for these excluded scenarios are

given below as a matter of convenience for individuals who regularly use many different Forest Service risk assessments—i.e., the section designations in all Forest Service risk assessments are consistent or nearly so.

The exposure scenarios developed for the general public are summarized in Worksheet E03. As with the worker exposure scenarios, the details about the assumptions and calculations involved in these exposure assessments are given in the worksheets that accompany this risk assessment (Worksheets D01–D11). 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

As noted Section in 3.2.3.1.1, direct spray scenarios are not relevant to aquatic applications of fluridone.

3.2.3.3. Dermal Exposure from Contaminated Vegetation

As noted Section in 3.2.3.1.1, scenarios involving dermal contact with contaminated vegetation are not relevant to aquatic applications of fluridone.

3.2.3.4. Contaminated Water

3.2.3.4.1. Peak Expected Concentrations

In terrestrial applications of pesticides, estimates of plausible concentrations in contaminated water can be elaborate and include modeling of runoff and leaching of the pesticide from contaminated soil, unintentional direct spray from aerial applications, or drift from either ground or aerial applications. For direct applications to water, most of these considerations are not relevant.

The estimated concentration in water is set to the target concentration. As summarized in Table 2, the highest labeled target concentration is 0.15 ppm, and this concentration is used in all exposure assessments. Applications of fluridone are likely to be inexact—i.e., there will be uncertainty and perhaps some error in estimating the volume of water to be treated, and the application devices used may also be associated with a margin of error. While this degree of imprecision is more obvious for aquatic applications, uncertainties and errors in actual, as opposed to nominal, application rates are inherent in all pesticide applications.

As illustrated in Figure 3, using monitoring data from Osborne et al. (1989), applications of liquid formulations of fluridone may result in fluridone concentrations in water that initially exceed the nominal application rate by a factor of 2 or more. These relatively high concentrations in the study by Osborne et al. (1989), however, occurred on the day of application and probably reflect incomplete mixing rather than an over-application.

Much greater differences between target concentrations and actual concentrations may occur after applications of granular formulations, particularly formulations such as Sonar SRP, which is designed to slowly release fluridone into the water column. These

differences are illustrated in Figure 2 of the current risk assessment using data from West et al. (1990) in which Sonar AS (liquid formulation) and Sonar SRP (slow-release formulation) were used to treat different ponds, each at nominal application rates of 150 ppb. As illustrated in Figure 2, concentrations of fluridone after application of the liquid formulation approached but did not exceed the nominal application rate. Unlike the study by Osborne et al. (1989), West et al. (1990) did not sample on the day of application, which may account for the failure to detect any concentrations that transiently exceeded the nominal application rate. The reason for the gradual increase in fluridone concentrations over the course of the first 4 days after applications of Sonar AS is not discussed in West et al. (1990) but may be related to the locations of the water sampling relative to the locations of the application.

After applications of Sonar SRP, the pattern of fluridone concentrations reported by West et al. (1990) are remarkably different from those for Sonar AS. Fluridone concentrations were very low, increasing linearly to about 30 ppb from Day 0 to Day 26 and then generally maintaining a plateau from about 20 ppb to 30 ppm from Day 26 to about Day 200. It is interesting to note that from Day 170 through Day 296, the concentrations of fluridone in the two ponds are virtually identical.

Thus, it appears that the use of nominal application rates to assess potential human exposures may overestimate, and perhaps substantially overestimate, exposures for members of the general public associated with concentrations of fluridone in ambient water. These potential overestimates of exposures associated with granular formulations of fluridone have no impact on the current risk assessment. As detailed further in Section 3.4.2 (Risk Characterization for members of the general public), the hazard quotients associated with fluridone in surface water are far below the level of concern, except for the accidental spill scenario (Section 3.2.3.4.3).

3.2.3.4.2. Longer-Term Expected Concentrations

While the peak concentrations of fluridone in ambient water are based on target concentrations, the longer-term concentrations used in this risk assessment are based on both the target concentration as well as the half-life of fluridone in surface water. Assuming first-order dissipation and/or degradation, which appears to be a reasonable assumption for fluridone, the concentration of fluridone in water (C_t) at time, t, is:

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

where C_0 is the concentration at time zero—i.e., the initial target concentration. As discussed in SERA 2007a (Section 3.2.3.6), the time-weighted average concentration (C_{TWA}) between time-zero and time t is simply the integral of the above equation for first-order dissipation divided by the interval, t:

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

The above equation is used to calculate the time-weighted average in all worksheets that require the longer-term concentration of fluridone in water (i.e., Worksheets D07, D09a,

and D09b). The time interval is taken as 90 days, a standard assumption used in all Forest Service risk assessments for this type of scenario (SERA 2007a, Section 3.2.3.6). The first-order dissipation coefficient, k, is based on reported first-order field half-lives ($T_{½}$) for fluridone in water using the general relationship, $k = \ln(2)/ T_{½}$. As summarized in Table 1, the reported field dissipation half-life of fluridone from surface water is highly variable ranging from about 4 days (Muir et al. 1980) to 97 days (Fox et al. 1996).

For the current risk assessment, the field dissipation half- life is taken as 20 days with a range of 5 to 97 days. The central estimate of the half -life is taken from West et al. (1983) and is approximated as the geometric mean of the range. The lower bound half-life of 5 days is taken as the half-time reported by West et al. (1979) based on studies of several lakes in Michigan as well as the average of the half-times reported by Muir et al. (1980). The upper bound of the half-time is taken as 97 days, the longest reported field dissipation half-time reported in the literature (Fox et al. 1996). The reported half-time of 2 days from Sanders et al. (1980) is not used because this study involved treatments of plots within a very large body of water – i.e., the Panama Canal. Thus, the very short half-times reported by Sanders et al. (1980) are probably dominated by dissipation rather than degradation and would not reflect half-times that might be seen in whole-lake applications.

3.2.3.4.3. Accidental Spills

The accidental spill scenario is presented for the acute consumption of contaminated water after an accidental spill into a small pond (0.25 acres in surface area and 1 meter deep). The accidental spill scenario assumes that a young child consumes contaminated water shortly after an accidental spill of 200 gallons of a field solution into a small pond. The specifics of this scenario are given in Worksheet D05. Because this scenario is based on the assumption that exposure occurs shortly after the spill, no dissipation or degradation is considered. This scenario is dominated by arbitrary variability, and the specific assumptions used will generally overestimate exposure. The actual concentrations in the water would depend heavily on the amount of compound spilled, the size of the water body into which it is spilled, the time at which water consumption occurs relative to the time of the spill, and the amount of contaminated water that is consumed. Based on the spill scenario used in this risk assessment, the concentration of fluridone in a small pond is estimated to range from about 3.6 to 72 mg/L with a central estimate of about 18 mg/L (Worksheet D05).

3.2.3.5. Oral Exposure from Contaminated Fish

Three sets of exposure scenarios are presented: one set for acute exposures following an accidental spill (Worksheets D08a and D08b), one set for acute exposures based on the target application rate (Worksheets D09c and D09d), and the other set for chronic exposures based on estimates of longer-term concentrations in water (Worksheets D09a and D09b). The two worksheets in each of the three sets are intended to account for consumption rates of caught fish among both the general population and subsistence populations. Details of these exposure scenarios are provided in Section 3.2.3.5 of SERA (2007).

In addition to estimated concentrations of the pesticide in water, scenarios involving the consumption of contaminated fish require information about the bioconcentration factor (BCF) in fish. Appendix 1 summarizes several reports of bioconcentration of fluridone in fish. Because fluridone degrades rapidly in water, the estimates of bioconcentration are somewhat variable and represent the processes of uptake and depuration in fish as well as dissipation and degradation in water (e.g., Kamarianos et al. 1989). The study by West et al. (1983) appears to provide the most directly relevant data on bioconcentration factors. This study summarizes a total of 175 bioconcentration measurements in edible tissue (10 species) and whole fish (8 species) from 30 field applications involving three Sonar formulations of fluridone (West et al. 1983, Table XI, p. 584). BCF factors varied remarkably among species. For edible tissue, the average BCF values ranged from 0.94 in bluegills to 2.46 in bullheads. For whole fish, the BCF factors ranged from 1.59 in green sunfish to 15.51 in rainbow trout. For the current risk assessment, the upper bound BCF of 2.46 in edible tissue is used for exposure assessments in the human health risk assessment, under the assumption that most individuals would consume only the fish fillet. As discussed in Section 4.2.2.3, the upper bound BCF of 15.51 for whole fish is used in the ecological risk assessment.

3.2.3.6. Dermal Exposure from Swimming in Contaminated Water

Some of the sites maintained by the Forest Service contain surface water that is intended for or could be used for swimming by members of the general public. To assess potential risks associated with swimming, an exposure assessment is developed for a young woman swimming in surface water for 1 hour (Worksheet D11).

Conceptually and computationally, this exposure scenario is virtually identical to the contaminated gloves scenario used for workers (Section 3.2.2.2)—i.e., a portion of the body is immersed in an aqueous solution of the compound at a fixed concentration for a fixed period of time. The major differences in the two scenarios involve the concentration in water and the surface area of the body that is exposed. For the worker wearing contaminated gloves, the assumption is made that both hands are exposed to the field solution—i.e., the concentration of the compound in the solution that is being applied. For the swimmer, the assumption is made that the entire body surface area is exposed to the expected peak concentrations in ambient water—i.e., the maximum target concentration for fluridone of 150 ppb or 0.15 mg/L. While the swimmer will not be immersed for 1 hour, the entire body surface is used both as a conservative approximation (i.e., the MEI) and to consider intermittent episodes during which the whole body might be immersed or at least wet.

As with the corresponding worker exposure scenario, the 1-hour period of exposure is somewhat arbitrary, and longer periods of exposure are plausible. The 1-hour period, however, is not completely arbitrary but is intended as a unit exposure estimate. In other words, the exposure and consequently the risk will increase linearly with the duration of exposure, as indicated in Worksheet D11. Thus, a 2-hour exposure would lead to a hazard quotient that is twice as high as that associated with an exposure period of 1 hour. In cases in which this or other similar exposures approach a level of concern, further

consideration is given to the duration of exposure in the risk characterization (Section 3.4).

3.2.3.7. Oral Exposure from Contaminated Vegetation

As noted in Section 3.2.3.1.1, scenarios involving the consumption of contaminated vegetation are not relevant to aquatic applications of fluridone.

3.3. DOSE-RESPONSE ASSESSMENT

3.3.1. Overview

The dose-response assessment for the human health risks associated with exposures to fluridone is relatively simple. Forest Service risk assessments typically adopt both acute and chronic RfD values from the U.S. EPA, unless there is a compelling basis to do otherwise. The U.S. EPA's Office of Pesticide Programs derived an acute RfD of 1.25 mg/kg bw for women of child-bearing age, based on a developmental study in rabbits. The EPA did not derive an acute RfD for other members of the general population. Accordingly, in the current Forest Service risk assessment, the acute RfD of 1.25 mg/kg bw is applied to all acute exposure scenarios. This approach, which is somewhat more conservative than that used by the U.S. EPA, reflects the generally conservative risk assessment methods used in all Forest Service risk assessments.

The U.S. EPA derived two chronic RfDs for fluridone: 0.08 mg/kg bw/day from the Office of Research and Development and 0.15 mg/kg bw/day from the Office of Pesticide Programs. The lower RfD is based on a life-time feeding study in rats. This study was reviewed by the Office of Pesticide Programs but was apparently not used because of reporting deficiencies. The Office of Research and Development also reviewed the rat feeding study as well as other supporting toxicity studies and judged that the feeding study using rats was suitable for deriving the lower chronic RfD of 0.08 mg/kg bw/day. Consistent with the conservative risk assessment methods used in all Forest Service risk assessments, the lower chronic RfD of 0.08 mg/kg bw/day is used in the current risk assessment to characterize risks associated with longer-term exposures to fluridone.

3.3.2. Chronic RfD

As noted in Section 3.1.5 (Subchronic or Chronic Systemic Toxic Effects), the U.S. EPA derived two chronic RfD values for fluridone: 0.08 mg/kg bw/day (U.S. EPA/ORD 1987) and 0.15 mg/kg bw/day (U.S. EPA/OPP 2003c). The lower RfD from U.S. EPA/ORD (1987) is based on a NOAEL of 8 mg/kg bw/day from a life-time feeding study in rats in which the LOAEL of about 25 mg/kg bw/day was characterized by decreased body weight as well as increases in liver and kidney weight. The higher RfD from U.S. EPA/OPP (2003c) is based on the NOAEL of 15 mg/kg bw/day from a life-time feeding study in mice (Probst 1981d,e) in which the corresponding LOAEL of 50 mg/kg bw/day was based on biochemical and histopathological indicators of liver damage—i.e., increased alkaline phosphatase activity and an increased incidence of hepatocellular hyperplasia. In deriving the RfDs, both the U.S. EPA/ORD (1987) and U.S. EPA/OPP (2003c) used an uncertainty factor of 100, a factor of 10 for extrapolating from an animal study to humans and a factor of 10 to account for sensitive individuals in the human population.

While the rationale for not using the lower rate NOAEL of 8 mg/kg bw/day as the basis for the chronic RfD in the TRED is not discussed explicitly in U.S. EPA/OPP (2004b), the rationale is probably associated with the classification of this study by OPP as *Supplemental* rather than *Acceptable*. As noted in Section 1 (Introduction), the U.S.

EPA/OPP specifies the study protocols that must be used in submissions to support the registration of pesticides, and OPP evaluates each study in terms of how well the studies meet the requirements of the EPA. The U.S. EPA/OPP uses classifications of *Unacceptable*, *Supplemental*, and *Acceptable* to generally rank each study. Studies classified as *Acceptable*—i.e., all guidelines are met—are generally given preference over studies classified as Supplemental—i.e., the study is valid but some guidelines are not met. As discussed in the primary DER for this study (Probst 1980b) as well as supplemental memoranda (Mauer 1985a,c) and reviews (U.S. EPA/OPP 2004g), the Agency did not classify the chronic rat study as *Acceptable* because of reporting deficiencies.

Conversely, no serious flaws in experimental design or conduct are noted in the rat feeding study used by U.S. EPA/ORD (1987) in deriving the lower RfD of 0.08 mg/kg bw/day. In addition, the rat feeding study along with other chronic and subchronic toxicity studies were reviewed by and are discussed in U.S. EPA/ORD (1987), and confidence in the RfD is classified as *High*. Thus, for the current Forest Service risk assessment, the lower chronic RfD of 0.08 mg/kg bw/day is used for characterizing risks associated with longer-term exposures to fluridone.

3.3.3. Acute RfD

Acute RfD values are used in this and other Forest Service risk assessments to assess the consequences of an exposure event that may occur on only a single day, such as the consumption of water at the peak concentration. This approach is identical to the application of acute RfDs in pesticide risk assessments conducted by the EPA. The EPA derived an acute RfD of 1.25 mg/kg bw (U.S. EPA/OPP 2004d). As noted in Section 3.1.9.1 (Teratology Studies), this acute RfD is based on a developmental study in rabbits (Probst and Adams 1980b) with a NOAEL of 125 mg/kg bw and a corresponding LOAEL for fetal and maternal toxicity of 300 mg/kg bw/day. The RfD was calculated by dividing the NOAEL of 125 mg/kg bw by an uncertainty factor of 100, as with the chronic RfD and for the same reasons.

As is customary in risk assessments prepared by U.S. EPA/OPP, the acute RfD, which is based on a developmental study, is applied by the U.S. EPA only to females from 13- to 50-years of age. While not explicitly discussed in U.S. EPA/OPP (2004d) or other EPA risk assessments, the apparent rationale for this restriction is that the endpoint on which the acute RfD is based, developmental effects, could be seen only in females of child-bearing age.

For other members of the general public, including children, the U.S. EPA/OPP (2004d) did not derive an acute RfD, and derivation of an acute RfD is classified as *Not Applicable* for the following reason:

> *A dose and endpoint were not selected for this population group because there were no effects observed in oral toxicology studies including maternal toxicity in the developmental toxicity studies in rats and rabbits that are attributable to a single exposure (dose).*
> – U.S. EPA/OPP (2004d, p. 13).

As with other Forest Service risk assessments, a different and more conservative approach is taken in the current risk assessment, and the acute RfD is applied to all members of the general public because no data are available to derive an alternative acute RfD. Although using the acute RfD from EPA has an impact on the risk characterization for many pesticides, the impact for fluridone is minimal. The reason that the impact is only minimal is that the hazard quotients associated with most acute exposure scenarios are far below the level of concern. The one exception, the consumption of contaminated water after an accidental spill, is discussed further in Section 3.4.3 (Risk Characterization for members of the general public).

3.4. RISK CHARACTERIZATION

3.4.1. Overview

The risk characterization for both workers and members of the general public is reasonably simple and unambiguous: based on a generally conservative and protective set of assumptions regarding both the toxicity of fluridone and potential exposures to fluridone, there is no basis for suggesting that adverse effects are likely in either workers or members of the general public, even at the maximum application rate that might be used in Forest Service programs.

For workers, no exposure scenarios, acute or chronic, exceed the RfD at the upper bound of the estimated dose associated with the highest application rate of 150 ppb (0.15 mg/L). The hazard quotients for general exposures associated with routine applications of fluridone to surface water are below the level of concern by factors of 20 to 100. Accidental exposure scenarios typically included in Forest Service risk assessments are also below the level of concern. The contaminated glove exposure scenario approaches the level of concern: wearing contaminated gloves for 1 hour results in a hazard quotient of 0.5.

For members of the general public, hazard quotients at the highest application rate are below a level of concern by factors of 20 to 20,000 for longer-term exposures. The upper bounds of acute exposure scenarios are below the level of concern by factors of at least 100. This risk characterization for members of the general public is consistent with the risk characterization presented by the U.S. EPA/OPP in their most recent risk assessment of fluridone.

Acute accidental exposure scenarios for members of the general public that involve the consumption of contaminated water after an accidental spill do exceed the level of concern with a maximum hazard quotient of 7. The accidental spill scenario is standard in all Forest Service risk assessments and is used to suggest the importance of mitigation measures in the event of an accidental spill.

3.4.2. Workers

The risk characterization for workers exposed to fluridone levels associated with the maximum application rate of 150 ppb is summarized quantitatively in Worksheets E02. The quantitative risk characterizations for workers are expressed as hazard quotients: the ratios of the estimated doses from Worksheet E01 to the RfD. For acute exposures—i.e., accidental or incidental exposures—the acute RfD of 1.25 mg/kg/day is used (Section 3.3.3). For general exposures—i.e., daily exposures that might occur over the course of an application season—the chronic RfD of 0.15 mg/kg/day is used (Section 3.3.2).

For general exposures, the hazard quotients range from 0.01 to 0.05 with a central estimate of 0.02. These hazard quotients are below the level of concern (1.0) by a factor of 50 for the central estimate with a range of 20-100. As detailed in Worksheet C01, the magnitude of these hazard quotients is driven by the assumed exposure rates and the

amount of fluridone that is handled. Despite uncertainties in the worker exposure assessment (Section 3.2.2.1), the methods to estimate worker exposure appear to be very conservative—i.e., they may over-estimate exposure. The amount of fluridone that each worker may handle will vary with the application rate, the volume of water being treated, and the number of workers involved in the application. These factors are considered in Worksheet A01 using a water volume of 6 million liters. The water volume of 6 million liters is selected for this risk assessment because it is concordant with water volumes used in EPA assessments of aquatic applications (Section 3.2.2.1). In program-specific applications, the value for the amount of water being treated may require adjustment. Given the very low hazard quotients, however, any such adjustment is not likely to affect the qualitative interpretation of risk. Based on the exposure assumptions and conservative worker exposure rates, there is no basis for asserting that workers will be exposed to fluridone at levels that exceed or even approach the level of concern—i.e., a hazard quotient of 1.

While the accidental exposure scenarios are not the most severe one might imagine (e.g., complete immersion of the worker or contamination of the entire body surface for a prolonged period of time), with respect to workers, these scenarios represent credible accidental exposures related to pesticide application. None of the hazard quotients for accidental exposures approach a level of concern, even at the upper bounds. The highest hazard quotient is 0.5—i.e., the upper bound hazard quotient for wearing contaminated gloves for 1 hour. The hazard quotient is directly proportional to the duration of exposure. Thus, wearing contaminated gloves would lead to a hazard quotient of 1 (i.e., the level of concern) for a 2-hour exposure, a hazard quotient of 2 for a 4-hour exposure, and so on.

The simple verbal interpretation of this quantitative characterization of risk is: under a protective set of exposure assumptions, workers would not be exposed to levels of fluridone that are regarded as unacceptable, so long as reasonable and prudent handling practices are followed.

As discussed in Section 3.1.11.3, granular formulations of fluridone may cause eye irritation with reversible corneal damage. There are no studies in the fluridone literature concerning the irritant effects of liquid formulations to the eye. Nonetheless, the introduction of any chemical in granular or liquid form into the eye should be avoided routinely in the application of any pesticide. Furthermore, cautionary statements to this effect are presented on all product labels for fluridone formulations.

3.4.3. General Public

The risk characterization for members of the general public exposed to fluridone is summarized quantitatively in Worksheet E04. As with workers, the quantitative risk characterizations are expressed as hazard quotients. Acute hazard quotients are based on the acute RfD of 1.25 mg/kg/day (Section 3.3.3), and longer-term hazard quotients are based on the chronic RfD of 0.15 mg/kg/day (Section 3.3.2). Worksheet E04 for members of the general public is based on the maximum application rate of 150 ppb (0.15 mg/L), as is Worksheet E02 for workers.

As indicated in Section 3.2.3.1.1 (Likelihood and Magnitude of Exposure), all upper bounds of exposure assessments used for members of the general public are based on the Most Exposed Individual (MEI). Consequently, the corresponding risk characterizations described in this section encompass the potential for adverse effects associated with recreational areas and other sites that may be used by large numbers of individuals.

Although there are several uncertainties in the longer-term exposure assessments for the general public, as discussed in Section 3.2.3, the upper bounds of hazard quotients associated with the longer-term exposures at the maximum application rate are all below a level of concern. The highest longer-term hazard quotient is associated with the longer-term consumption of contaminated water. The upper bound of this hazard quotient is 0.05, which is below the level of concern by a factor of 20. The other longer-term hazard quotients range from 0.00005 (the lower bound for the consumption of contaminated fish by the general public) to 0.005 (the upper bound for the consumption of contaminated fish by subsistence populations). These hazard quotients are below the level of concern by factors of 200-20,000. Thus, the risk characterization for longer-term exposures is unambiguous: based on the available information and under the foreseeable conditions of application, there is no indication that the general public will be at any substantial risk from longer-term exposure to fluridone, even when the compound is applied at the maximum labeled application rate.

As with chronic exposures, none of the hazard quotients associated with acute non-accidental exposure scenarios exceed the level of concern, even at the upper bounds of the hazard quotients at the maximum application rate (Worksheet E04). The highest upper bound hazard quotient is 0.01 (the consumption of contaminated water by a small child), which is below the level of concern by a factor of 100.

For aquatic applications, only one accidental exposure scenario is considered—i.e., the spill of a large volume of a field solution into a small pond (Section 3.2.3.4.3). The highest hazard quotient for this scenario is 7, the upper bound hazard quotient for child who consumes contaminated water from a small pond immediately after an accidental spill. The central estimate for this exposure scenario is 1.1, modestly above the level of concern. For this accidental scenario, the upper bound of the hazard quotient is also above the level of concern for the consumption of contaminated fish by subsistence populations (HQ = 1.6).

As detailed in Section 3.2.3.4.3, the accidental spill scenario is intentionally extreme—i.e., 200 gallons of a field solution are spilled into a small pond (0.25 acres in surface area and 1 meter deep). This exposure scenario is standard in all Forest Service risk assessments and is used to suggest the importance of mitigation measures in the event of an accidental spill. While typical applications of fluridone are not likely to present a risk to workers or members of the general public, accidental spills would require measures to ensure that members of the general public are not exposed to water contaminated with fluridone. Site-specific assessments of accidental incidents could then be made and longer-term mitigation measures could be developed as needed.

Each of the hazard quotients summarized in Worksheets E04 involves a single exposure scenario. In some cases, however, individuals may come into contact with fluridone via multiple routes of exposure, and, in such cases, risk can be quantitatively characterized simply by adding the hazard quotients for each exposure scenario. For fluridone, considerations about multiple routes of exposure have no impact on the risk assessment. For example, take the upper bounds of the hazard quotients for a combined scenario where an individual swims for 4 hours (HQ = 0.0005 x 4= 0.002), drinks a day's worth of water (HQ = 0.01), and consumes a large amount of fish (typical of a member of a substance population) (HQ = 0.003). In such a case, the combined hazard quotient would be 0.015 (0.002 + 0.01 + 0.003), which is below the level of concern by a factor of about 66.

The risk characterization for members of the general public given in this Forest Service risk assessment is concordant with the assessment given in the most recent U.S. EPA risk assessment in which no exceedances of the level of concern for fluridone were noted in any exposure scenarios (U.S. EPA/OPP 2004b). The types of accidental exposure scenarios that do exceed the level of concern in this Forest Service risk assessment are not considered in EPA risk assessment.

3.4.4. Sensitive Subgroups

The acute RfD is based on reproductive effects (Section 3.3.3). By definition, pregnant women and, more generally, any women of child-bearing age could be classified as a potentially sensitive subgroup. This group could include workers as well as members of the general public. Because the current risk assessment applies the acute RfD to all acute exposure scenarios for workers and members of the general public, this subgroup is explicitly considered in the current risk assessment.

There is no information to suggest that other specific groups or individuals may be especially sensitive to the systemic effects of fluridone. Due to the lack of human data on fluridone, the critical effect, if any, in humans, cannot be identified. High doses of fluridone are associated with toxic effects in the liver (Section 3.1.5). Accordingly, it seems reasonable to speculate that individuals with some types of liver disease could be more sensitive than others to fluridone exposures. In addition, it is obvious that any individuals with a severe disease or in generally poor health may be more sensitive than others to any form of stress, including stresses associated with pesticide exposure.

3.4.5. Connected Actions

Considerations of connected actions are required under NEPA (National Environmental Policy Act). The Council on Environmental Quality (CEQ), which provides the framework for implementing NEPA, defines connected actions (40 CFR 1508.25) as actions which occur in close association with the action of concern; in this case, the use of fluridone as proposed in Section 2. Actions are considered to be connected if they: (i) automatically trigger other actions which may require environmental impact statements; (ii) cannot or will not proceed unless other actions are taken previously or simultaneously, and (iii) are interdependent parts of a larger action and depend on the

larger action for their justification. Within the context of this assessment of fluridone, "connected actions" include actions or the use of other chemicals which are necessary and occur ***in close association*** with use of fluridone.

The use of inerts and adjuvants as well as the occurrence of impurities and metabolites would be classified as connected actions under the CEQ definition. As discussed in detail in Section 3.1.14 (Inerts and Adjuvants), there is little information concerning the toxicity of the inerts in fluridone formulations; moreover, this information does not suggest that inerts in fluridone formulations are likely to impact the risk assessment. This conclusion is supported by comparative data on the toxicity of fluridone and fluridone formulations in aquatic species (Sections 4.1.3.1.1 and 4.1.3.3.1).

U.S. EPA/OPP (2004f) identifies N-methylformamide (NMF) as an environmental metabolite of concern. The formation of NMF in water could be classified as an action connected with the use of fluridone. As discussed in Section 3.1.15.1 (Metabolites), a fuller consideration of the formation and degradation of NMF as well as some very focused monitoring studies indicate that NMF is not likely to form in toxicologically significant or detectable amounts.

3.4.6. Cumulative Effects

Cumulative effects may involve either repeated exposures to an individual agent or simultaneous exposures to the agent of concern (in this case fluridone) and other agents that may cause the same effect or effects by the same or a similar mode of action. Under the Food Quality Protection Act (FQPA), the U.S. EPA is required to consider cumulative effects.

In the TRED on fluridone, the U.S. EPA makes the following assessment:

> *Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to fluridone and any other substances and fluridone does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that fluridone has a common mechanism of toxicity with other substances.*
>
> – U.S. EPA/OPP 2004b, p. 4

As discussed further in Section 4.1.2.4, fluridone does share a common mechanism of herbicidal action with several other herbicides, including norflurazon, diflufenican, and difunon (Sandmann and Albrecht 1990). There is no indication, however, that this mechanism of herbicidal action would be relevant to considerations of potential human health risks. In addition, the Forest Service does specifically consider and address applications of multiple pesticides on a program specific basis.

In terms of repeated exposures, the current risk assessment does specifically consider the effect of repeated and longer-term exposures to fluridone for both workers and members of the general public. The chronic RfD is used as an index of acceptable longer-term exposures. Consequently, the risk characterizations presented in this risk assessment for longer-term exposures specifically address and encompass the potential impact of the cumulative effects of longer-term exposures to fluridone. As discussed in Sections 3.4.2 and 3.4.3, there is no basis for asserting that cumulative adverse effects associated with longer-term or repeated exposures to fluridone are plausible.

4. ECOLOGICAL RISK ASSESSMENT

4.1. HAZARD IDENTIFICATION

4.1.1. Overview

Fluridone is an herbicide used to control unwanted aquatic macrophytes. In aquatic plants, as with terrestrial plants, fluridone acts by inhibiting phytoene desaturase, which leads to decreased levels of carotenes, which, in turn, leads to decreases in chlorophylls, photosynthesis, and carbohydrate stores. While these mechanisms of action appear to be relevant to all plants, the relationship of phytoene desaturase inhibition as well as other biochemical indicators of toxicity are not simply related to gross signs of toxicity, such as decreased biomass. Both laboratory toxicity bioassays as well as field studies indicate marked differences in species sensitivity within aquatic macrophytes. Common target macrophytes, such as watermilfoil and hydrilla, appear to be very sensitive to fluridone, based on measures of reduced biomass. Other species, like wild celery and some species of pondweed (*Potamogeton* sp.), are much more tolerant. The species differences and the apparent lack of a simple correlation between biochemical effects and gross toxic effects appear to be related to the slow-acting nature of fluridone (in terms of progressing from biochemical effects to gross signs of toxicity) and differences in adaptation mechanisms among different species of aquatic macrophytes.

Field applications of fluridone will lead to relatively high peak or target concentrations of fluridone in water, followed by gradual to rapid decreases in fluridone concentrations. The available studies on aquatic macrophytes suggest that the declining pattern of concentrations does not markedly reduce the effects of fluridone on aquatic macrophytes, since the lower residual concentrations seem to impair the ability of aquatic macrophytes to recover from the effects of initially higher target concentrations.

While the laboratory and field data on algae are highly variable, algae appear to be less sensitive than many species of macrophytes to fluridone, and green algae appear to be more sensitive than blue-green algae. For both macrophytes and algae, immature organisms appear to be more sensitive to fluridone, relative to mature organisms of the same species.

While fluridone is an effective herbicide, no specific mechanism of action can be identified in terrestrial or aquatic animals. In both terrestrial and aquatic animals, the most frequently noted sign of short-term high-level exposures is some form of abnormal movement, typically characterized as ataxia or erratic movement. These general signs of toxicity are very often noted in animals after exposures to very large amounts (i.e., doses or concentrations) of pesticides and other compounds, and these signs of toxicity do not necessarily reflect a specific mechanism of action. Based on standard criteria used by the U.S. EPA for categorizing the inherent toxicity of pesticides, fluridone is classified as *Practically Nontoxic* to mammals and birds, and *Slightly Toxic* to *Moderately Toxic* in fish and aquatic invertebrates.

4.1.2. Toxicity to Terrestrial Organisms

4.1.2.1. Mammals

As summarized in the human health risk assessment (see Section 3.1), the toxicity database for mammalian exposure to fluridone is relatively standard for a pesticide. As with the hazard identification in the human health risk assessment (Section 3.1), the hazard identification for species of mammalian wildlife is based on studies in experimental mammals. Thus, the qualitative hazard identification for terrestrial mammals is essentially the same as that in the human health risk assessment. Fluridone is likely to be readily absorbed and eliminated in mammals with extensive metabolism. The liver appears to be the primary target organ (Section 3.1.5); however, there is also concern for decreases in body weight as well as effects on the developing fetus (Section 3.1.9).

For many chemicals, systematic or allometric relationships are apparent between body weight and toxicity (e.g., Boxenbaum and D'Souza 1990). For some chemicals, larger mammals are more sensitive than smaller mammals, and the opposite relationship is true for other chemicals. In terms of acute toxicity, the available data on fluridone are of limited use in assessing differences among species, because all of the available acute toxicity values, such as oral LD_{50} values, are based on limit studies in which only a single dose is used (Section 3.1.4). Based on chronic toxicity studies, however, it appears dogs are less sensitive than rats are to fluridone. As detailed in Section 3.1.5, the chronic NOAEL in dogs is 75 mg/kg bw/day, which is substantially above the chronic NOAEL in rats (8 mg/kg bw/day) and mice (15 mg/kg/day).

As summarized in Section 3.1.4, the EPA classifies fluridone as Category IV in terms of acute oral hazard for humans, based on the LD_{50} value in rats of >10,000 mg/kg bw. The U.S. EPA's Ecological Fate and Effects Division (EFED) uses a conceptually similar classification system in ecological risk assessments (SERA 2007a, Table 4-1). Based on the EFED classification scheme, the LD_{50} value of >10,000 mg/kg bw in rats would be used to classify fluridone as *Practically Nontoxic* to terrestrial mammals. Consistent with this classification and as discussed further in Section 4.4.2.1 (Risk Characterization for Mammals), the levels of exposure of terrestrial mammals to fluridone are far below levels of concern.

4.1.2.2. Birds

The published literature on fluridone does not include information about toxicity to birds. As summarized in Appendix 4, a standard set of toxicity studies was submitted to and reviewed by the EPA: a single dose gavage study in quail, two 8-day dietary studies (i.e., 5 days of dietary exposure and a 3-day recovery period) in mallards and quail, and two standard chronic/reproduction studies in mallards and quail. The results of these studies are unremarkable and suggest that fluridone poses no identifiable risks to birds.

In the general categories used by the EPA for acute toxicity studies in birds (SERA 2007a, Table 4-1), fluridone is classified as *Practically Nontoxic* to birds. The classification is based on both the acute gavage LD_{50} of >2000 mg/kg in quail (Kehr et al.

1979b) as well as the acute dietary LC_{50} values of >5000 ppm in both mallards (Kehr et al. 1978a) and quail (Zucker et al. 1982).

Similar results are reported for the chronic/reproduction studies in birds. As described in SERA (2007a, Section 4.1.2.2), the chronic/reproduction studies in birds do not involve exposures over a life-time, as is the case with studies on mammalian exposure. Instead, birds are fed for about 1.5-2 months prior to mating and for an additional 10 weeks after mating. In both studies involving mallards (Ringer et al. 1981a) and quail (Ringer et al. 1981b), no adverse effects attributable to treatment were observed at dietary concentrations of up to 1000 ppm. While the EPA review of Ringer et al. (1981b) suggested some issues with animal husbandry (as detailed in Appendix 3), both of these studies were classified by the EPA as *Core*. The term *Core* is an older designation analogous to the terms *Acceptable* or *Guideline*.

4.1.2.3. Terrestrial Invertebrates

Very little information is available on the toxicity of fluridone to terrestrial invertebrates. Because this pesticide is used primarily as an aquatic herbicide, the limited nature of the data has little impact on the current risk assessment.

In an EPA review (Zucker et al. 1983), a contact NOEC of 362.58 µg/bee is reported and attributed to a ... *study performed by E. Atkins (U. of California)*; nevertheless, the compendia of studies by Atkins et al. (1975) do not include a toxicity value for fluridone. Moreover, this toxicity value is not in ECOTOX, which is the EPA's database of toxicity values for ecological risk assessments (U.S. EPA/ORD 2008). While the source of this toxicity value is unclear, Zucker et al. (1983) clearly indicate that the study was available and was reviewed by the EPA. Whatever the case, this is the only reported toxicity value in terrestrial insects for fluridone.

Although not reviewed in Zucker et al. (1983), one soil incorporation bioassay using earthworms was submitted to the U.S. EPA/OPP (Karnak et al. 1978a). This study involved a 14-day exposure to fluridone at soil concentrations of 0 (control), 10.3 or 102.5 ppm using two replicates with five earthworms/test vessel. No mortality was noted except for one worm in the control group. Two worms at 10.3 ppm and one at 102.6 ppm were flaccid after 14 days, but showed no appreciable changes in weight, compared with controls or other treated worms. Thus, no dose-related adverse effects attributable to fluridone were noted. This study was classified by the EPA as *Supplemental*. In this case, the classification of *Supplemental* is used simply because this test was not required. In other words, because this type of study is not required, the U.S. EPA does not have guidelines for this type of study. Thus, the study cannot be classified as *Guideline* or *Acceptable*. In this instance, the classification of the study as *Supplemental* does not imply a deficiency in the study.

4.1.2.4. Terrestrial Plants (Macrophytes)

For terrestrial herbicides, testing requirements for terrestrial plants are typically very detailed and rigorous involving bioassays for seedling germination and emergence (soil exposures) as well as vegetative vigor (foliar exposures) in several species of dicots and

several species of monocots. These kinds of studies have not been conducted on fluridone, presumably because this herbicide is registered only for aquatic applications. Thus, the toxicity of fluridone to terrestrial plants is not a major consideration in the current risk assessment. Nonetheless, fluridone was once evaluated as a terrestrial herbicide, and much of the early literature on the mechanisms of the phytotoxic action of fluridone involves terrestrial plant species (e.g., Berard and Rainey 1978).

As noted in the early work on fluridone (Bartels and Watson 1978; Loh et al. 1979a), the pesticide is a reversible noncompetitive inhibitor of phytoene desaturase, an enzyme responsible for the metabolism of phytoene to phytofluene, a precursor of carotene. Thus, fluridone is similar to other herbicide inhibitors of phytoene desaturase, like norflurazon, diflufenican, and difunon (Sandmann and Albrecht 1990). The inhibition of carotene synthesis is a critical effect because carotene protects chlorophyll from photooxidation (Wagner et al. 2002). Thus, the inhibition of carotene synthesis decreases photosynthesis, which results in a corresponding loss of chlorophylls, leading to discoloration (bleaching or chlorosis) in plants. These effects impair the ability of the plant to produce nutrients, resulting in a decrease in growth rate. At sufficiently high exposures over prolonged periods of time, the affected plant will die (Rafii and Ashton 1979). As detailed by Jin-Seog et al. (2004), the mechanism of action of fluridone may differ according to the life stage of the plant, with mature plants being damaged primarily by oxidative stress, while developing plants may be damaged by carbohydrate insufficiency secondary to a reduction in photosynthesis.

In addition to interfering with carotene production, fluridone will also block or reduce the synthesis of abscisic acid in terrestrial plants (Moore and Smith 1984; Ober and Sharp 1997; Oishi and Bewley 1990; Pence 1992). Abscisic acid is a plant hormone involved in root development and stress response in plants. The inhibition of abscisic acid production may be linked to the inhibition of carotene synthesis in that one pathway for the synthesis of abscisic acid in plants may proceed through the photolysis of carotenoids (Ng and Moore 1985). These mechanisms in terrestrial plants appear to be relevant to potential effects in aquatic plants (Section 4.1.3.4) in that both abscisic acid and carotene are critical to the health of aquatic plant species (e.g., Kobayashi et al. 1997; Sarmad et al. 2007).

4.1.2.5. Terrestrial Microorganisms

In the published literature on fluridone, there is no information about the toxicity of fluridone to terrestrial microorganisms. Early internal reviews by the EPA (Zucker et al. 1982, 1983) on the environmental toxicology of fluridone indicate that fluridone is not likely to cause adverse effects in bacteria, fungi, or protozoa. The studies on which these statements are based are not specified.

4.1.3. Aquatic Organisms

4.1.3.1. Fish

4.1.3.1.1. Acute Toxicity

Standard 96-hour toxicity bioassays to assess the effects of acute exposure of fish to fluridone are summarized in Appendix 5. Acute toxicity studies were conducted in four species of freshwater fish (bluegill sunfish, channel catfish, fathead minnows, and rainbow trout) and one species of saltwater fish (sheepshead minnow). All of these species are commonly used in toxicity tests submitted for the registration of pesticides.

While the database on the acute toxicity of fluridone to fish is not particularly large or complex, there does appear to be redundancy in reporting. Most of the available acute toxicity studies on fluridone were initially published by Hamelink et al. (1986). This publication appears to be the product of the collaboration between Lilly Research Laboratories and the U.S. Fish and Wildlife Service. As noted in Section 2, fluridone was initially developed by Eli Lilly (Tomlin 2004). Most of the information published in the Hamelink et al. (1986) paper is also summarized in Mayer and Ellersieck (1986), a compendium of aquatic toxicity studies conducted by the U.S. Fish and Wildlife Service. As noted in Appendix 5, data from Mayer and Ellersieck (1986) that are obvious duplicates of data from Hamelink et al. (1986) are not included in Appendix 5. A few other acute toxicity studies in fish were identified in the DERs from the EPA (Probst and Negilski 1981b,c; Heitmuller 1981d,h) as well as in the published literature (Paul et al. 1994).

One minor but potentially confusing reporting difference between Hamelink et al. (1986) and Mayer and Ellersieck (1986) involves toxicity data on fluridone formulations. Hamelink et al. (1986) report toxicity values for a formulation specified as *...48% active ingredient (479 g/L)*. Mayer and Ellersieck (1986) report results for a formulation characterized as a *41% liquid*. Hamelink et al. (1986) are clearly dealing with a liquid Sonar formulation. As specified in Table 2, Sonar AS (from SEPRO) and the earlier Avast! Aquatic Herbicide formulation (from Griffin) both contain 4 lb a.i./gallon, which is equivalent to 479.4 g/L. Thus, the 48% formulation referred to by Hamelink et al. (1986) refers to 48% w/v. Apparently, the 41% liquid formulation referenced in Mayer and Ellersieck (1986) refers to 41% w/w, the approximate composition of Sonar AS (41.7 % w/w).

The one substantial discrepancy between the data in Hamelink et al. (1986) and Mayer and Ellersieck (1986) involves the toxicity of the a.i. relative to the formulation in fathead minnows. Hamelink et al. (1986) reports LC_{50} values for technical grade fluridone as 22 mg/L with a 95% confidence interval of 17 to 28 mg/L, which is identical to the value reported in Mayer and Ellersieck (1986). For the formulation, however, Hamelink et al. (1986) do not report an LC_{50} value for fathead, and the study simply indicates that the LC_{50} is greater than 9.5 mg/L but less than 10.2 mg/L. Mayer and Ellersieck (1986, p.245), on the other hand, report an LC_{50} for the fluridone formulation as 41 mg/L with a 95% confidence interval of 32 to 52 mg/L. This discrepancy is somewhat significant because the other paired studies on the toxicity of technical grade fluridone and the

fluridone formulation reported in Hamelink et al. (1986) indicate that the fluridone formulation is generally less toxic and never substantially more toxic than technical grade fluridone. In discussing the paired studies in fish along with the studies in invertebrates (covered in Section 4.1.3.3 of this risk assessment), Hamelink et al. (1986, p. 93) note that *…a statistical evaluation with 13 pairs of the studies demonstrated that there was no significant (p = 0.05) difference in the toxicity of the two test materials*.

The acute toxicity values for fluridone range from 1.8 mg/L in the bioassay on walleye from the study by Paul et al. (1994) to 22 mg/L in the study in fathead minnows in the study by Hamelink et al. (1986). While this range is not remarkable (i.e., a factor of about 12), the specific values span two toxicity classifications used by the U.S. EPA (SERA 2007a, Table 4-1)—i.e., *Moderately Toxic* to fish ($LC_{50} \geq 1$ mg/L but < 10 mg/L), and *Slightly Toxic* to fish ($LC_{50} \geq 10$ mg/L but < 100 mg/L). Hamelink et al. (1986) conducted a series of bioassays trout (n=12) and catfish (n=10) at different temperature, pH, and water hardness (see Hamelink et al. 1986, Table 2, p. 89). There are no substantial or consistent differences in toxicity to fish with these exposure variables.

Sublethal effects in fish are not described extensively in the studies available on fluridone. The most consistently noted signs of toxicity include hypoactivity, prostration, and irregular swimming behavior (Probst and Negilski 1981b,d; Kehr et al. 1978d). These signs of toxicity are relatively similar to effects observed in mammals after exposure to fluridone—i.e., weakness and ataxia. Like the effects observed in mammals (Section 3.1.6, Effects on the Nervous System), the effects observed in fish are very general and do not necessarily indicate a neurotoxic mechanism.

Neither the published studies nor the study reviews (DERs) from U.S. EPA/OPP give full dose-response data or slopes of the dose-response curves. Karnak et al. (1978b) did note an apparently steep dose-response curve in bluegill sunfish, with no mortality at 9 mg/L and 90% mortality at 12.5 ppm. As discussed above, Hamelink et al. (1986) report an LC_{50} for a fluridone formulation in fathead minnows as greater than 9.5 mg/L but less than 10.2 mg/L. This type of report generally suggests that partial mortality was not observed at one or both of the values, which would also suggest a steep dose-response curve. While not providing full dose-response data, Paul et al. (1994) do provide information, considered further in the dose-response assessment, on NOEC and LOEC values. Moreover, in several instances, the interval between the NOEC and LOEC is less than 2 (Appendix 5).

4.1.3.1.2. Chronic Toxicity

Two studies are available on the longer-term effects of fluridone to fish: a 60-day growth and survival study in channel catfish and a life-cycle study in fathead minnows (Appendix 5). Both of these studies are part of the publication by Hamelink et al. (1986). The fathead minnow study is also reviewed in an EPA DER with a citation to Probst et al. (1981). As with the acute toxicity studies discussed above, it is not unusual for the same study to be submitted to the EPA for pesticide registration (i.e., Probst et al. 1981) and published separately in the open literature—i.e., (Hamelink et al. 1986). Separate entries

for the fathead minnow study are given in Appendix 5 for Hamelink et al. (1986) and Probst et al. (1981), because the DER from EPA contains some relevant commentary that is not included in Hamelink et al. (1986).

Both the 60-day day study in channel catfish and the life-cycle study in fathead minnows yielded essentially the same result: a NOEC of 0.5 mg/L for catfish and 0.48 mg/L for fatheads. In the catfish study, growth was significantly reduced at 1 mg/L. No significant differences in survival were noted at 1 mg/L. In the 2 mg/L group, reported survival was substantially less than controls on test Day 30 (i.e., 94% survival in controls and 70% survival in the 2 mg/L group). As discussed by Hamelink et al. (1986, p.91), this mortality was associated with a malfunction in the proportional diluter … *on the 20th day resulted in an approximate 2.5-fold increase in exposure concentrations.*

The fathead minnow study is analogous to the 2-generation reproduction study in mammals (Section 3.1.9.2.) in that the fish are reared from egg to maturity (F_0) and a subset of these fish are mated to produce one or more sets of offspring (F_1). In the fathead minnow study, no effects on growth, survival, or hatching were noted at 0.48 mg/L. No eggs (F_1 offspring) hatched, however, at the two next higher concentrations, 0.96 and 1.9 mg/L. For these exposure groups, the study was continued using eggs from either the control group or the 0.12 mg/L exposure group. As with some of the acute toxicity studies, this pronounced difference between egg hatching in the 0.48 mg/L group (no effect) and the 0.96 mg/L group (no hatching) suggests a relatively steep dose-response relationship.

4.1.3.2. Amphibians

There is no information about the toxicity of fluridone to amphibians in either the open literature or the studies submitted to the U.S. EPA. Specifically, toxicity data involving the exposure of amphibians to fluridone are not contained in either the U.S. EPA ECOTOX database (U.S. EPA/ORD 2008) or the database on amphibian and reptile toxicity data maintained by the Canadian National Wildlife Research Centre (Pauli et al. 2000).

4.1.3.3. Aquatic Invertebrates

4.1.3.3.1. Acute Toxicity

The data on the acute toxicity of fluridone to aquatic invertebrates is summarized in Appendix 6. The data are similar to toxicity data on fish (Section 4.1.3.1) in that most toxicity values are reported as time-specific LC_{50} values: 48-hours for smaller invertebrates (i.e., daphnids, midges, oysters) and 96 hours for larger invertebrates (amphipods, pink shrimp, blue crabs). There is one fluridone study on crayfish involving a 14-day exposure.

As is also the case with fish, there is some redundancy in reporting. Most of the toxicity information on aquatic invertebrates is published in the study by Hamelink et al. (1986) and Naqvi and Hawkins (1989). An early study by Arnold (1979) provides some semi-quantitative information, as discussed below. All of the reported acute toxicity values

given in the compendium by Mayer and Ellersieck (1986) are taken from the published study by Hamelink et al. (1986), and there are no apparent discrepancies in the reporting. Thus, the Mayer and Ellersieck (1986) compendium is not further considered. Apparently, some of the daphnid and shrimp toxicity studies in Hamelink et al. (1986) were submitted and reviewed separately by U.S. EPA/OPP (e.g., Heitmuller 1981a; Kehr et al. 1978c; Probst and Negilski 1981a). These studies are summarized in Appendix 6 because they provide some dose-duration data as well as a brief description of signs of toxicity.

The toxicity values for aquatic invertebrates span a much wider range than those for fish. As noted in Section 4.1.1, reported 96-hour LC_{50} values in fish encompass a relatively modest range: 1.8 to 22 mg/L or about a factor of 12. For aquatic invertebrates, the acute toxicity values span a factor of over 50, ranging from LC_{50} values of 1.3 mg/L (several bioassays in midges from Hamelink et al. 1985) to up to 71 mg/L (juvenile blue crabs in the study by Heitmuller 1981b). Based on the EPA ranking scheme for toxicity (SERA 2007a, Table 4-1), this range of LC_{50} values can be used to classify fluridone as *Moderately Toxic* ($LC_{50} \geq 1$ mg/L but <10 mg/L) to *Slightly Toxic* ($LC_{50} \geq 10$ mg/L but <100 mg/L) to aquatic invertebrates.

For many pesticides, daphnids (a very small zooplankton) are typically the most sensitive aquatic invertebrates. For fluridone, however, the acute LC_{50} values for daphnids range from about 3.6 to 6.3 mg/L. Speculatively, the greater sensitivity of midge larvae to fluridone exposure, relative to daphnids, may relate to the type of bioassay conducted. While Hamelink et al. (1986) do not specify the protocol that was used for the midge bioassay, midges (which are benthic invertebrates) are typically tested in a sediment-water system (e.g., U.S. EPA/OPPTS 1996a) whereas daphnids are tested only in water. As noted in the publications by Muir et al. (1982, 1983), fluridone will partition from water to sediment and will bioconcentrate in midges by factors of about 10 to 20 at high concentrations and factors of up to 128 at lower concentrations. Thus, the lower LC_{50} values reported for midges may reflect exposure to higher concentration of fluridone in sediment pore-water than are reflected in the nominal or measured concentrations in the water column. No substantial impact on benthic organisms has been reported in field studies but the reports are not very detailed. In the study by Arnold (1979), pond treatment with 300 ppb fluridone had little impact on benthic organisms, but treatment with 1000 ppb decreased populations. Similarly, Sanders et al. (1980) reported no substantial impact on benthic organisms after fluridone treatments at initial concentrations of about 20 to 50 pp.

Hamelink et al. (1986) conducted several paired bioassays using technical grade fluridone and a formulation that is consistent with Sonar AS. None of the paired bioassays noted a substantially higher toxicity in the formulation, relative to technical grade fluridone. One somewhat unusual difference is apparent in the toxicity studies on amphipods in which the LC_{50} values for technical grade fluridone are 2.1 mg/L (soft water) and 4.1 mg/L (hard water), while the LC_{50} values for the formulation are >32 mg/L in both soft and hard water. Solubility issues were noted in some studies involving the fluridone formulations (Probst and Negilski 1981a; Hollister 1981b). While Hamelink et al. (1986)

note solubility limitations in the chronic bioassays, they do not mention solubility issues in the acute bioassays.

Very little information is available on the signs of toxicity in aquatic invertebrates that are associated with exposure to fluridone. At sublethal exposures – i.e., 2 mg/L – Kehr et al. (1978c) report hypoactivity in daphnids. This is consistent with signs of toxicity in both mammals and fish (Section 4.1.3.1) but this is a very general and common sign of toxicity for many toxic agents at elevated and physiologically significant levels of exposure.

4.1.3.3.2. Chronic Toxicity

Hamelink et al. (1986) include three chronic toxicity studies in aquatic invertebrates: a 60-day growth and survival study in amphipods, a 30-day emergence study in midges, and a 21-day reproduction study in daphnids. All three studies involved exposure to technical grade fluridone.

Unlike the case with the acute toxicity studies in which the midge was the most sensitive species, daphnids are the most sensitive species in chronic toxicity studies, with a nominal NOEC of 0.2 mg/L and a corresponding LOEC 0.4 mg/L for decreased number of offspring. In midges and amphipods, the NOEC values were both 0.6 mg/L, and the LOEC values were 1.2 mg/L. While the daphnid study involved the briefest period of exposure, daphnids are very short-lived organisms, and the standard 21-day study is essentially a life-cycle study in which the F_0 or parental generation is exposed from Day 1 throughout its lifespan and is allowed to produce several F_1 broods. The NOEC of 0.2 mg/L is referenced as *nominal* because no statistically significant differences between control survival and numbers of offspring were noted at 0.2 mg/L. Nonetheless, at the concentration of 0.2 mg/L, adult survival was only 80% of controls and the production of young was only 55% of controls (see Hamelink et al. 1986, Table 3, p. 90). While these differences are not statistically significant, the responses may be viewed as biologically significant and are substantially greater than the responses at 0.1 mg/L—i.e., 95% adult survival and a significant increase in the production of offspring—i.e., 173% of controls. This effect is discussed further in the dose-response assessment (Section 4.3.3.3).

4.1.3.4. Aquatic Plants

4.1.3.4.1. Macrophytes

For many pesticides, including many herbicides, toxicity data on aquatic macrophytes are limited to relatively standardized bioassays on duckweed, either *Lemna gibba* or *Lemna minor* (e.g., U.S. EPA/OPPTS 1996b). Fluridone, however, is an aquatic herbicide registered for the control of aquatic macrophytes; accordingly, there is a relatively large and diverse literature on the effects of fluridone on aquatic macrophytes. Laboratory toxicity studies on fluridone are summarized in Appendix 6, and aquatic field studies, many of which focus on the effects of fluridone on aquatic macrophytes, are summarized in Appendix 7.

As noted in Section 4.1.2.4 (Terrestrial Plants), the biochemical mechanism of action for fluridone involves the inhibition of phytoene desaturase which results in an inhibition of carotene synthesis. This biochemical mechanism leads to general oxidative damage, reduced photosynthesis, and bleaching of plant tissue (both secondary to chlorophyll destruction), carbohydrate insufficiency (resulting in reduced plant growth), and eventually plant death. This general series of effects occurs in aquatic macrophytes as well as terrestrial macrophytes. While biochemical effects may occur very quickly, overt signs of toxicity take longer to develop. Hence, fluridone is classified as a relatively slow acting herbicide (e.g., Anderson 1981; Doong et al. 1993; Nelson et al. 1998; Netherland and Getsinger 1995a; Netherland et al. 1993; Poovey et al. 2004, 2008).

While the inhibition of phytoene desaturase is clearly a biochemical mechanism of action, desaturase inhibition and gross signs of toxicity—e.g., decreased growth or plant mortality—do not appear to be simply correlated. This finding is illustrated in several of the studies summarized in Appendix 7 (i.e., Anderson 1981; Doong et al. 1993 with MacDonald et al. 1993; Netherland and Getsinger 1995a; Poovey et al. 2004).

The study by Poovey et al. (2004) provides the best detail as an example of the relationship of biochemical response to growth inhibition. In this study, five plant species were assayed: Eurasian watermilfoil (*Myriophyllum spicatum*), wild celery (*Vallisneria americana*, also referred to a tape grass or eelgrass), *Elodea canadensis*, sago pondweed (*Stuckenia pectinata*), and Illinois pondweed (*Potamogeton illinoensis*). As detailed in Appendix 7, each species was exposed to fluridone at target concentrations of 0, 6, 12, or 24 ppb for 56 days. Observations included measures of biomass as well as shoot concentrations of phytoene, β-carotene, and chlorophylls. Data on β-carotene levels and NOEC values for biomass are illustrated in Figure 4 of the current risk assessment. The data on β-carotene are taken from Table 3 in Poovey et al. (2004) but are normalized to the proportion of β-carotene with respect to controls. Data on NOEC values are taken from Figure 6 in Poovey et al. (2004) and are indicated on the x-axis in Figure 4 by downward pointing arrows. Data on β-carotene is for Day 28 of exposure because this is the only time in which β-carotene data are presented for all five species. The biomass data are for Day 56.

As illustrated in Figure 4 of this risk assessment, there is no clear relationship between the reduction in β-carotene and the NOEC values among species. While substantial scatter among species is apparent at 6 ppb, the overall concentration-response relationships for β-carotene reduction are similar. In terms of biomass reduction, however, watermilfoil is clearly the most sensitive species with a LOEC of 6 ppb and wild celery is clearly the most tolerant species with a NOEC of 24 ppb. While not illustrated in Figure 4, the available data on β-carotene at Day 56 as well as additional data on chlorophyll reduction at Days 28 and 56 (Table 3 in Poovey et al. 2004) also do not suggest a clear relationship between biochemical measures of effect and biomass reduction.

The reasons for the lack of an apparent correlation between biochemical measures of toxicity and gross signs of toxicity do not appear to be well understood. It seems likely

that many different factors may be involved, and that the importance of the different factors may vary among species. For example, Marquis et al. (1981) noted that sago pondweed and Richardson pondweed (*Potamogeton* sp) translocate fluridone slowly, which might account for the relative tolerance of *Potamogeton* sp noted in the bioassays by Poovey et al. (2004) as well as in field studies by Smith and Pullman (1997), as detailed in Appendix 8. While somewhat speculative, Sprecher et al. (1993) noted a greater increase in peroxidase activity in hydrilla, relative to watermilfoil. While increased peroxidase activity may be viewed as an indicator of stress, it may also be viewed as an adaptive response to oxidative damage. As discussed further in Section 4.3.3.4 (Dose-Response for Aquatic Plants), the endpoints selected for defining toxicity values are all based on observable growth inhibition, because these endpoints more clearly relate to intent of fluridone applications—i.e., vegetation management—and provide a basis for assessing biologically and ecologically significant differences among species.

Another common feature in all of the toxicity studies on macrophytes is the lack of uniformity in the concentrations of fluridone in water over the course of the bioassays. Again using Poovey et al. (2004) as an example, the concentrations listed in Appendix 7—i.e., 6, 12 and 24 ppb—correspond to nominal or target concentrations that are analogous to those specified on the product labels (Section 2). As noted in Table 2, the half- life of fluridone in water is variable, with estimates ranging from 1 to nearly 100 days. In the study by Poovey et al. (2004), the concentrations of fluridone in water declined over time with approximate first-order half-lives from about 23 to 25 days. While details of fluridone concentrations in water are not reported in all studies, it is certain that the reported nominal concentrations were not evenly maintained in those studies that involve prolonged periods of exposure. While these variable concentrations may be viewed as a complication, they reflect conditions in the field studies summarized in Appendix 8 and illustrated in Figures 2 and 3 of the current risk assessment. For example, Netherland and Getsinger (1995b) note that recovery from early injury caused by initially high treatment levels—i.e., target application rates—is inhibited by much lower residual concentrations of fluridone (e.g., 1—3 ppb). Furthermore, this inhibition of recovery may account for the long-term control of aquatic macrophytes that can be achieved with declining field concentrations of fluridone.

The impact of fluridone on aquatic macrophytes may also be affected by the stage of development, the occurrence of plant pathogens, and the development of resistance. The impact of life-stage is illustrated most clearly in the study on hydrilla in which young plants appeared to be much more sensitive to fluridone, relative to mature plants, in terms of both biochemical measures of toxicity (Doong et al. 1993) as well as growth inhibition (MacDonald et al. 1993). The study by Nelson et al. (1998) noted that co-exposures to fluridone and a fungal plant pathogen (M*ycoleptodiscus terrestris*) substantially enhanced toxicity to hydrilla, relative to exposures to fluridone alone. Consistent with the species variability in other studies, Nelson et al. (1998) noted that nontarget species like American pondweed are less susceptible to fluridone as well as to fluridone and pathogen co-exposures. Speculatively, it seems that fluridone toxicity may generally enhance the impact of plant pathogens, particularly in sensitive species of aquatic macrophytes. The

development of genetic resistance is a common issue with pesticides. Resistance to fluridone has been demonstrated in field populations of hydrilla that are more tolerant to fluridone exposures by factors of 2-6 (Arias et al. 2005, 2006; Michel et al. 2004).

4.1.3.4.2. Algae

Fluridone is not registered as an algaecide, and the amount of information regarding the toxicity of fluridone to algae is limited, relative to the information on macrophytes. Nevertheless, the available information is summarized in Appendix 7, additional observations from field studies are summarized in Appendix 8.

The effects of fluridone on algae, as is true with macrophytes, are strongly related to the duration of exposure, which must be considered when comparing studies in different species. For example, Hess (1980) reports a NOEC of 329 ppb for the freshwater green alga, *Chlamydomonas eugametos*. This NOEC, however, is based on an exposure period of only 48 hours. As illustrated in the study by Schrader et al. (1997) with another species of freshwater green alga, (*Scenedesmus capricornutum*), a concentration of 329 ppb caused no marked growth inhibition after Day 1 but caused modest reduction in growth by Day 2 which progressed over 6 days of exposure. The significance of exposure duration is similarly demonstrated in the studies by Burkhart and Stross (1990) and Trevors and Vedelage (1985). Also in algae, as in macrophytes, biochemical responses—i.e., the inhibition of carotenoid synthesis—occur more quickly and at lower concentrations than biomass inhibition (Millie et al. 1990).

Two fluridone studies (Schrader et al. 1997; Trevors and Vedelago 1985) involve parallel bioassays on green alga and blue-green alga (cyanobacteria), and, in both studies, green algae were somewhat more sensitive than blue-green algae. The study by Trevors and Vedelago (1985) also noted a marked difference in the sensitivity of green algae (*Scenedesmus quadricauda*) based on culture conditions. With exposure to fluridone at the start of culturing, growth was completely inhibited at a fluridone concentration of 0.5 mg/L. When fluridone was added to a mature culture (i.e., on Day 7 of culturing), no reduction in growth occurred at 1 mg/L and only a modest reduction in growth was noted at 10 mg/L during 14 days of exposure. This result is similar to observations in fluridone studies in which immature macrophytes appear to be much more sensitive than older plants (Doong et al. 1993; MacDonald et al. 1993).

There are few field studies regarding the effects of fluridone on algae; moreover, the results of the available field studies are generally inconsistent. According to Arnold (1979), fluridone concentrations of 1000 ppb (1 mg/L) caused only transient decreases in phytoplankton over a 22-day observation period. At initial fluridone concentrations in the range of 20 to 50 ppb, Sanders et al. (1980) report no consistent impact on phytoplankton. Kamarianos et al. (1989), however, reported a substantial decrease in phytoplankton density at a treatment rate of 42 ppb that continued over an 84 day observation period. The field study by Struve et al. (1991) suggests that the inconsistent reports may relate to differences in site-specific conditions that are not well characterized. In this study, two applications of fluridone, separated by 25 days, were made at a target concentration of 125 ppb to two fish ponds and algal populations were

monitored for 2 weeks after the last application. In one pond, significant decreases were noted in both phytoplankton density and assays for chlorophyll *a*, and these changes persisted over the course of the study. In the other pond, decreases in phytoplankton density and chlorophyll-*a* were much less marked, and no substantial differences were noted at 2 weeks after the last application. Struve et al. (1991) note the inconsistency; however, they do not suggest any differences between the two ponds that would account for this disparity.

As with macrophytes, resistance to fluridone was demonstrated in both green algae (Chen et al. 2003) and blue-green algae (Sandmann and Frase 1993). The extent to which resistant strains of algae might account for some of the inconsistencies reported in field studies regarding the effects of fluridone on algae is unclear.

4.2. EXPOSURE ASSESSMENT

4.2.1. Overview

The exposure assessments for the ecological risk assessment generally parallel those used for the general public in the human health risk assessment. In other words, the exposure scenarios are similar in the basic assumptions concerning the application of fluridone, and the differences in the estimated doses from those in the human health risk assessment are attributable to differences in body size and consumption rates for food or water. Also, as in the human health risk assessment, the exposure scenarios for terrestrial vertebrates are a subset of those used in most Forest Service risk assessments. Some exposure scenarios, such as the consumption of terrestrial vegetation, are not relevant to aquatic applications of fluridone.

The exposure scenarios for terrestrial wildlife are summarized in Worksheet G01 of the EXCEL workbook that accompanies this risk assessment. The highest exposure scenarios involve the accidental spill of 200 gallons of a field solution into a small pond. The estimated doses for birds and mammals cover a relatively narrow range: from about 0.5 to 20 mg/kg body weight. The expected non-accidental acute exposures are much lower, spanning a range from about 0.02 to 0.04 mg/kg body weight. Because fluridone degrades and dissipates in water with half lives of about 5 to 100 days, the range of the expected doses in the longer-term exposure scenarios is very low: from about 0.002 to about 0.25 mg/kg body weight/day.

Exposure of aquatic organisms to fluridone is taken as the nominal application rate or target concentration. In the EXCEL workbook that accompanies this risk assessment, the maximum application rate of 150 ppb is used. The consequences of using lower application rates are considered in the risk characterization.

4.2.2. Terrestrial Animals

All exposure scenarios for terrestrial animals are summarized in Worksheet G01 in the EXCEL workbook that accompanies this risk assessment (Attachment 1). As with the exposure assessments for members of the general public (Section 3.2.3), the exposure assessments for terrestrial animals are a subset of those typically included in Forest Service risk assessments. Fluridone will be applied directly to surface water; consequently exposure scenarios concerning the consumption of contaminated vegetation or fruit, the direct spray of a small mammal, and the consumption of a sprayed small mammal by a predator are not included in the ecological risk assessment.

While not all standard exposure scenarios are relevant to fluridone applications, the section designations for the excluded scenarios are given below as a matter of convenience for individuals who regularly use many different Forest Service risk assessments—i.e., the section designations in all Forest Service risk assessments are consistent.

4.2.2.1. Direct Spray

This scenario is not relevant to aquatic applications.

4.2.2.2. Contact with Contaminated Vegetation

This scenario is not relevant to aquatic applications.

4.2.2.3. Ingestion of Contaminated Vegetation or Prey

This scenario is not relevant to aquatic applications.

4.2.2.4. Ingestion of Contaminated Water

Since ingestion of contaminated water by terrestrial wildlife is likely to occur, three sets of exposure scenarios, each involving water consumption by a small mammal and a small bird, are included for an accidental spill (Worksheets F05a and F05b), the peak expected concentration in water (Worksheets F06a and F06b), and the longer-term consumption of contaminated water (Worksheets F07a and F07b). The accidental spill scenario is identical to that considered in the exposure assessment for members of the general pubic (Section 3.2.3.4). Also like the exposure assessment for members of the general public, the peak concentration in surface water is taken as the target application rate. Although longer-term exposures are unlikely, they are considered based on a 90-day average using the target application rate and the estimated field dissipation half-lives in surface water of 20 (5–97) days, as detailed in Section 3.2.3.4. Although Worksheets F07a and F07b calculate the longer-term doses based on water consumption estimates for a small mammal and a small bird, respectively, both of these worksheets use the longer-term concentrations in water calculated in Worksheet B04b.

The exposure scenarios for contaminated water are based on metabolic water requirements, and the assumption is made that the mammal or bird gets all of its water from the contaminated water body. In most instances, both mammals and birds may obtain a significant fraction of their metabolic water requirements from natural food sources—e.g., vegetation or prey. As discussed further in Section 4.4 (Risk Characterization), these conservative assumptions have no impact on the interpretation of risk because the resulting hazard quotients for terrestrial mammals and birds are far below the level of concern.

4.2.2.5. Oral Exposure from Contaminated Fish

The consumption of contaminated fish by a a fish-eating bird is handled similarly to the corresponding exposure scenarios for human health (Section 3.2.3.5). As with the exposure scenarios in the human health risk assessment, three specific exposure scenarios are provided based on an accidental spill (Worksheet F08), expected peak concentrations (Worksheet F09a), and expected longer-term concentrations (F09b).

The only exception involves the bioconcentration factor (BCF) used for the longer-term exposure scenario. In the human health risk assessment, the longer-term BCF is taken as 2.46 based on bioconcentration in fish muscle—i.e., fish fillet—under the assumption that most members of the general public will not consume the entire fish. For wildlife, the assumption is made that the entire fish is consumed. Thus, a higher BCF of 15.51 is

used based on bioconcentration factors in whole fish from the study by West et al. (1983). As discussed in Section 3.2.3.5, actual concentrations of fluridone in fish will vary considerably, due to the relatively rapid degradation and dissipation of fluridone in surface waters. The upper bound BCF from West et al. (1983) is used because this study determined bioconcentration factors in several species of fish in lake and pond field trials with fluridone, and these estimates appear to be the most directly relevant to assessing actual exposures to which wildlife (mammals or birds) might be subject.

4.2.3. Terrestrial Plants

Exposure scenarios for terrestrial plants are not relevant to aquatic applications.

4.2.4. Soil Organisms

Exposure scenarios for soil organisms are not relevant to aquatic applications. Exposure scenarios for benthic aquatic species are considered in the assessment for aquatic species (Section 4.2.5).

4.2.5. Aquatic Organisms

Expected peak concentrations to which aquatic organisms will be exposed from the direct application of fluridone to water are based on the target concentration; fluridone water concentrations from accidental spills and longer-term concentrations of fluridone in water are based on the same values used in the exposure assessment for mammals (Section 4.2.2.4). As in the human health risk assessment, the EXCEL workbook that accompanies this risk assessment is based on the highest allowable application rate, 150 ppb (0.15 mg/L). The consequences of using lower application rates are discussed in the risk characterization (Section 4.4).

4.3. DOSE-RESPONSE ASSESSMENT

4.3.1. Overview

The specific toxicity values used in this risk assessment are summarized in Table 5, and the derivation of each of these values is discussed in the various subsections of this dose-response assessment. The available toxicity data support separate dose-response assessments in seven groups of organisms: terrestrial mammals, birds, terrestrial invertebrates, fish, aquatic invertebrates, aquatic macrophytes, and aquatic algae. 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.

For terrestrial mammals, the toxicity endpoints correspond to the NOAEL values used in the human health risk assessment to derive the acute and chronic RfDs—i.e., an acute NOAEL of 125 mg/kg body weight and a chronic NOAEL of 8 mg/kg body weight/day. NOAEL values for birds, 1500 mg/kg bw for acute exposures and 68 mg/kg bw/day for longer-term exposures, are substantially higher than those for mammals. Although terrestrial invertebrates are not likely to be exposed to fluridone, and risks to this group are not quantified, the single available acute NOAEL of 3900 mg/kg bw suggests that terrestrial insects are less sensitive than mammals or birds to the effects of fluridone exposure.

As would be expected for an aquatic herbicide registered for the control of macrophytes, aquatic macrophytes are the most sensitive group of aquatic organisms with NOEC values ranging from 0.001 mg/L (1 ppb) in sensitive species to 0.024 mg/L (24 ppb) in tolerant species. All of these toxicity values correspond to target concentrations over periods of exposure ranging from 22 to 90 days. Generally, with respect to fluridone exposure, algae appear to be less sensitive than macrophytes, with NOEC values ranging from 0.02 mg/L (20 ppb) in sensitive species of algae to 0.5 mg/L (500 ppb) in tolerant species of algae. These NOEC values, however, all involve much shorter periods of exposure (from 4 to 6 days) than those for macrophytes; moreover, some field studies indicate that mixed algal populations may be adversely affected after longer-term exposures associated with field applications of fluridone.

The data on fish and aquatic invertebrates are sparse, relative to the data on aquatic plants. The available acute toxicity data suggest that fish and invertebrates are about equally sensitive to fluridone, with acute NOEC values in sensitive species of 0.5 mg/L (fish) and 0.6 mg/L (invertebrates) and NOEC values in tolerant species of 2 mg/L (fish) and 3.35 mg/L (invertebrates). Longer-term NOEC values are similar for fish and aquatic invertebrates: NOEC values in sensitive species of 0.04 mg/L (fish) and 0.1 mg/L (invertebrates). Corresponding NOEC values for tolerant species are 0.48 mg/L (fish) and 0.6 mg/L (invertebrates).

4.3.2. Toxicity to Terrestrial Organisms

4.3.2.1. Mammals

As summarized in the dose-response assessment for the human health risk assessment (Section 3.3.3), the Office of Pesticide Programs of the U.S. EPA used an acute NOAEL of 125 mg/kg/day with a corresponding acute LOAEL of 300 mg/kg/day based on maternal and fetal toxicity from a rabbit study to derive the acute RfD. Thus, the NOAEL of 125 mg/kg bw is used as the toxicity value to characterize risk associated with single (i.e., 1 day peak) exposure levels. As also discussed in Section 3.3.3 as well as Section 3.4.4, the application of this NOAEL to all organisms and not just pregnant mammals may be conservative in that pregnant mammals may be more sensitive than other mammals. As noted in Section 4.1.2.1, there is some indication that dogs and perhaps other canid species may be more tolerant than small rodents to the effects of fluridone exposure. The tolerance of dogs relative to smaller mammals can be quantified for longer-term exposures. The available acute toxicity data in dogs, however, cannot be used to quantify differences in the sensitivity of dogs relative to smaller mammals (Section 4.1.2.1). Thus, the acute NOAEL of 125 mg/kg bw is used for all groups of terrestrial mammals, including canids.

Chronic NOAELs are available in mice (15 mg/kg bw/day), rats (8 mg/kg bw/day), and dogs (75 mg/kg bw/day) (Section 3.1.5). As discussed in Section 3.3.2 (Chronic RfD), the U.S. EPA derived two chronic RfDs for fluridone based on the NOAELs in mice and rats. The current Forest Service risk assessment for human health adopts the lower RfD based on the rat NOAEL of 8 mg/kg bw/day, which is also used in this ecological risk assessment to characterize risks associated with longer-term exposures.

The dog NOAEL of 75 mg/kg bw/day is higher than the rat NOAEL of 8 mg/kg bw/day by a factor of almost 10. As noted in Table 5, the chronic NOAEL of 75 mg/kg bw/day is used as a longer-term toxicity value for canids, which, incidentally, has no practical impact on the current risk assessment. As detailed in Section 4.4.2.1 (Risk Characterization for Mammals), all of the longer-term hazard quotients for the small mammal are far below the level of concern. Because allometric relationships between body weight and food or water consumption dictate that smaller mammals will be subject to higher doses per unit body weight (i.e., small mammals are the *Most Exposed*) and because smaller mammals are more sensitive than larger animals to the effects of fluridone exposure, longer-term exposure assessments are not made for canid species.

4.3.2.2. Birds

As discussed in Section 4.1.2.2 (Hazard Identification for birds) and detailed in Appendix 4, there are two types of acute toxicity studies on birds: gavage dosing and acute dietary dosing. These are very standard toxicity studies generally used to estimate acute lethal potency—i.e., gavage LD_{50} values and acute dietary LC_{50} values. Fluridone, however, is practically nontoxic to birds, and none of the available studies resulted in sufficient mortality to estimate LD_{50} or LC_{50} values (Section 4.1.2.2). This limitation has no impact on the current risk assessment because the Forest Service prefers to base acute risk characterizations on the NOAEL rather than the LD_{50} or LC_{50}.

The acute gavage study in birds (Kehr et al. 1978b) did not result in any mortality attributable to fluridone at a dose of 2000 mg/kg bw. Both control and treated birds evidenced lethargy through Day 6 after dosing, suggesting that both control and treated birds were responding to stress associated with the gavage administration rather than toxic stress associated with fluridone.

The acute dietary studies in ducks and quail failed to note any signs of toxicity at dietary concentrations of fluridone of up to 5000 ppm. The DER for the study in ducks (Kehr et al. 1978a) as well as the EPA summary of the study in quail (Zucker et al. 1982) do not specify levels of food consumption. While food consumption rates are typically measured in dietary studies on birds, the lack of reporting of this information is not unusual in older DERs. Based on much more recent acute dietary studies in birds on another herbicide, aminopyralid, acute food consumption factors—i.e., kg food/kg body weight per day—for mallard ducks and bobwhite quail are in the range of 0.3 for mallards and 0.42 for quail (SERA 2007c). Using these factors, the dietary concentration of 5000 ppm corresponds to daily doses of about 1500 mg/kg bw/day for mallards and 2100 mg/kg bw/day for quail. For the current risk assessment, the lower NOAEL dose of 1500 mg/kg bw/day is used to characterize risks associated with acute exposures in birds.

As also discussed in Section 4.1.2.2, two standard reproduction studies are available, one in mallards (Ringer et al. 1981a) and the other in quail (Ringer et al. 1981b). In both of these studies, no adverse effects were noted at the maximum dietary exposure of 1000 ppm. As with the acute studies, these relatively old DERs do not provide information on food consumption. Again using food consumption data from more recent reproduction studies on aminopyralid, food consumption factors for mallard ducks and bobwhite quail in longer-term dietary studies are generally in the range of 0.07 for mallards and 0.068 for quail (SERA 2007c). Using the somewhat lower factor of 0.068 kg food/kg bw, the dietary NOEC of 1000 ppm corresponds to a daily dose of 68 mg/kg bw/day, and the NOEC is used to characterize risks associated with longer-term exposures in birds.

4.3.2.3. Terrestrial Invertebrates

As summarized in Section 4.1.2.3, an acute contact NOEC of 362.58 µg/bee is reported in an U.S. EPA/OPP review on fluridone (Zucker et al. 1983). For terrestrial applications of pesticides, this toxicity value would be used with an estimated body weight bee of 0.093 g (USDA/APHIS 1993) for a honey to derive a NOEC of about 3900 mg/kg bw [0.36258 mg/0.000093 kg ≈ 3,898.7 mg/kg bw]. While this toxicity value is included in Table 5, it is not otherwise used in this risk assessment because aquatic applications are not likely to involve exposures to terrestrial insects.

4.3.2.4. Terrestrial Plants (Macrophytes)

As discussed in Section 4.1.2.4, the mechanism of action of fluridone in terrestrial plants appears to be identical to the mechanism of action of fluridone in aquatic plants. In addition, fluridone has been evaluated as a terrestrial herbicide, and it is likely that significant exposure levels of fluridone would damage terrestrial vegetation. Nonetheless, fluridone is not labeled for terrestrial applications and will only be used in

Forest Service programs in direct aquatic applications; therefore, a dose-response assessment for terrestrial plants is not developed in this risk assessment.

4.3.3. Aquatic Organisms

4.3.3.1. Fish

4.3.3.1.1 Acute Toxicity

The database concerning the toxicity of fluridone to fish is neither large nor complex. As summarized in Section 4.1.3.1.1 and detailed in Appendix 5, 96-hour LC_{50} values range from 1.8 mg/L (walleye from Paul et al. 1994) to 22 mg/L (fathead minnows from Hamelink et al. 1986). While the LC_{50} values could be used directly for risk characterization, Forest Service risk assessments prefer to identify and use NOEC values with a level of concern set at a hazard quotient of 1. In contrast, the U.S. EPA/OPP (U.S. EPA/EFED 1998) prefers to use LC_{50} values with LOCs that vary from 0.5 (acute risk) to 0.05 (threatened and endangered species).

As noted in Appendix 5, Paul et al. (1994) provides both NOEC and LC_{50} values, and the NOEC in the walleye bioassay is 0.78 mg/L, which is only a factor of about 2.3 below the LC_{50} of 1.8 mg/L. The NOEC of 0.78 mg/L is used to characterize risks associated with acute exposures to sensitive species of fish. Hamelink et al. (1986) does not provide a NOEC value for the LC_{50} of 22 mg/L in fathead minnows.

While the data from Paul et al. (1994) suggest that LC_{50} to NOEC ratios for fluridone range from about 1.3 to 2.3, the bioassay by Probst and Negilski (1981c) notes a 96-hour LC_{50} of 14.3 mg/L in bluegills with a corresponding NOEC of 2 mg/L, for a NOEC/LC_{50} ratio of about 7.15. The major difference between these two ratios is that the NOEC in the study by Probst and Negilski (1981c) is based on sublethal effects – i.e., hypoactivity. The NOEC from the study by Pau et al. (1994) appears to be based on a lack of mortality. Thus, the study by Probst and Negilski (1981c) provide a more relevant and protective basis for estimating NOEC values from LC_{50} values.

The study by Probst and Negilski (1981c) also used very narrowly spaced concentrations—i.e., 1.0, 1.4, 2.0, 2.75, 3.65, 5.0, 7.0, 9.0, 10.0, 11.0, 12.5, 14.0, 16 mg/L. Thus, this study is well-designed to reflect meaningful NOEC/LC_{50} ratios. The ratio of 7.15 is applied to the LC_{50} of 22 mg/L for tolerant species to estimate a NOEC of about 3 mg/L [22 mg/L/7.15 ≈ 3.078 mg/L], and this estimated NOEC is used to characterize risks of acute exposures to tolerant species of fish.

4.3.3.1.2. Longer-term Toxicity

There are only two available studies concerned with effects in fish after longer-term exposure to fluridone: a 60-day growth and survival study in channel catfish and a life-cycle study in fathead minnows (Section 4.1.3.1.2). Both of these studies are from the open literature publication by Hamelink et al. (1986), and the minnow study is reviewed and summarized also in a DER from the U.S. EPA (Probst et al. 1981). For both species, the NOEC values are virtually identical: 0.5 mg/L for catfish and 0.48 mg/L for fatheads.

As noted above, fathead minnows appear to be a tolerant species, based on acute toxicity studies. In the absence of additional chronic data, the NOEC of 0.48 mg/L is used as the chronic toxicity value for tolerant species of fish.

As also noted in the above discussion on acute toxicity values, the walleye appears to be the most sensitive species of fish with a 96-hour LC_{50} value of 1.8 mg/L. No chronic toxicity data, however, are available on walleye or other apparently sensitive species of fish. Based on the acute LC_{50} values in the most sensitive species (1.8 mg/L) and the most tolerant species (22 mg/L), the ratio of sensitivities is about 0.081 [1.8 mg/L divided by 22 mg/L ≈ 0.082]. This ratio can be used to estimate a chronic value of about 0.04 mg/L [0.48 mg/L x 0.081 ≈ 0.03888 mg/L] for sensitive fish species; in addition, this value is used to approximate the longer-term NOEC for sensitive fish species.

4.3.3.2. Amphibians

Since the literature on fluridone does not include information about its toxicity to amphibians, a dose-response assessment is not made for this group of organisms. As discussed further in Section 4.4.3.2, risks to amphibians are characterized by analogy to risks in fish.

4.3.3.3. Aquatic Invertebrates

4.3.3.3.1. Acute Toxicity

Most of the toxicity data for fluridone with respect to aquatic invertebrates are expressed as time-specific LC_{50} values, which range from 1.3 to 71 mg/L. As discussed in the dose-response assessment for fish (Section 4.3.3.1), Forest Service risk assessments prefer to use NOEC values rather than LC_{50} values for dose-response assessments. Unlike the case with fish, NOEC values are not available for the most sensitive group of aquatic invertebrates—i.e., midges. For the most tolerant species, the blue crab, a 96-hour LC_{50} of 71 ppm as well as a NOEC for mortality of 5.8 ppm (Heitmuller 1981b) are available.

In the dose-response assessment for fish (Section 4.3.3.1), NOEC values are estimated from LC_{50} values based on highest reported ratio of LC_{50}/NOEC values—i.e., 7.15 from the study in bluegills by Probst and Negilski (1981c). This approach is used because the DER for the Probst and Negilski (1981c) study reports NOEC values for both mortality (NOEC = 11 ppm) as well as sublethal effects (NOEC = 2 ppm), and the NOEC for sublethal effects is used to develop the ratio for estimating a surrogate NOEC from an LC_{50}.

As noted above, the NOEC of 5.8 ppm reported for the blue crab in Heitmuller (1981b) is based on mortality rather than sublethal effects. The DER for the study by Heitmuller (1981b) does not note whether signs of sublethal toxicity were observed at the NOEC for mortality. Other ratios of the LC_{50} to the NOEC that can be developed for invertebrates range from 1.4 to 14.6, as indicated in Appendix 6. All of these ratios, however, are based on NOEC values for mortality. One acute toxicity study in daphnids (Kehr et al. 1978c) explicitly notes that the NOEC for mortality, 2 ppm, was associated with hypoactivity, a common endpoint observed in fluridone studies.

An alternative to using the acute LC_{50} values for risk characterization would be to adopt a modification of the U.S. EPA method (e.g., U.S. EPA/EFED 1998) in which variable levels of concern are used for acute risk (LOC=0.5), acute restricted use (LOC=0.1), and endangered species (LOC=0.05). While all of the categories used by the U.S. EPA are not directly germane to Forest Service risk assessments, the reciprocals of these values may be viewed as uncertainty or safety factors that could be applied to an LC_{50} value to derive a surrogate NOEC (LOC=1). Taking the most conservative value, the LOC of 0.05 for endangered species, a surrogate NOEC of 0.065 mg/L [1.3 mg/L x 0.05] could be derived for the most sensitive species and a surrogate NOEC of 3.55 mg/L [71 mg/L x 0.05] could be derived for tolerant species.

Using the LOC adjustment of 0.05, however, would not be sensible for sensitive species given the chronic toxicity data on fluridone. As detailed in Section 4.1.3.3.2 and discussed further below, the chronic NOEC value for the most sensitive aquatic invertebrate is taken as 0.1 mg/L, which is a factor of 0.05 above the surrogate value of 0.065 mg/L calculated using the EPA LOC. In other words, it would not be sensible to propose a surrogate acute NOEC that is lower than the chronic NOEC.

Midges are the most sensitive group of aquatic invertebrates. As noted in Section 4.1.3.3.2 and discussed further below, the chronic NOEC for midges is 0.6 mg/L. It is reasonable to assume that the acute NOEC for midges is higher than the chronic NOEC for midges. Thus, in the absence of a clear sublethal acute NOEC for midges, the chronic NOEC for midges of 0.6 mg/L is used as the acute NOEC for sensitive species of aquatic invertebrates. For tolerant species, the reported NOEC for mortality in the blue crab, 5.8 mg/L from Heitmuller (1981b), is not substantially different from the adjusted NOEC of 3.55 mg/L based on the LC_{50} value of 71 mg/L and the factor of 0.05. The lower value of 3.55 mg/L is used in this risk assessment to characterize acute risks in tolerant species of aquatic invertebrates.

4.3.3.3.2. Chronic Toxicity

Three longer-term toxicity studies are available in aquatic invertebrates: a 60-day growth and survival study in amphipods, a 30-day emergence study in midges, and a 21-day reproduction study in daphnids. These studies are all taken from the publication by Hamelink et al. (1986).

The most sensitive species is clearly *Daphnia magna*. Hamelink et al. (1986) report a NOEC of 0.2 mg/L based on a statistically significant reduction in the total average number of offspring produced by Day 21 at 0.4 mg/L (Hamelink et al. 1986, Table 3, p. 90). The Hamelink et al. (1986) paper does not provide data on individual broods but does note a significant increase in the average number of young at 0.1 mg/L (about 174% of controls) and a decrease in the average number of young (55% of controls) at 0.2 mg/L. While the response at 0.2 mg/L is not reported as statistically significant, it can be viewed as biologically significant. Speculatively, the significant increase in the number of young produced at 0.1 mg/L could be viewed as an indicator of stress—i.e., a hormetic response (Calabrese 2008). For the current risk assessment, the concentration of 0.1

mg/L is used as the longer-term chronic NOEC. Although the increase in the number of offspring could be interpreted as a stress response, the response itself is not generally regarded as adverse. While the next higher exposure level, 0.2 mg/L, was not associated with a statistically significant decrease in offspring, the observed response (55% of controls) is not an appropriate NOEC for a Forest Service risk assessment.

The other two chronic bioassays—i.e., midge emergence and amphipod growth—both yield the same NOEC, 0.6 mg/L. Neither of these bioassays provides any clear indication of potentially adverse effects at lower concentrations. Consequently, 0.6 mg/L is used as the longer-term NOEC for tolerant species of aquatic invertebrates.

4.3.3.4. Aquatic Plants

4.3.3.4.1. Macrophytes

The data concerning the toxicity of fluridone to aquatic macrophytes are relatively numerous and complex. In some respects, a formal dose-response assessment on fluridone for aquatic macrophytes may seem somewhat superfluous. Fluridone is an effective aquatic herbicide. If fluridone is applied to surface water at labeled target application rates, at least some aquatic plants will be damaged and probably killed. Nonetheless, substantial differences in sensitivity are apparent among different species of aquatic macrophytes and these can be reflected in the dose-response assessment.

Table 6 provides an overview of the available laboratory toxicity studies on fluridone. Furthermore, these studies are discussed in Section 4.1.3.4.1, with additional details included in Appendix 7. Table 6 summarizes the NOEC and LOEC values for growth inhibition. The entries in this table are sorted by species arranged roughly in order of decreasing sensitivity to fluridone. One study, Anderson (1981), is excluded from Table 6. As indicated in Appendix 7, Anderson (1981) reports an LOEC of 1000 µg/L for American pondweed and Sago pondweed; however, these data are atypical in that the bioassays were conducted using winter buds rather than actively growing vegetation. There is little doubt that 1000 µg/L (i.e., 1 ppm) would cause adverse effects in aquatic macrophytes; nevertheless, these data are omitted from Table 6 because these bioassays are not comparable to the other information available on fluridone.

Quantitative comparisons among studies in Table 6 are not straightforward. As summarized in Section 4.1.3.4.1 (Hazard Identification for Aquatic Macrophytes), the response of a particular species to fluridone will vary with the duration of treatment, the maturity of the plant, as well as a number of specific experimental conditions which vary from study to study. A further complication is that the concentration of fluridone will diminish as the bioassay proceeds. In other words, all of the studies summarized in Table 6 involve static exposures, and the provided NOEC and LOEC values refer to the nominal initial concentration of fluridone, analogous to the target concentration as discussed in Section 2.4.1.

Poovey et al. (2004, 2008) provide data on the greatest number of species in bioassays which follow approximately the same culture methods, duration of exposure, and range of concentrations tested. Based on these data species sensitivity appears to follow

roughly the following order: Eurasian watermilfoil (most sensitive) > curlyleaf pondweed > Elodea ≈ Sago pondweed > Illinois pondweed > wild celery (most tolerant). This evident order of sensitivity is consistent with the general categorizations on the product labels for fluridone formulations, which indicate that watermilfoil, hydrilla, elodea, and most pondweeds (*Potamogeton* sp.) are controlled by fluridone but that Illinois pondweed and wild celery (designated as American eelgrass on the product labels) are only partially controlled by fluridone. The other studies summarized in Table 6 are generally consistent with the classification of sensitivity from Poovey et al. (2004, 2008) as well as the product labels.

For the current risk assessment, the NOEC of 1 µg/L (ppb) for Eurasian watermilfoil (Netherland and Getsinger 1995a) is used to characterize risks to sensitive species and the NOEC of 24 µg/L for wild celery (Poovey et al. 2004) is used to characterize risks to tolerant species. These toxicity values intentionally do not consider a distinction between target and nontarget species. Aquatic macrophytes as well as Eurasian watermilfoil and hydrilla are virtually always considered a target species. Duckweed and elodea, on the other hand, may or may not be considered a target species depending on the management objectives for a particular body of water. In addition, while the available data clearly indicate that typical target species, like Eurasian watermilfoil and hydrilla, are more sensitive than some species that may not be considered as target species under all situations, these relationships do not rule out the possibility that some nontarget aquatic macrophytes could be as sensitive to fluridone as are sensitive target species.

4.3.3.4.2. Algae

Aquatic algae appear to be less sensitive than aquatic macrophytes to fluridone, and this pattern is consistent with the product labels for fluridone, all of which indicate that aquatic algae are not well controlled by fluridone. Furthermore, the field study by Arnold (1979) suggests that fluridone applications do not have a substantial impact on algae. As discussed in Section 4.1.3.4.2, paired studies on green algae and blue-green algae (Hess 1980; Schrader et al. 1997) suggest that green algae are somewhat more sensitive than blue-green algae to fluridone. The lowest reported NOEC, however, is 20 ppb (0.02 mg/L) for *Oscillatoria agardhii*, a species of blue-green algae (Millie et al. 1990). This NOEC of 20 ppb is used in the current risk assessment for sensitive species of aquatic algae.

For tolerant species of algae, the NOEC is taken as 0.5 mg/L (500 ppb), the 96-hour NOEC for another species of blue-green algae, *Anabaena cylindrica* (Trevors and Vedelago 1985). This concentration is very close to the NOEC of 0.329 mg/L (329 ppb) for Oscillatoria chalybea, another blue-green algae (Schrader et al. 1997) as well as *Chlamydomonas eugametos*, a species of green algae (Hess 1980).

All of the studies in algae involve exposure periods of 6 days or fewer. Exposure periods ranging from 4 to 6 days are common for algal bioassays, and, except for field observations, effects associated with longer-term periods of exposure are seldom reported. It is not clear that this limitation is important but, as discussed in Section 4.1.3.4.2, the field study by Kamarianos et al. (1989) does associate a nominal

application rate of 42 ppb over an 84-day period of exposure with decreases in algal populations.

All of the NOEC values used in this risk assessment involve growth rather than biochemical endpoints such as the inhibition of carotenoid synthesis. While most studies in algae do not report biochemical endpoints, Millie et al. (1990) noted a significant inhibition in carotenoids at the 20 ppb NOEC for growth inhibition. As with macrophytes, it seems likely that the inhibition of phytoene desaturase, with the consequent inhibition of carotene synthesis, will be a non-threshold response. Growth inhibition is used as an endpoint in the current risk assessment to reflect changes in algal growth that would be regarded as functionally adverse.

4.4. RISK CHARACTERIZATION

4.4.1. Overview

The quantitative risk characterization for terrestrial species is given in Worksheet G02, and the corresponding risk characterization for aquatic species is given in Worksheet G03. Both of these worksheets are in the EXCEL workbook that accompanies this risk assessment (Attachment 1). As in the human health risk assessment, the quantitative risk characterization is given as the hazard quotient—i.e., the level of exposure divided by a toxicity value. Unlike the human health risk assessment, however, the toxicity values used in the ecological risk assessment involve different endpoints for different groups of organisms and different durations of exposure. These differences are necessitated by the nature of the available data on the different groups of organisms.

Applications of fluridone to water are likely to cause adverse effects in at least some species of aquatic macrophytes. Except for accidental spills, there is no basis for asserting that toxic effects in any aquatic animals are plausible. For terrestrial animals, no exposure scenarios, including the accidental spill, result in hazard quotients that exceed the level of concern.

Fluridone is an effective aquatic herbicide for some sensitive target species of aquatic macrophytes, like Eurasian watermilfoil and hydrilla. Over the range of labelled application rates—i.e., 10 to 150 ppb—adverse effects are likely in sensitive species of aquatic macrophytes. The available data clearly indicate that the target species are sensitive aquatic macrophytes. At application rates of up to about 20-30 ppb, which encompasses labelled rates recommended for treatment of target species in canals, effects on aquatic plants are likely to be limited to sensitive macrophytes, and perhaps some more tolerant species of macrophytes as well as some species of algae. Higher application rates are more likely to cause adverse effects in tolerant species of macrophytes and sensitive species of algae; whereas, the highest application rate of 150 ppb is likely to cause adverse effects in many if not all species of aquatic macrophytes as well as in some species of algae. Tolerant species of algae, however, are not likely to be affected even at the maximum application rate. The toxicity of fluridone—i.e., both the efficacy as well as unintended effects in nontarget species—can be influenced by the life-stage of the aquatic plant, the timing of the application, and the co-occurrence of plant pathogens.

Since applications of fluridone are likely to alter aquatic vegetation, secondary effects on fish, aquatic invertebrates, as well as some species of aquatic plants are likely. Secondary effects on terrestrial organisms associated with changes in water quality and perhaps the availability of some food items are also plausible. In that the application of fluridone is intended to alter the composition of aquatic macrophyte communities, these secondary effects must be considered in any site-specific application of fluridone to surface water. Implicit in the application of fluridone, however, is the assumption that changing the composition of aquatic vegetation is a desirable water management objective.

4.4.2. Terrestrial Organisms

4.4.2.1. Mammals

The risk characterization for mammals is simple and unambiguous: there is no basis for asserting that adverse effects are plausible at the highest application rate at which fluridone will be applied. As summarized in Worksheet G02 of Attachment 1, the hazard quotients for mammals range from 0.0002 (the consumption of contaminated water) to 0.09 (the upper bound of the hazard quotient associated with an accidental spill of fluridone into a small pond). This range is below the level of concern (1.0) by factors from about 11 to 5000.

The application of any effective aquatic herbicide, including fluridone, will alter aquatic vegetation. This alteration is likely to lead to some secondary changes that could have an impact on mammals—e.g., changes in water quality or food availability. These secondary effects are likely to vary over time and among different species of mammals.

4.4.2.2. Birds

The risk characterization for birds is similar to that of mammals in that no hazard quotients exceed the level of concern (1.0). At the highest labeled application rate—i.e., 150 ppb—the upper bounds of the hazard quotients associated with acute and chronic exposures are 0.00005 and 0.004, respectively, and are below the level of concern by factors of 20,000 and 250. For the accidental spill scenario, the upper bound of the hazard quotient for the consumption of contaminated fish is 0.1, which is below the level of concern by a factor of 10.

4.4.2.3. Terrestrial Invertebrates

As described in the exposure assessment and the dose-response assessment, terrestrial invertebrates will not be exposed to significant exposure levels of fluridone during aquatic applications. Consequently, this risk assessment does not include a quantitative risk characterization for terrestrial insects. Furthermore, there is no basis for asserting that aquatic applications of fluridone will cause substantial or significant effects in terrestrial invertebrates. This assessment also applies to terrestrial plants and soil microorganisms.

4.4.2.4. Terrestrial Plants

See Section 4.4.2.3.

4.4.2.5. Soil Microorganisms

See Section 4.4.2.3.

4.4.3. Aquatic Organisms

4.4.3.1. Fish

As with terrestrial species, the quantitative risk characterization for fish and other aquatic organisms is expressed as the hazard quotient, and the hazard quotients for aquatic organisms are given in Worksheet G03 of the EXCEL workbook that accompanies this

risk assessment (Attachment 1). As with other risk characterization worksheets, Worksheet G03 is based on the maximum application rate considered in this risk assessment, 150 ppb. The hazard quotients are linearly related to the application rate. Thus, an application rate of 100 ppb would decrease the hazard quotients by a factor of one-third, and an application rate of 50 ppb would decrease the hazard quotients by a factor of two-thirds, and so on.

As indicated from the data on non-accidental, acute exposures as well as chronic exposures, there is no basis for asserting that fluridone will cause direct toxic effects in fish. All acute exposures are based on the maximum target application rate of 150 ppb. Thus, the central estimate as well as the upper and lower bounds of the hazard quotients are identical. For acute non-accidental exposures, the hazard quotients are 0.08 and 0.3 for tolerant and sensitive species, respectively. For chronic exposures, the central estimates and bounds of the hazard quotients are not identical because the longer term exposures are based on field dissipation half-lives. As discussed in Section 3.2.3.4.2 (Longer-Term Expected Concentrations), the dissipation/degradation field half-life for fluridone is 20 days with a range from 5 to 97 days. All upper bound estimates of the hazard quotients for fish and other aquatic species are based on the very conservative half-life of 97 days. For chronic exposures, the upper bounds of the hazard quotients are 0.2 for sensitive species and 0.06 for tolerant species, which are below the level of concern by factors of 5 and about 17, respectively.

Unlike the risk characterization for expected peak and longer-term concentrations, the risk characterization for an accidental spill leads to hazard quotients that substantially exceed the level of concern. This is a standard but extreme exposure scenario included in all Forest Service risk assessments. As discussed in Section 3.2.3.4.3, this scenario involves the accidental spill of a large amount of fluridone—i.e., 200 gallons of a field solution—into a small pond resulting in concentrations that range from 3.6 to 72 mg/L. The bounds of this range of concentrations exceed the range of LC_{50} values in sensitive and tolerant species of fish—i.e., 1.8-22 mg/L (Section 4.3.3.1.1). Thus, in the event of a severe spill, it is plausible and perhaps likely that substantial fish mortality could occur.

There are uncertainties in the risk characterization for fish. As discussed in the dose-response assessment for fish (Section 4.3.3.1.1), the NOEC values for sensitive species are estimated from LC_{50} values and adjustment factors based on NOEC and LC_{50} values in other species of fish. While an attempt is made to use protective and conservative assumptions, these types of estimates do introduce uncertainty. In addition, all hazard quotients are based on the target concentration. As discussed in Section 3.2.3.4.1, actual concentrations may exceed the target concentration, at least for brief periods of time, which would tend to increase risk. On the other hand, applications of granular formulations, particularly slow-release formulations, would likely lead to concentrations of fluridone in water that are below, and perhaps substantially below, the nominal target concentration, which would tend to decrease risk. These types of uncertainties are inherent in many pesticide risk assessments and cannot be further characterized. This is one of the reasons that risk assessments prefer to use conservative assumptions.

4.4.3.2. Amphibians

Owing to the lack of data regarding the toxicity of fluridone to amphibians, a risk characterization for amphibians is not developed in this risk assessment. The U.S. EPA often reasons that risks to amphibians will be comparable to those for fish (e.g., U.S. EPA/EFED 2001). For fluridone, there basically is no other approach.

4.4.3.3. Aquatic Invertebrates

As summarized in Table 5 and discussed in Section 4.3.3 (Dose-Response Assessment for aquatic organisms), the acute and chronic toxicity values for sensitive and tolerant groups of aquatic invertebrates are only slightly greater than those for fish. Consequently, the quantitative risk characterization for aquatic invertebrates is virtually identical to that for fish.

Based on expected concentrations of fluridone in water, no direct adverse effects on aquatic invertebrates are anticipated. For acute exposures, the hazard quotient is 0.3 for sensitive species and 0.04 for tolerant species. For longer-term exposures, the hazard quotient is 0.2 for sensitive species and 0.03 for tolerant species.

In the event of an accidental spill, the hazard quotients are substantial: 30 (ranging from 6 to 121) for sensitive species and 5 (ranging from 1 to 21) for tolerant species. The estimated concentrations of fluridone in water in the accidental spill scenario range from 3.6 to 72 mg/L. Again as with fish, these concentrations are similar to the range of LC_{50} values for aquatic invertebrates, 1.3-71 mg/L. Thus, some and perhaps substantial mortality could occur in aquatic invertebrates after a severe spill.

Uncertainties in this risk characterization are similar to those expressed in the risk characterization for fish. As detailed in Section 4.3.3.3.1 (acute dose-response assessment for aquatic invertebrates), the acute NOEC values for both sensitive and tolerant species are estimated. For tolerant species, the acute NOEC is based on the chronic NOEC. For tolerant species, the acute NOEC is estimated from the LC_{50} using an adjustment factor of 0.05, based on the EPA LOC used for hazard quotients in endangered species.

Similar to the risk characterization for fish, another uncertainty involves differences between liquid and granular formulations. Granular formulations may result in lower and perhaps much lower concentrations of fluridone in the water column, compared with applications of liquid formulations at the same target application rate, as illustrated in Figure 2. As with risks to fish, this difference is likely to result in lower risks to zooplankton (e.g., daphnids) after applications of granular, as opposed to liquid, formulations. For benthic species (e.g., midges), the opposite relationship may hold. After applications of granular formulations, concentrations of fluridone in sediment are likely to be substantially higher, relative to concentrations of fluridone in sediment after liquid formulations are applied.

4.4.3.4. Aquatic Plants

In terms of the quantitative risk characterization, aquatic plants can be classified into three groups, based on toxicity values from Table 5:

highest risk:	sensitive species of macrophytes (NOEC = 0.001 mg/L),
moderate risk:	a combination of tolerant macrophytes (NOEC = 0.024 mg/L) and sensitive species of algae (NOEC = 0.024 mg/L), and
lowest risk:	tolerant species of algae (NOEC = 0.5 mg/L).

This general classification is, of course, a simplification. As summarized in Table 6, there are not simply two groups of aquatic macrophytes, sensitive and tolerant. The sensitivity of different species could be better characterized by a continuum, as is true for all organisms and all pesticides. The selection of toxicity values for sensitive and tolerant species is only an extension of the extreme value approach used in Forest Service risk assessments (Section 3.2.3.1). The selection of the most sensitive and tolerant species is a basis for discussing the range of effects that might be observed in any particular application.

For sensitive species of macrophytes, the central estimate of the hazard quotient is 46 with a range from 12 to 111. As with all other hazard quotients in Worksheet G03 of Attachment 1, these hazard quotients are associated with a nominal application rate of 0.15 mg/L (150 ppb), the highest labeled application rate for fluridone. This application rate is expected to cause adverse effects in sensitive species of aquatic macrophytes.

The magnitude of the hazard quotient is directly and linearly related to the application rate. For example, the lowest labeled rate for fluridone is 10 ppb. At this application rate, the longer-term hazard quotients for sensitive aquatic macrophytes would be lower by a factor of about 0.066 [10 ppb/150 ppb], and the resulting HQ values would be about 3 (ranging from 0.8 to 7). Basically, this quantitative risk characterization is little more than a statement on efficacy. Fluridone is an effective herbicide for some species of sensitive aquatic macrophytes. Over the range of labeled application rates, fluridone will damage/control sensitive species of aquatic macrophytes. The upper range of the hazard quotient at 10 ppb—i.e., HQ=7—is consistent with some field studies suggesting that lower application rates may be effective in some instances (e.g., Getsinger et al. 2002).

The above discussion on sensitive species of aquatic macrophytes is focused on longer-term exposures. Worksheet G03 also gives a risk quotient of 150 for acute exposures. This value is mathematically correct—i.e., a concentration of 150 ppb is 150 times a concentration of 1 ppb, the NOEC. For fluridone, however, the acute HQ has little practical significance. As discussed in Section 4.1.3.4.1, fluridone is a slow-acting herbicide. While short-term peak exposures would likely result in a rapid inhibition of phytoene desaturase activity, this inhibition would probably not result in observable damage to aquatic macrophytes, unless residual concentrations of fluridone remain to prolong the inhibition of phytoene desaturase activity and prevent recovery.

For aquatic plants at moderate risk, the longer-term risk quotients are essentially identical: 1.9 (ranging from 0.5 to 5) for tolerant species of aquatic macrophytes and 2 (ranging from 0.6 to 6) for sensitive species of algae. Qualitatively, this indicates that if fluridone is applied at the maximum application rate of 150 ppb, adverse effects could be anticipated in most if not all aquatic macrophytes as well as in some species of algae. Conversely, at the lowest labeled application rate of 10 ppb, the upper bound of the hazard quotient would range from about 0.3 [5 x 0.066] to 0.4 [6 x 0.066], and no adverse effects would be anticipated in tolerant species of macrophytes or sensitive species of algae.

The application rate that would reach the LOC of 1 for tolerant species of aquatic macrophytes and sensitive species of algae ranges from about 25 ppb [150 ppb / 6] to 30 ppb [150 ppb / 5]. While the numerical precision of hazard quotients should not be overly interpreted, these calculated applications rates are only modestly above the recommended application rates of up to 20 ppb for Eurasian watermilfoil and curlyleaf pondweed (Table 2). In other words, the quantitative risk characterization is consistent with the product labels indicating that fluridone can be applied at application rates that will control target species of aquatic macrophytes without substantial risks to tolerant species of macrophytes or any groups of aquatic algae.

The third group of aquatic plants least sensitive to fluridone are tolerant species of aquatic algae (NOEC = 0.5 mg/L). For this group of organisms, the acute hazard quotient is 0.3 and the longer-term hazard quotient is 0.09 with a range of 0.02 to 0.2. All of these hazard quotients are for the maximum application rate of 150 ppb. Thus, there is no basis for asserting that tolerant species of aquatic algae are likely to be adversely affected by aquatic applications of fluridone.

The quantitative risk characterization for aquatic plants is reasonably consistent with the expectations for effective and, at least somewhat, selective aquatic herbicides. In addition, as summarized in Appendix 7, the risk characterization is generally consistent with field studies that indicate the effective control of target species (Fox et al. 1994; Getsinger et al. 2002; Leslie et al. 1993; Netherland et al. 1993, 1997; Wersal et al. 2007) with little impact on nontarget macrophytes (Farone and McNabb 1993) and algae (Arnold 1979; Struve 1991).

The risk characterization is generally focused on assessing impacts to sensitive life stages. As discussed in Section 4.1.2.4 and suggested by some field observations (e.g., Kay 1991), the time of application as well as the growth stage or maturity of the aquatic plants can affect the toxicity of fluridone. Furthermore, the study by Nelson et al. (1998) suggests that the presence of plant pathogens also may affect the response of plant populations to fluridone. What is more, populations of aquatic plants (both target and nontarget) that are not completely eliminated may recover (e.g., Leslie et al. 1993). The duration required for recovery is likely to be highly variable and to depend on the particular plant species as well as the intensity and duration of treatment. Finally, aquatic plant populations repeatedly exposed to fluridone or other herbicides with the same or similar modes of action may become resistant over time. Most studies on pesticide

resistance focus on target species; nevertheless, it seems reasonable to assume that resistance could occur in nontarget species as well. All of these factors—i.e., life stage, application timing, population recovery, the occurrence of plant pathogens, and the development of resistance—may affect both the efficacy as well as unintended effects in nontarget species; however, these factors are difficult to assess quantitatively.

5. REFERENCES

NOTE: The initial entry for each reference in braces {} simply specifies how the reference is cited in the text. The final entry for each reference in brackets [] indicates the source for identifying the reference. For FOIA01 citations, the brackets are preceded by the tif file name of the document received from EPA.

SET01– Ordered from NAL in Aug. 2007 [n=56].
SET02– Ordered from NAL in January, 2008 [n=27].
SET03– July 08 update literature search and tree search of Sets 1 and 2. Requested July 24, 2008 [n=25].
SET04- Sundry references identified after Aug. 1, 2008 [n=3].
Internet– Various reports on fluridone.
Std- Standard references used in most Forest Service risk assessments.
FOIA01– Obtained from EPA via a Freedom of Information Act request: HQ-RIN-01406-07 [n=91].
E-Docket– These are from the following E-Dockets maintained by U.S. EPA: OPP-2004-0235. To get the complete listing of items available, go to http://www.regulations.gov/search/index.jsp and enter the docket number in the Search box. Last screened in detail on July 31, 2008.

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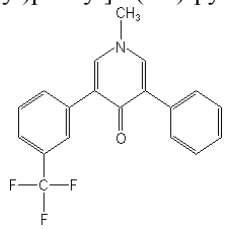
Table 1: Physical and chemical properties of fluridone

Property	Value	Reference
Nomenclature	fluridone	Tomlin 2004
Common Name		
IUPAC Name	1-methyl-3-phenyl-5-(α, α, α -trifluoro-m-tolyl)-4-pyridone	
CAS Name	1-methyl-3-phenyl-5-[3-(trifluoromethyl)phenyl]-4(1H)-pyridinone	
Structure		
Appearance/state, ambient	White crystalline solid	Tomlin 2004
Bioconcentration	3 to 10	Hamelink et al. 1986
	1.5	Magnussen and Rainey 1982
	3.23	West et al. 1982
	0.96 to 2.46 (edible tissue in 10 fish species) 1.59 to 15.51 (whole fish in 8 fish species)	West et al. 1983
	Values used in this risk assessment: **2.46: edible tissue** **15.51: whole fish**	West et al. 1983: See discussion in Section 3.2.3.5.
CAS number	59756-60-4	Tomlin 2004
Density	loose 0.358 g/cm^3, packed 0.515 g/cm^3	Tomlin 2004
Henry's law constant	3.57×10^{-4} Pa m^3 mol^{-1} (calc.)	Tomlin 2004
	8.10×10^{-9} atm-m^3/mole (exp.)	Meylan and Howard 2007a
K_a	2.6 to 38 depending on soil type	Weber et al. 1986
K_d and K_{oc}	See table below	USDA/ARS 1999 Also cited in Tomlin 2004
K_d	270 to 6400	Swann et al. 1986 (ENSR 2005)

Texture	Kd	Koc
Loamy sand	3	350
Sand	6	1000
Clay loam	11	1000
Silty clay loam	11	460
Loam	16	1100

Recommended K_{oc} = 862 (350-2462)

Table 1: Physical and chemical properties of fluridone

Property	Value	Reference
K_a/K_d	Highly variable with soil:water ratios	Malik and Drennan 1989
K_{oc}	1000	Knissel and Davis 2000
log K_{ow}	1.87 (pH 7, 25 °C) [K_{ow} = 74.1]	Tomlin 2004; Zucker et al. 1982; USDA/ARA 1999
	3.16 (expl.) [K_{ow} = 1445] 4.48 (QSAR) [K_{ow} = 30,200]	Meylan and Howard 2007a
	2.98	Mackay et al. 1997 (ENSR 2005)
Melting point	154 to 155 °C	Tomlin 2004
Metabolites of potential concern	N-methylformamide (NMF)	See Section 3.1.15.1
Molecular formula	$C_{19}H_{14}F_3NO$	Tomlin 2004
Molecular weight (g/mole)	329.3	Tomlin 2004
pH		
pK_a	12.3	Tomlin 2004; USDA/ARS 1999
Sediment-Water halftimes	90 days	Tomlin 2004
	21 days	USDA/ARS 1999
	17 weeks (field)	Muir and Grift 1982
	12 months (laboratory)	
	1 year or more	Muir et al. 1980
SMILES Notation	`Cn1cc(c2ccccc2)c(=O)c(c1)c3cccc(c3)C(F)(F)F`	Tomlin 2004
	`CN1C=C(c2ccccc2)C(=O)C(c3cc(C(F)(F)F)ccc3)=C1`	Meylan and Howard 2007
Soil halftimes (NOS)	>343 days	Tomlin 2004
	Generally 6 months. Occasionally 2-5 years	Davis 1978
	44 to 192 days	Howard et al. 1991 (ENSR 2005b)
	51 to 257 days	Malik and Drennan 1990a
	21 days	Knissel and Davis 2000
Soil halftimes, field dissipation (range)	Recommended values: 34 (4 to 90) days	USDA/ARS 1999
Soil halftimes (aerobic)	89% degradation in 49 weeks	Davis 1978
Soil halftimes (anaerobic)	92% degradation in 49 weeks	Davis 1978
U.S. EPA Docket Number	OPP-2004-0235 at http://www.regulations.gov/search/index.jsp	

Table 1: Physical and chemical properties of fluridone

Property	Value	Reference
Vapor pressure	0.013 mPa (25 °C)	Tomlin 2004
	$<1x10^{-7}$ mm Hg (25 °C)	Weber et al. 1986 (ENSR 2005b)
	$1x10^{-7}$ mm Hg (25 °C)	Hornsby 1996 (ENSR 2005b)
	9.8×10^{-8} mm Hg (25 °C)	Mackay et al. 1997 (ENSR 2005b)
Water halftime (field dissipation)	97 days	Fox et al. 1996
	50.8 days	Muir and Grift 1982
	4 to 7 days	Muir et al. 1980
	31 to 35 days (mesocosm)	Netherland et al. 1997
	23 to 24 days (mesocosm)	Poovey et al. 2004
	2 to 5 days	Sanders et al. 1980
	21 to 26 days	West and Parka 1981
	5 days	West et al. 1979
	20 days	West et al. 1983
	20 (5 – 97) days	Section 3.2.3.4.
Water halftime (NOS)	9 months (anaerobic)	Tomlin 2004
Water hydrolysis halftime	Stable to hydrolysis at pH 3-9	Tomlin 2004; Davis 1978; Zucker et al. 1982
Water, aquatic metabolism		
Water photolysis halftime	23 hours	Tomlin 2004
	22 to 55 hours	Saunders and Mosier 1983
Water solubility (mg/L)	12 mg/L (pH 7, 25 °C)	Tomlin 2004
	10 mg/L	Knissel and Davis 2000

Table 2: Commercial formulations of fluridone

Trade Name	Type of Formulation, EPA Reg. No.	Active Ingredient (% by weight)	Lbs a.i. per Unit, Bulk density of formulation	Application Rates and Recommended Uses
Sonar AS (SePRO) [See Table 3] Avast! Aquatic Herbicide, Griffin	Liquid, 67690-4	41.7%	4 lbs/gal., 9.57 lb/gal [Based on specific gravity of 1.15 and water density of 8.3290 lb/gal.]	Maximum application rates [a]: ponds [b] : 90 ppb: lakes and reservoirs [c]: 150 ppb Canals: 2 quarts per treated surface acre 10 – 20 ppb for Eurasian watermilfoil 15 – 20 ppb for curlyleaf pondweed
Avast! SC Aquatic Herbicide	Liquid, 67690-30	41.7%	4 lbs/gal., 9.57 lb/gal [Based on specific gravity of 1.15 and water density of 8.3290 lb/gal.]	Same as Sonar AS. Recommended for ponds, lakes an reservoirs. More economical than other formulations (http://www.sepro.com/default.php?page=avast).
Sonar PR (Precision Release) Formerly Avast! SPR (Griffin)	Granular, 67690-12	5.0%	1.5 lbs per 30 lb container (40 lb container for Griffin formulation)	Maximum application rates [a]: ponds [b] : 90 ppb: lakes and reservoirs [c]: 150 ppb canals or rivers: 10-40 ppb for a minimum of 45 days. May be applied through metering system. Recommended to maintain a more constant concentration over a more prolonged period of time relative to Sonar AS or SRP (http://www.sepro.com/default.php?page=sonarprecisionrelease&b=s).
Sonar Q (a.k.a. Sonar Quick Release	Pellets, 67690-3	5.0%	0.05 lb a.i. per lb formulation	Rates identical to Sonar PR. Quick release formulation recommended for ponds with muck sediments and high organic content. (http://www.sepro.com/default.php?page=sonarquickrelease&b=s)
Sonar SRP (Slow Release Pellets) d	Pellets, 67690-3	5.0%	0.05 lb a.i. per lb formulation	Rates identical to Sonar PR. Slow release formulation recommended for streams with rapid water movement. (http://www.sepro.com/default.php?page=sonarsrp&b=s)

[a] Application rates expressed as ppb based on the amount of a.i. applied and estimated volume of water and NOT based on the monitored concentrations. These are the maximum cumulative concentrations based on the calculated a.i. applied. Cannot apply at a rate greater than 20 ppb in lakes or reservoirs that are used as sources for potable water. Rates of 6 to 20 ppb are allowed in sources for potable water. Applications of >20 ppb cannot be made within 1320 feet of potable water source. Recommended intervals of 7 to 30 days for using treated water for irrigation.

[b] For labeling purposes, a pond is defined as a body of water that covers an area of 10 acres or less. Larger surfaces areas are classified as lakes or reservoirs.

[c] For lakes and reservoirs, the treatment area should cover at least 5 acres of the surface area of the water body.

[d] A MSDS for Sonar SRP indicates an EPA Registration Number of 67690-3, identical to Sonar Q.

Table 3: Known inerts contained in commercial formulations of Fluridone

Formulation (% of formulation classified as inerts) [a]	Inerts: Name, CAS No., Worker Right-to-Know Classification [b]	Inert % by Weight
Avast! SC (58.3% inerts)	Propylene glycol, 000057-55-6, listed in Pennsylvania as a hazardous substance when present at ≥1%	N.S.
Sonar A.S. (58.3% inerts)	Proprietary surfactants (NOS)	N.S.
	Propylene glycol, 000057-55-6, listed in Pennsylvania as a hazardous substance when present at ≥1%	N.S.
Sonar PR, Sonar SRP, and Sonar Q (95% inerts)	Clay (Crystalline silica), 001332-58-7, listed in Pennsylvania and New Jersey as a hazardous substance when present at ≥1%	N.S.

[a] See Table 2 for additional information on formulations.
[b] See Section 3.1.14 for a discussion of the EPA classification.
NOTE: No fluridone inerts are listed at the NCAP web site: http://www.pesticide.org/FOIA/inertslinks.html

Table 4: Physical and chemical properties of n-methyl formamide (NMF)

Property	Value [1]	Reference
Nomenclature		
Common Name	n-methyl formamide	U.S. EPA/OPP 2004f
Abbreviation	NMF	U.S. EPA/OPP 2004f
Structure	O = CH – NH – CH_3	Meylan and Howard 2007b
Biodegradation	Readily biodegradable	Meylan and Howard 2007b
Boiling point	199.5 deg C (Experimental)	Meylan and Howard 2007b
CAS number	123-39-7	Meylan and Howard 2007b
Molar conversion factor relative to fluridone	0.179 [59.07/329.3]	Ratio of MW of NMF to MW of Fluridone
Henry's law constant	1.97 atm-m^3/mole	Meylan and Howard 2007b
K_{oc}	2.076	Meylan and Howard 2007b
log K_{ow}	-0.97 [K_{ow} =0.11] (Experimental)	Meylan and Howard 2007b
Melting point	-3.8 deg C (Experimental)	Meylan and Howard 2007b
Molecular formula	C_2H_5NO	Meylan and Howard 2007b
Molecular weight (g/mole)	59.07	Meylan and Howard 2007b
SMILES Notation	O=CNC	Meylan and Howard 2007b
U.S. EPA Docket Number	N/A	Meylan and Howard 2007b
Vapor pressure	2.53E-01 mm Hg at 25 deg C (Experimental)	Meylan and Howard 2007b
Formation from photolysis of fluridone	0.74^{-day} of fluridone concentration	U.S. EPA/OPP 2004f, MRID 41940104
	74% of theoretic concentration formed from fluridone in 27 days in distilled water.	Saunders and Mosier 1983
	36% of theoretic concentration formed from fluridone in 27 days in distilled water	Saunders and Mosier 1983
Water biodegradation	98% of BOD in 3 days	U.S. EPA/HPVIS 2004
Water biodegradation [dimethylformamide]	30 mg/L eliminated in 6 days in unacclimated river die away test	CERI 2007
Water solubility	1,000,000 mg/L (Experimental)	Meylan and Howard 2007b

Table 5:Summary of toxicity values used in ecological risk assessment

(all amounts expressed as a.i.)

Organism Group/Duration	Endpoint	Toxicity Value	Reference
Terrestrial Animals			
Acute			
Non-canine Mammals	Devel. NOAEL	125 mg/kg bw	Section 4.3.2.1.
Canine Mammals	Devel. NOAEL	125 mg/kg bw	Section 4.3.2.1.
Birds (Mallards)	Acute dietary NOAEL	1500 mg/kg bw	Section 4.3.2.2
Honey Bee	NOAEL	3,900 mg/kg bw	Section 4.3.2.3
Longer-term			
Non-canine Mammals	Chronic NOAEL	8 mg/kg bw/day	Section 4.3.2.1
Canine Mammals	Chronic NOAEL	75 mg/kg bw/day	Section 4.3.2.1
Birds	Repro. NOAEL	68 mg/kg bw/day	Section 4.3.2.2.
Aquatic Animals			
Acute			
Amphibians Sensitive ()	N/A	N/A	
Tolerant ()	N/A	N/A	
Fish Sensitive (trout)	Est. NOEC	0.5 mg/L	Section 4.3.3.1.1.
Tolerant (bluegill)	Est. NOEC	2 mg/L	Section 4.3.3.1.1.
Invertebrates			
Sensitive (midges)	Chronic NOEC	0.6 mg/L	Section 4.3.3.3.1.
Tolerant (blue crab)	Est. NOEC	3.35 mg/L	Section 4.3.3.3.1.
Longer-term			
Amphibians Sensitive ()	N/A	N/A	
Tolerant ()	N/A	N/A	
Fish Sensitive ()	Est. Chronic NOEC	0.04 mg/L	Section 4.3.3.1.2
Tolerant (minnows)	Chronic NOEC	0.48 mg/L	Section 4.3.3.1.2
Invertebrates Sensitive (*Daphnia*)	Chronic NOEC	0.1 mg/L	Section 4.3.3.3.2
Tolerant (midges)	Chronic NOEC	0.6 mg/L	Section 4.3.3.3.2
Aquatic Plants			
Algae			
Sensitive (*Oscillatoria*)	96-h NOEC	0.02 mg/L	Section 4.3.3.4.2
Tolerant (*Anabaena*)	NOEC	0.5 mg/L	Section 4.3.3.4.2
Macrophytes			
Sensitive (several sp)	90-day NOEC	0.001 mg/L	Section 4.3.3.4.1
Tolerant(Illinois pondweed)	56-day NOEC	0.024 mg/L	Section 4.3.3.4.1

NOTE TO REVIEWERS:
The following is a snapshot of the entries for fluridone in the toxicity database used for WorksheetMaker. The snapshot is intended only for internal QC and will be deleted when the final report is submitted.

Recept	Dur	Sens	ToxCode	Value	Units	DocReference
Alg		Sn	NOEC	0.02	mg/L	Table 5
Alg		Tl	NOEC	0.5	mg/L	Table 5
Aqlnv	Ac	Sn	NOEC	0.6	mg/L	Table 5
Aqlnv	Ac	Tl	NOEC	3.5	mg/L	Table 5
Aqlnv	Ch	Sn	NOEC	0.1	mg/L	Table 5
Aqlnv	Ch	Tl	NOEC	0.6	mg/L	Table 5
Brd	Ac		NOEC	1500	mg/kg bw	Table 5
Brd	Ch		NOAEL	68	mg/kg bw/day	Table 5
Fsh	Ac	Sn	NOEC	0.5	mg/L	Table 5
Fsh	Ac	Tl	NOEC	2	mg/L	Table 5
Fsh	Ch	Sn	NOEC	0.04	mg/L	Table 5
Fsh	Ch	Tl	NOEC	0.48	mg/L	Table 5
HonBee	Ac		NOAEL	3900	mg/kg bw	Table 5
Hum	Ac		RfD	1.25	mg/kg bw	Section 3.3.3
Hum	Ch		RfD	0.08	mg/kg bw/day	Section 3.3.2
Mam	Ac		NOAEL	125	mg/kg bw	Table 5
Mam	Ch		NOAEL	8	mg/kg bw/day	Table 5
MamCrn	Ac		NOAEL	125	mg/kg bw	Table 5
MamCrn	Ch		NOAEL	75	mg/kg bw/day	Table 5
Mcrph		Sn	NOEC	0.001	mg/L	Table 5
Mcrph		Tl	NOEC	0.024	mg/L	Table 5

INTERNAL NOTE : Ensure that all of the above entries (except for the two RfDs) are consistent with Table 5.

Table 6: Summary of toxicity values for macrophytes

Species	Duration (Days)	NOEC (ppb)	LOEC (ppb)	Reference
Eurasian watermilfoil	90	1	2	Netherland and Getsinger 1995a
Eurasian watermilfoil	84		5	Nelson et al. 1998
Eurasian watermilfoil	56		6	Poovey et al. 2004
Eurasian watermilfoil	90		12	Netherland et al. 1993
Hydrilla	90	1	2	Netherland and Getsinger 1995a
Hydrilla	84		5	Nelson et al. 1998
Hydrilla	90		12	Netherland et al. 1993
Hydrilla (immature)	84	0.5	5	MacDonald et al. 1993
Hydrilla (mature, 8 m.)	84	50		MacDonald et al. 1993
Curlyleaf pondweed	56		3	Poovey et al. 2008
American Pondweed	84		5	Nelson et al. 1998
Duckweed	22		10.4	Lockhart et al. 1983
Elodea	56	6	12	Poovey et al. 2004
Sago pondweed	56	6	12	Poovey et al. 2004
Illinois pondweed	56	12	24	Poovey et al. 2004
Wild celery	56	24		Poovey et al. 2004
Wild celery	84	5		Nelson et al. 1998

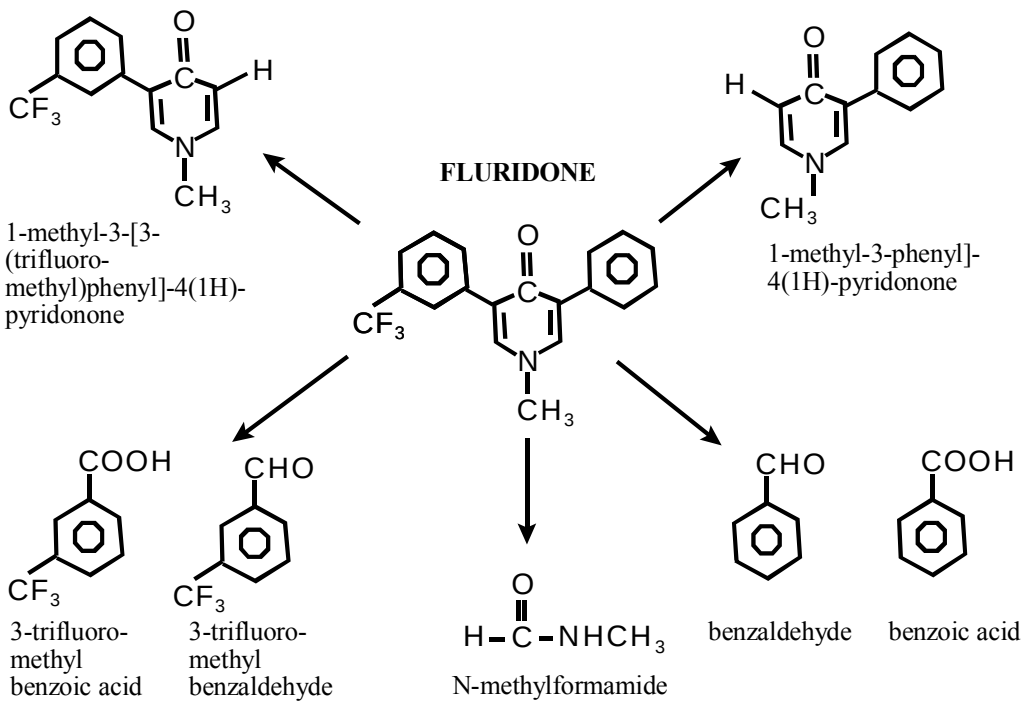


Figure 1: Photolysis products of fluridone

(redrawn from Figure 1 in Saunders and Mosier, 1983)

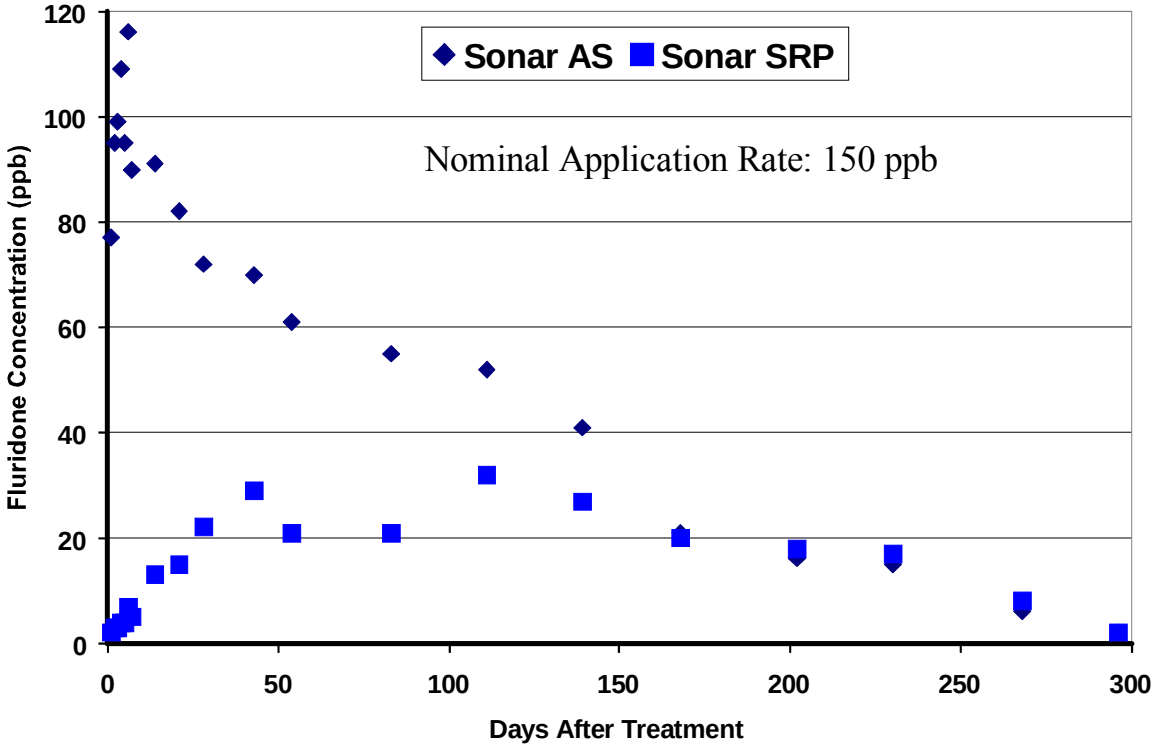


Figure 2: Concentration of fluridone in pond water (West et al. 1990)

(Data from Table IV in West et al. 1990)

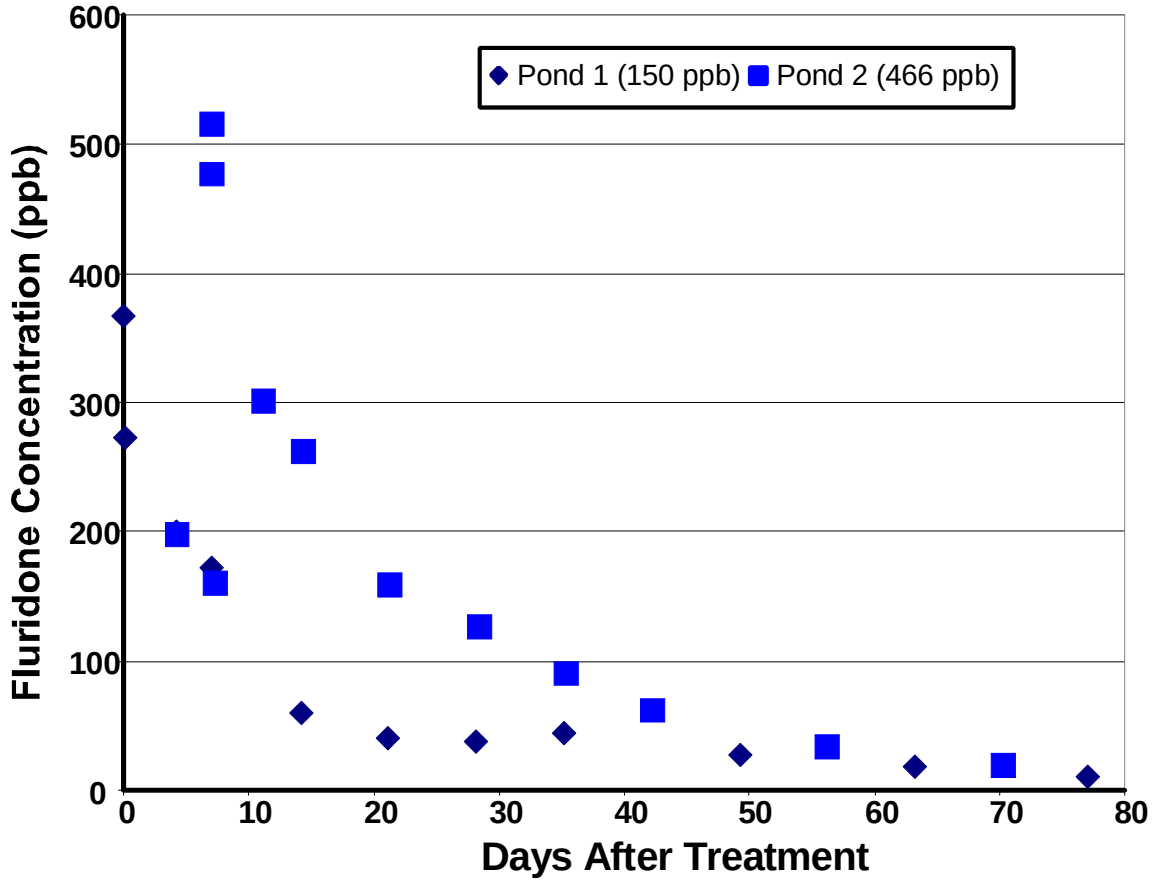


Figure 3: Concentrations of fluridone (liquid formulation) in two experimental ponds
(redrawn from Figure 1 in Osborne et al. 1989)

Note: Data from Osborne et al. (1989) after 80 days, not illustrated above, showed a gradual decline from about 10 ppb to 1 ppb by DAT 167.

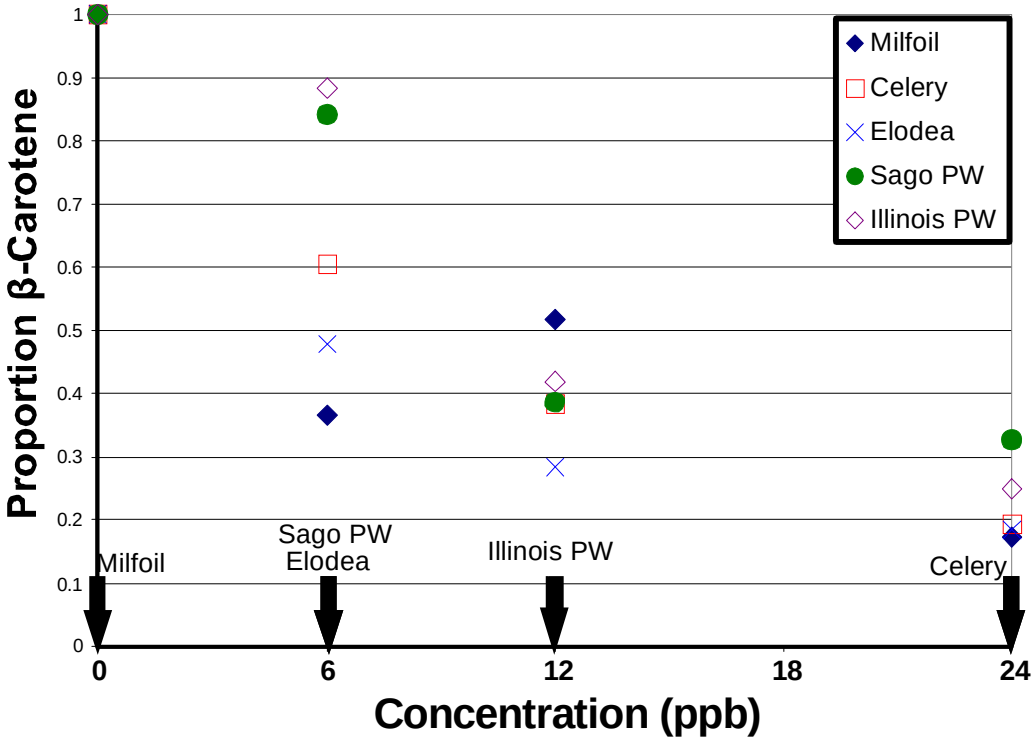


Figure 4: Macrophyte variability in response to fluridone (Poovey et al. 2004)

Note: Data from Poovey et al. (2004). The proportion of β-carotene with respect to controls is for Day 28 is based on data in Table 3, p. 16, of Poovey et al. (2004). The downward pointing arrows on the X-axis are NOEC values at Day 56 and these values are taken from Figure 6, p. 14, of Poovey et al. (2004).

Appendix 1: Laboratory and Simulation Studies on the Environmental Fate

Appendix 2: Acute Toxicity to Mammals

Appendix 3: Longer-term Toxicity to Mammals

Appendix 4: Toxicity to Birds

Appendix 5: Toxicity to Fish

Appendix 6: Toxicity to Aquatic Invertebrates

Appendix 7: Toxicity Bioassays in Aquatic Plants

Appendix 8: Aquatic Field Studies

Data Summary	Reference
Bioconcentration in Fish	
BCF (whole body) values ranged from 2 to 9 in channel catfish exposed continuously to fluridone for 60 days. 4-hydroxy fluridone (metabolite) represented 15 to 23% of the total fluridone based residue. BCF values based on the total of the two compounds ranged from 3 to 10. (See table 7 of the study for details.)	Hamelink et al. 1986
Fluridone levels in carp, *Cyprinus carpio*, reached a maximum of 484 µg/kg on day 13 after a man-made pond (8 m wide x 70 m long x 1 m deep) in Northern Greece was treated with an aqueous suspension of formulated fluridone (Sonar 4AS) sprayed over the water surface to produce a concentration of 0.042 mg/L a.i. (42 ppb) in the pond water. Maximum monitored concentrations, however, were only about 2.9 ppb. Concentrations in carp peaked at 0.484 ppb between Day 15 and Day 20 (see Figure 2 in paper). At this time, the concentration of fluridone was about 0.5 ppb.	Kamarianos et al. 1989
Residues in bluegill sunfish (1.0-3.0 g) exposed to 0.15 ppm (actual measured water concentration = 1.44 ppm) ^{14}C-fluridone under static conditions for 72 hours were 60X in non-edible tissue and 1.5X in edible tissue. Water characteristics not reported. Residue in whole fish not reported. **Note**: Zucker et al. 1982 (EFB Review of Sonar AS and Sonar SP) indicates that principal residues in carcass were fluridone and its 4-hydroxyphenyl metabolite (no other major metabolites present); total carcass residue only 1.5 times greater than fluridone concentration in treated water at equilibrium.	Magnussen and Rainey 1982 (Summarized in Fletcher 1982)
Estimated whole fish bioconcentration factor of 91 (±30) in juvenile rainbow (6 to 12 g) trout based on kinetic analyses of uptake and depuration. Exposures were to 50 ppb fluridone in water. Maximum concentration in fish did approach about 4 mg/kg bw or 4,000 µg/kg [BCF = 80]. As discussed by Muir et al. (1982), small fish will absorb more rapidly than larger game size fish.	Muir et al. 1982
In a 144-hour uptake study at 5 ppm fluridone (technical NOS) for 5 days in a static system with aeration, fluridone accumulated relatively quickly in bluegill sunfish (fluridone whole-body residues = 210-220 ppm in 72 hours); in a 120-hour study for metabolite isolation at 0.1 or 5 ppm fluridone (technical NOS) under the same conditions stated above, fluridone bioaccumulation factors were 92.3x and 40.5x, respectively. Furthermore, the DER indicates that fluridone accumulation in bluegills was inversely proportional to the concentration in water, and fluridone was significantly metabolized by the bluegills. This DER includes at a table of whole-body tissue residue by exposure time (hours) on page 3; a table of calculated and measured exposure concentrations in water, with the corresponding average weights of fish, whole-body residues, and bioaccumulation factors on page 4; a table of results from the metabolite isolation study on page 5.	Rainy 1978

Data Summary	Reference
BCF ranges from 0 (not detected in fish) to 1.7.	West et al. 1979
This is a BCF life cycle study with fathead minnows. Residues in fathead minnows exposed to mean measured concentrations of 0.12 (± 0.02), 0.24 (± 0.02), 0.48 (± 0.03), 0.96 (± 0.06), or 1.9 (± 0.20) ppm non-labeled fluridone for 9 months (life cycle) under flow-through conditions had an average BCF of 3.23X (± 1.65) for fluridone, with small differences ranging from 4.62 ± 1.89 (30-day old fry) to 1.96 (165-day old mature fish). **Note**: Zucker et al. 1982 (EFB Review of Sonar AS and Sonar SP) indicates that the concentration of fluridone in all life stages of the fish was directly related to the exposure concentration. The average BCF = 3.23 for all life stages and exposure concentrations.	West et al. 1980 (also reviewed in Fletcher 1982)
In pond and lake field trials with 10 species of fish: average BCF = 1.33 in edible fish tissue and 6.08 in whole fish. BCF values varied with species. Based on complete data sets – i.e., edible tissue, offal, and whole fish – the lowest BCF was in bluegills [0.94 (edible tissue), 4.58 (whole fish)] and the highest BCF was in rainbow trout [2.3 (edible tissue), 15.51 (whole fish)]. See Table XI, p. 584, in publication.	West et al. 1983. (also reviewed in Zucker et al. 1982, page 8).
Soil Metabolism	
Application of fluridone at 0.3 or 0.4 lbs a.i/acre resulted in half lives ranging from 38 to 159 days; soil incorporation of 0.3 to 0.1(?) lbs a.i/acre fluridone resulted in half lives ranging from 43 to 575 days with a central value of about 6 months.	West 1978 (Summarized in Davis 1978)
Hydrolysis	
A man-made pond (8 m wide x 70 m long x 1 m deep) in Northern Greece was treated with an aqueous suspension of formulated fluridone (Sonar 4AS) containing 48% fluridone sprayed over the water surface to produce a concentration of 0.042 mg/L a.i. in the pond water. Fluridone concentrations in water decreased rapidly during the first few days after treatment, and no fluridone was detected in the water two months after treatment. [See Figure 1 of the study for the results of the dissipation study.]	Kamarianos et al. 1989
Fluridone (Sonar 4 AS) was applied at a rate of 1.14 kg a.i./ha to two ponds with negligible water exchange in May 1984. The fluridone concentrations decreased logarithmically with time, approaching 0 in 64 or 69 days after treatment. Fluridone (5P) was applied at a rate of 2.27 kg a.i./ha to one pond with negligible water exchange in May 1984. No significant decrease in fluridone concentrations was observed after 53 days.	Langeland and Warner 1986

Data Summary	Reference
Photolysis	
Three outdoor artificial ponds (6 inches loam hydrosoil consisting of 7.6% organic matter; 30 inches water) treated with 1 lb/surface area of ^{14}C-phenyl, -carbonyl-, or –methyl labeled and non-labeled fluridone (calculated concentration in 30 inches water column = 0.147 ppm). Half-live = approx 21 days in all three ponds. No metabolites identified. Likely mechanisms of dissipation: photolysis and/or soil adsorption. Soil not sampled.	Berard and Rainey 1980 (Summarized in Fletcher 1982)
In distilled water, under sunlight conditions, fluridone degraded steadily; unchanged parent compound accounted for 20% of the initial applied ^{14}C after 27 days. In lake water, under sunlight conditions, fluridone degraded steadily; unchanged parent compound accounted for 16% of the initial applied ^{14}C after 27 days. Conclusion: *Fluridone will photodegrade in the aqueous environment with a half-life ranging from 26 to 55 hours*. *Photoproducts include volatile and non-volatile compounds. Volatile photoproducts form with the destruction of the pyridinone ring*.	Mosier and Saunders 1982 Also summarized in Fletcher 1982
Water Degradation/Dissipation	
In an anaerobic aquatic metabolism study, 1.5 lb ai/surface acre ^{14}C carbonyl fluridone was added to pond water and hydrosoil (sediment) from Florida, Mississippi, and California, and samples were taken at 0, 0.5, 1.5, 3, 6, 9, and 12 months. After 12 months, the amount of unchanged ^{14}C fluridone was 88.5% in the Florida soil, 74.7% in the Mississippi soil, and 62.6% in the California soil. No half-life was calculated. Degradation did not occur until after 9 months incubation in the Mississippi and California soils, suggesting that microbial activity will degrade fluridone under anaerobic condition, but only after a lengthy lag time. 1,4-dihydro-1-methyl-4-oxo-5-(3-(trifuouromethyl)-phenyl)-3-pyridinecarboxylic acid was the only degradation product found in the two soils and was not found in the field dissipation study. Conclusion: *Fluridone is stable under anaerobic aquatic conditions in the laboratory*.	Rainey 1981 (Summarized in Fletcher 1982)
In the laboratory, aqueous fluridone readily absorbed onto hydrosoil: adsorption coefficients of 37 (loam hydrosoil) and 45 (silt loam hydrosoil). Fluridone also desorbed from the hydrosoil, accordingly under field conditions it would be expected to dissipate from hydrosoil by gradual desorption in the water where it would undergo photodegradation.	Zucker et al. 1982 (EFB Branch Review of Sonar AS and Sonar SP)
Microbial Degradation	
No remarkable effects on bacteria, fungi, protozoa, sewage sludge microorganisms, and indigenous soil microbial populations. No significant effect observed on rates of nitrogen fixation, nitrification or degradation of starch, cellulose, or protein.	Zucker et al. 1982 (EFB Branch Review of Sonar AS and Sonar SP)

Table arranged as follows: ORAL (rats, mice, dogs, cats), SUBCUTANEOUS (rats, mice), DERMAL (rabbits, guinea pigs), OCCULAR (rabbits), INHALATION (rats)

Species	Exposure	Response	Reference
ORAL			
Rats, Oral			
Wistar, male (122 g mean bw), female (118g mean bw), 5-6 wks old, 5/sex	Single gavage dose of 500 mg/kg equivalent to 125 mg/kg a.i. test material [Sonar 5P (formulation containing 5% fluridone by wt)] pellets ground to powder (5% suspension in 10% acacia)	No mortalities; no signs of toxicity during 14-day observation period. ***Note: the DER appears to miscalculate the equivalent dose of active ingredient (fluridone)***.	Ansley and Arthur 1980a MRID 103260
Fischer 344, male (159 ± 5.1 g mean bw) and female (136 ± 4.3 g mean bw), 8-9 wks old, 5/sex	Single gavage dose of 500 mg/kg equivalent to 25 mg/kg a.i. test material [Sonar 5P (formulation containing 5% fluridone by wt)] (5% suspension of formulation in 10% aqueous acacia)	No mortalities; no signs of toxicity during 7-day observation period.	Ansley and Levitt 1981a MRID 103259
Fischer 344, 5 males/5 females	Single gavage dose of 5000 mg/kg a.i. test material (Sonar 5P pellet formulation containing 5% fluridone) dissolved in 10% aqueous acacia	LD_{50} >5000 mg/kg No mortality; only sign of toxicity was leg weakness in all rats 1-5 hours post dosing no longer apparent at 24 hours post dosing; all rats appeared normal throughout the 14-day observation period.	Mauer 1985b
Harlan Wistar, adult males (119.5 ±1.8 g mean bw) and females (121.0±1.0 g mean bw), 4-5 wks old, 10/sex	Single gavage dose of 10,000 mg/kg EL-171 (fluridone technical grade 97%) aqueous suspension in 5% acacia	LD_{50} >10,000 mg/kg Mortalities: 0/10 females; 3/10 males; signs of toxicity included hypoactivity, leg weakness, ataxia, and diuresis 1-4 hours post dosing; all surviving rats appeared normal after 24 hours. Findings were negative for gross necropsy performed on five surviving rats/sex after 14-day observation period.	Frick 1979b (tif 112900.009)
Harlan Wistar females, (116±0.8 g mean bw), 10/dose group	Single gavage dose of 2000, 3000, 4500, 7000, or 10,000 mg/kg formulation (wettable powder containing 50% technical EL-171)	LD_{50} >10,000 mg/kg No mortality; signs of toxicity included diuresis, ptosis, leg weakness, loss of righting reflex, hypoactivity and dyspnea on days 1 and 2 post dosing, on day 3, test animals appeared to be normal.	Frick 1979a (tif 112900.008)

Appendix 2: Acute toxicity to Experimental Mammals *(continued)*

Species	Exposure	Response	Reference
Harlan Wistar, males (114 ±1.4 g mean bw) and females (120±4.5 g mean bw), 5/sex	Single gavage dose 0.5 mL/kg aqueous suspension containing 45% technical EL-171	LD_{50} > 0.5 mL/kg No mortality, signs of toxicity included ptosis and hypoactivity on day 1; all test animals appeared normal on days 2-14.	Frick 1979a (tif 112900.008)
Mice, Oral			
Harlan, ICR, males (17.1±0.2 g mean bw) and females (16.6±0.2g mean bw), 4-5 wks old, 10/sex	Single gavage dose of 10,000 mg/kg EL-171 (fluridone technical grade 97%) aqueous suspension in 5% acacia	LD_{50} >10,000 mg/kg Mortalities: 2/10 females; 3/10 males; signs of toxicity included hypoactivity , leg weakness, ptosis, ataxia, clonic convulsion, loss of righting reflex, and dyspnea 48 hours post dosing; surviving mice appeared normal by 72 hours; findings were negative for gross necropsy performed on five surviving mice/sex after 14-day observation period.	Frick 1979a,b (tif 112900.008)
Dogs, Oral			
Beagle, 2/sex, 10.3±0.7 kg mean bw	Single oral dose 500 mg/kg EL-171 (fluridone technical grade 97%) by capsule	LD_{50} >500 mg/kg No mortality and no apparent signs of toxicity, emesis observed twice in one dog; 5 hours post dosing, material believed to be test compound appeared in vomitus; necropsy not performed.	Frick 1979a,b (tif 112900.008)
Cats, Oral			
Cat, domestic, 2/sex, 3.41±0.22 kg mean bw	Single oral dose 250 mg/kg EL-171 (fluridone technical grade 97%) by capsule	LD_{50} >250 mg/kg No mortality and no apparent signs of toxicity, emesis observed in one female cat on day following treatment; necropsy not performed	Frick 1979a,b (tif 112900.008)

Species	Exposure	Response	Reference
SUBCUTANEOUS			
Rats, Subcutaneous			
Harlan Wistar, adult females (118.7±1.8g mean bw), 4-5 wks old, 5/dose group	Single subcutaneous dose of 1000, 1800, 3000, or 5000 mg/kg EL-171 (fluridone technical grade 97%) aqueous suspension in 5% acacia	LD_{50} >5000 mg/kg No mortality; signs of toxicity includes hypoactivity observed 1-24 hours post dosing; findings were negative for gross necropsy performed on five surviving rats in high dose group after 14-day observation period.	Frick 1979a (tif 112900.008)
Harlan Wistar, adult males (122.5 ±1.5g mean bw) and females (128.0±2.3 g mean bw), 4-5 wks old, 10/sex	Single subcutaneous dose of 2000 EL-171 (fluridone technical grade 97%) aqueous suspension in 5% acacia	LD_{50} >2000 mg/kg No mortality; no signs of toxicity; findings were negative for gross necropsy performed on surviving rats after 14-day observation period.	Frick 1979a (tif 112900.008)
Mice, Subcutaneous			
Harlan ICR, adult females (15.7±0.2 g mean bw), 4-5 wks old, 5/dose group	Single subcutaneous dose of 1000, 1800, 3000, or 5000 mg/kg EL-171 (fluridone technical grade 97%) aqueous suspension in 5% acacia	LD_{50} >5000 mg/kg No mortality; signs of toxicity included hypoactivity, leg weakness, ptosis, and clonic convulsions 2-24 hours post dosing; necropsy not performed.	Frick 1979a,b (tif 112900.008)
Harlan, ICR, males (16.8±0.2 g mean bw) and females (16.8±0.2g mean bw), 4-5 wks old, 10/sex	Single subcutaneous dose of 2000 mg/kg EL-171 (fluridone technical grade 97%) aqueous suspension in 5% acacia	LD_{50} >2000 mg/kg Mortalities: 1/10 females; 1/10 males; signs of toxicity included hypoactivity, leg weakness, partial loss of righting reflex, and ptosis 2-24 hours post dosing; tissues examined during necropsy not stated; however, findings were negative.	Frick 1979a,b (tif 112900.008)
DERMAL			
New Zealand white rabbits: 3 males (2.10 ± 0.06 kg) and 3 females (2.32 ± 0.17 kg); 12-14 wks old	2000 mg/kg ground (powder) Sonar 5P (5% fluridone by wt) applied to shaved, skin abraded backs of 2 females and 1 male. Test sites were covered with damp gauze, occlusive dressing, and adhesive sleeve for 24 hours.	No deaths, no signs of toxicity or dermal irritation observed during 14-day observation period. Body weight gains were normal.	Ansley and Arthur 1980c MRID 103260
New Zealand white rabbits: 3 males (3.84 ± 0.15 kg) and 3 females (3.68 ± 0.15 kg); 12-18 wks old	2000 mg/kg bw undiluted ground (powder) Sonar 5P (5% fluridone by wt) applied to shaved, skin abraded backs of 2 females and 1 male. Test sites were covered with damp gauze, occlusive dressing, and adhesive sleeve for 24 hours.	No deaths, no signs of toxicity or dermal irritation observed during 14-day observation period. Body weight gains were normal.	Ansley and Levitt 1981c MRID 103259

Species	Exposure	Response	Reference
New Zealand albino, 2/sex, 2.94±0.12 kg mean bw,	500 mg/kg EL-171 (fluridone technical grade 97%) applied to clipped (all animals) and abraded (2 animals) backs covered with occlusive dressing for 24 hours. Test sites were rinsed with tap water.	LD_{50} >500 mg/kg No mortality; no signs of toxicity, no dermal irritation during 14-day observation period. Application vehicle not stated.	Frick 1979a (tif 112900.008)
Albino rabbits, 3/sex weighing 2.3-2.95 kg	2 g/kg topical application of undiluted fluridone formulation (wettable powder containing 50% technical EL-171) to clipped (all animals) and abraded (3 animals) backs covered with occlusive dressing for 24 hours. Treated sites were rinsed with tap water.	LD_{50} >2 g/kg No mortality; no signs of toxicity, no dermal irritation during 14-day observation period. Application vehicle not stated.	Frick 1979a (tif 112900.008)
Albino rabbits, 3/sex weighing 2.40-2.80 kg	2 mL/kg topical application of undiluted aqueous suspension containing 45% technical EL-171 to clipped (all animals) and abraded (3 animals) backs covered with occlusive dressing for 24 hours. Treated sites were washed with water.	LD_{50} >2 mL/kg All treated rabbits developed mild erythema and mild edema at treated site (no scoring). No clinical signs of toxicity observed; all rabbits appeared normal on days 6-14.	Frick 1979a (tif 112900.008)
New Zealand white rabbits, 5 males and 5 females, average weight = 2.64 kg	5000 mg/kg bw a.i. (test material Sonar SRP/5P formulation containing 5.0% a.i. by wtg) applied to clipped backs, dressing affixed to treatment site for 24 hours, treatment sites rinsed after dressing removal; observation period = 14 days	LD_{50} >5000 mg/kg Non-treatment related death of one male on day 11 No overt signs of toxicity; necropsy revealed no gross abnormalities.	Pohland et al.1989a MRID No. 41424102 Summarized in Moats 1990
New Zealand white rabbits, males and females, 12-24 weeks old, average weight = 2.64 kg	5000 mg/kg bw a.i. (test material Sonar SRP/5P formulation containing 5.0% a.i. by wtg) applied to clipped backs, dressing affixed to treatment site for 24 hours, treatment sites rinsed after dressing removal; observation period = 14 days	No dermal irritation observed during the 14-day observation period.	Pohland et al.1989a MRID No. 41424102 Summarized in Moats 1990

Species	Exposure	Response	Reference
Guinea pigs (NOS)	Test material: Sonar SRP/5P formulation containing 5% fluridone by weight and ethanol (95%) used in sensitization study; exposure NOS	Data (not provided but referenced in DER) indicate that test material is not a sensitizer. *Handwritten DER indicates that the study was previously submitted to the CA Dept of Food and Agriculture and the individual induction and challenge scores were not provided*.	Pohland and St. Clair 1989 MRID No. 41424105 Summarized in Moats 1990
Guinea pigs, female Hartley, 10-14 weeks old, 10/group	Induction/challenge test involving topical application of 0.2 mL technical grade fluridone (98.7%) to nuchal area (hair clipped) and occluding application site with square pitch band aid, which was removed after 6 hours.	No evidence of sensitization or dermal irritation in guinea pigs receiving induction and challenge with technical fluridone; DNCB induced moderate erythema and slight edema at 24 hour, which was also observed at 48 and 72 hours.	Probst and Pierson 1981
OCCULAR			
New Zealand white rabbits: 3/sex (wt not given); 12-14 wks old	138 mg ground test material (= 0.1 mL) Sonar 5P (5% fluridone by wt) instilled over corneal surface and into conjunctival cul-de-sac of one eye/rabbit. Eyelids held closed for several seconds and not rinsed.	Conjunctival hyperemia observed in all rabbits 1 hour after treatment (maximum score of 1 on a scale of 1-3) and in 5/6 rabbits (2 males, 3 females) for 2 days after treatment; hyperemia not observed in any rabbits by day 3 after treatment. No corneal lesions observed by fluorescein dye test 7 days after treatment.	Ansley and Arthur 1980b MRID 103260
New Zealand white rabbits: male (3.20 ± 0.14 kg mean bw) and female (3.31 ± 0.08 kg mean bw); 12-18 wks old; number not specified	98 mg ground test material (= 0.1 mL) Sonar 5P (5% fluridone by wt) instilled over corneal surface and into conjunctival cul-de-sac of one eye/rabbit. Eyelids held closed for several seconds	Slight iritis and corneal dullness observed at 1 hour in one male and one female rabbit; conjunctival hyperemia and chemoisis observed in all treated rabbits at 1 hour (maximum score of 1 on scale of 1-3 and 1-4, respectively); irritation reversed within 3 days with no signs of corneal lesions.	Ansley and Levitt 1981b MRID 103259
New Zealand albino rabbits, 3/sex, (approx. 2.5 kg)	44 mg (=0.1cc) EL-171 (fluridone technical grade 97%) instilled over corneal surface and into conjunctival cul-de-sac of one eye/rabbit. Eyelids held closed for 3 seconds; eyes not rinsed.	No mortality; slight to moderate corneal dullness, iritis, and conjunctivitis after 1 hour; all eyes appeared normal after (4?)* days except for one male with pannus involving 10% of the corneal surface; four rabbits had dulling of corneal luster through day 3; conjunctiva hyperemia and chemosis observed in all rabbits through day 4. *protocol states no examination made between days 3-7.	Frick 1979a (tif 112900.008)

Species	Exposure	Response	Reference
New Zealand albino rabbits, 3 males and 6 females, (approx. 2.5 kg)	26 mg (=0.1cc) EL-171 (fluridone technical grade 97%) instilled over corneal surface and into conjunctival cul-de-sac of one eye/rabbit. Treated eyes of 3 rabbits rinsed with 300 mL saline for 2 minutes after exposure; eyes of remaining rabbits not rinsed.	Slight conjunctival redness in three of the unrinsed eyes after 1 hour but clearing by 24-48 hours; no other signs of irritation noted. **EFB notes differences in this eye irritation study, relative to the study captured above, in both quantity of test material and irritation observed and states: *Till these inconsistencies are resolved, this technical will rank as Category II on the basis of eye irritation*.**	Frick 1979a (tif 112900.008)
New Zealand albino rabbits, 3 males and 3 females (NOS)	27 mg (= 0.1cc) undiluted fluridone formulation (wettable powder containing 50% technical EL-171) instilled over corneal surface and into conjunctival cul-de-sac of one eye/rabbit; eyelids held closed for approx. 3 seconds	Slight conjunctivitis developed in all treated eyes within 1 hour of exposure; irritation cleared within 72 hours; corneal and iris membranes appeared unaffected.	Frick 1979a (tif 112900.008)
New Zealand albino rabbits, 3 males and 3 females (NOS)	0.1 mL undiluted aqueous suspension containing 45% technical EL-171 instilled into one eye of each rabbit (no other details reported).	Slight conjunctival hyperemia developed in all treated eyes within 1 hour of exposure and 3 rabbits had slight conjunctival chemosis. All eyes appeared normal within 24-48 hours and remained so throughout the 7-day observation period.	Frick 1979a (tif 112900.008)
New Zealand white rabbits, males and females, six in total (NOS)	0.1 cc a.i. (test material: Sonar SRP/5P containing 5.0% fluridone by weight) instilled into conjunctival sac of one eye of each rabbit; eyes examined and scored at 1, 24, 48, and 72 hours and 7 days after treatment	No cornea opacity; no conjunctivae redness, chemoisis, or discharge. *This handwritten DER classifies the study as supplemental because the narrative description does not agree with the tabular data concerning the use of fluorescein dye 24 hours after treatment.*	Pohland et al. 1989c MRID No. 41424104 (Cited in Moats 1990)
INHALATION			
Harlan Wistar rats, adult males and females (180.0-220 g), 5-6 wks old, 5/sex	Head only exposure to 2130 mg/m3 air or 2.13 mg/L EL-171 (fluridone technical grade 97%) for 1 hour	LD_{50} > 2.13 mg/L No mortality; no signs of toxicity observed daily for 14 days.	Frick 1979a (tif 112900.008)

Species	Exposure	Response	Reference
Harlan Wistar rats, 5/sex (NOS)	Head only exposure to atmosphere containing fluridone formulation (wettable powder containing 50% technical EL-171) at 2.45 mg/L* air (dust particle size not stated) for 1 hour	LD_{50} >2.45 mg/L No mortality; no signs of toxicity observed daily for 14 days EFB notes that study summary gave concentration of 2.48 mg/L	Frick 1979a (tif 112900.008)
Wistar rats, 5/sex (NOS)	Head only exposure to aqueous suspension containing 45% technical EL-171 at atmospheric concentration of 9.6 mL/L air (suspension diluted to 25% (v/v) in distilled water) for 1 hour	LD_{50} >9.6 mg/L Slight chromorhiorrhea and chromodacryorrhea (red tears) observed in all rats post exposure; however, all rats returned to normal within 1 hour and remained so throughout 14-day observation period.	Frick 1979a (tif 112900.008)
Fischer 344 rats, 10/sex, weighing 150-246 g	Nose only exposure to 4.12 mg/L a.i. (test material: Sonar SRP/5P formulation containing 5.0% fluridone by weight) for 4 hours	LC_{50} >4.12 mg/L No mortality; clinical signs of toxicity included hypoactivity, chromodacryorrhea (red tears), and ataxia among exposed females. All rats appeared normal on day 5; necropsy revealed no gross abnormalities.	Pohland et al. 1989b MRID No. 41424103 Summarized in Moats 1990

Separate tables for Subchronic Oral, Subchronic Dermal, Developmental/Teratology, Reproduction, Chronic Oral. Each table sorted by author, date.

Subchronic Dietary (15 days to 90 days)

Species	Exposure	Response	Reference
Harlan Wistar rats, 28-35 days old, 15/sex/dose group	Dietary concentrations of 0, 0.2, 0.4, or 0.8% (0.0, 166, 300, or 536 mg/kg/day for males and 0.0, 163, 302, or 478 mg/kg/day for females) based on initial food consumption) technical grade fluridone (EL-171) for 89 days (males) and 90 days (females)	No mortality; no treatment related effects on clinical chemistry parameters; all treated males had decreased erythrocyte counts, hemoglobin values, and hematocrit values; reduced food consumption was observed in all rats at 0.8% dietary test compound; decreases in growth rate and terminal weight were observed in all rats at 0.4 and 0.8% dietary test compound; all treated rats had increased liver weights and kidney weights were increased among female rats; an increase in activity of hepatic enzyme p-nitoanisole 0-demethylase was observed in males at 0.4 and 0.8% dietary test compound. The observed treatment-related increases in absolute and relative liver weights precluded the identification of a NOEC.	Frick 1979b (tif 112900.009)
SPF-CD Fischer 344 rats; 41/2 - 51/2 wks old, 15/sex/dose	Dietary concentrations of 0.0, 0.033, 0.056, 0.1, 0.14, or 0.2%. Corresponds to concentrations of 0, 330, 560, 1000, 1400, or 2000 ppm. Base on recovery of 81.9% of nominal concentration at the end of the study, doses calculated as 25, 44, 87, 114, or 146 mg/kg/d day for males.	No mortality; no treatment related effects on body weight, food consumption, hematology, or clinical chemistry parameters and microsomal enzyme activity; treatment related effects included dose-related increases in absolute and relative liver and kidney weights in males and females; histological alterations were limited to liver centrilobular hypertrophy in males at the two highest concentrations. NOAEL: 25 mg/kg bw/day LOAEL: 44 mg/kg bw/day	Frick 1979b (tif 112900.009) Also summarized in U.S. EPA/OPP 2004d as MRID 135209.

Subchronic Dietary (15 days to 90 days)			
Species	**Exposure**	**Response**	**Reference**
ICR/SPF mice, males (27.5±1.3 g) and females (23.2±2.2 g), 4-6 wks old, 15/sex/dose group	Dietary concentrations of 0.0, 0.033, 0.056, 0.100, 0.140, or 0.200% (0.02, 49.5, 84.0 150, 210, or 300 mg/kg day) fluridone (EL-171) for 92-94 days. NOTE: The dietary level of 0.033% bw is reported in Frick 1979b as being associated with a dose of 0.02 mg/kg bw/day. This appears to be an error. By analogy to the 0.056% group, the dose would have been about 29 mg/kg bw/day.	1 death that could not be attributed to treatment; slight increase in leukocyte count in females (but not males) in 0.100, 0.140, or 0.200% test compound dose groups; increases in absolute liver weights among all mice in 100, 0.140, or 0.200% test compound dose groups; increase in relative liver weights in all males and in females in 0.100, 0.140, or 0.200% test compound dose groups; significant increase in activity of hepatic enzyme p-nitoanisole 0-demethylase in males in 0.140, or 0.200% test compound dose groups and females in 0.100, 0.140, or 0.200% test compound dose groups; and dose-dependent incidence of hepatic centrilobular hypertrophy. **Conclusion:** mice exposed to dietary levels of 0.033, 0.056, 0.100, 0.140, or 0.200% technical grade fluridone for 3 months had treatment-related liver alterations, and mice maintained on diets containing at least 0.033% technical grade fluridone had morphologic liver alterations. The observed treatment-related effects at all dose levels precluded the identification of a NOEC.	Frick 1979b (tif 112900.009)
ICR/SPF mice, males (30.4±0.2 g) and females (22.3 ±0.2 g), 15/sex/dose group	Dietary concentrations of 0.0, 0.0062, 0.011, 0.02, 0.33, 0.56% or 62, 110, 200, 330, and 560 ppm. Fluridone (EL-171) for 91-93 days. Corrected doses based on recovery of 48% of test compound after 3-months are: 4.6, 8.3, 15, 25, and 42 mg/kg/day.	5 mice died the deaths were attributed to treatment; a dose-dependent incidence of hepatic centrilobular hypertrophy was the only treatment related tissue alteration: 0/30, 1/28, 2/29, 3/29, and 6/30 cases in control, low-, mid-, high- and highest-doses). On the high dose response is significantly different from the control group based on the Fisher Exact Test (p=0.01186) All other responses are associated with p-values ≥0.11. NOAEL: 15 mg/kg bw/day LOAEL: 25 mg/kg bw/day	Frick 1979b (tif 112900.009) Also summarized in U.S. EPA/OPP 2004d as MRID 82342.

Subchronic Dietary (15 days to 90 days)			
Species	**Exposure**	**Response**	**Reference**
Dog, beagle, males (13-24 months) and females (11-12 months), 4/sex/dose group	Oral exposure (capsules) to 0, 50, 100, or 200 mg/kg/day fluridone (EL-171) for 91 days (males) and 92 days (females)	No mortality; no adverse effects on body weight, urinalysis, or organ weights; slightly decreased (but within normal range) erythrocytes count, hemoglobin, hematocrit and slightly increased alkaline phosphatase and BUN values at 200 mg/kg/day (effects on considered toxicologically significant); no compound-related pathology upon gross or microscopic examination; Conclusion: No clear dose related toxicity. NEL=200 mg/kg/day.	Frick 1979b (tif 112900.009) Also summarized in U.S. EPA/OPP 2004d as MRID 82344.

Subchronic Dermal (15 days to 90 days)			
Species	**Exposure**	**Response**	**Reference**
New Zealand white rabbits, 12-16 weeks old, 5/sex/dose group (except 20% formulation group contained 6 males and 4 females)	Fluridone 4AS/Compound 112371/ aqueous suspension containing, by weight, 44.5% fluridone tech. (EL-171, 98.7%) Topical application of 2 mL/kg of 0 (water control), 20%, 40%, or 80% fluridone. Equivalent doses of 192, 384, or 786 mg/kg fluridone Applied to dorsal skin (clipped of fur) 5 days/week for 3 weeks (to increase skin permeability treated areas of 50% of rabbits in each group were abraded once/week prior to treatment).	Dose-related irritation observed in all dose groups; no significant differences between abraded and non-abraded skin. 20% - transient, slight erythema and desquamation in 9/10 rabbits; 40% - moderate, well-defined erythema, slight edema and mild desquamation, and epidermal fissures in 3/10 rabbits; 80% - moderate to severe erythema with epidermal fissures, but only slight edema in 8/10 rabbits. One control male died; no signs of toxicity observed at any dose level; no changes in body weight or food consumption among treated rabbits, relative to controls; except for slight hematological changes, no signs of systemic toxicity from exposure to ≤ 384 mg/kg/day; at 786 mg/kg/day, there was a decreased kidney-to-body weight ratio without abnormal histopathological findings.	Probst et al. 1981b Cited in U.S. EPA/OPP 2004d as MRID 103299

Teratology Studies

Species	Exposure/Response	Reference
Fischer 344 virgin, adult female rats, 25 assumed pregnant rats/dose group	Daily gavage doses of 0, 20, 65, or 200 mg/kg/day fluridone (99.4% pure) suspended in 10% (w/v) aqueous acacia solution on days 6-15 of gestation. Vehicle control group received dose volume of 5.0 mL/kg of 10% (w/v) aqueous acacia solution. No indication of maternal or fetal toxicity; no clear evidence of reproductive toxicity or teratogenicity. *According to DER, study is considered to be seriously limited by lack of a dose level to cause overt maternal toxicity*.	Probst and Adams 1980a
CD Rats	0, 100, 300, or 1000 mg/kg/day by gavage on Days 6 to 15 of gestation. **Maternal toxicity**: Decreased body weight and food consumption at 300 mg/kg bw/day and above. Maternal NOAEL = 100 mg/kg bw/day. **Fetal Effects**: Decreased fetal body weight, delayed ossification (sternebrae and pelvic girdle), rudimentary ribs at 1000 mg/kg bw/day. Fetal NOAEL = 300 mg/kg bw/day	U.S. EPA/OPP 2004d), MRID 159963. Note: No cleared review of this study is available.
Rabbits, Dutch belted, pregnant, 15/sex/dose	Daily gavage doses of 0, 125, 300, or 750 mg/kg/day fluridone (99.5% pure) in 10% acacia solution on days 6-18 of gestation. **Maternal Toxicity**: no mortality at 0 or 125 mg/kg/day; one death at 300 mg/kg/day on day 23 of gestation (acute upper respiratory tract infection and focal acute pneumonia observed at necropsy); two deaths at 700 mg/kg/day on day 23 of gestation (acute upper respiratory tract infection and acute pneumonia observed in one of two at necropsy); no other signs of toxicity observed in surviving rabbits. No effects on mean body weights or food consumption at 125 mg/kg/day, relative to controls; at 300 mg/kg/day, increased incidence of abortions and slight (not statistically significant) decreases in body weight and food consumption during first half of treatment period (days 6-12 of gestation) with full recovery during days 7-18 of gestation; at 750 mg/kg/day, increased incidence of abortion; statistically significant decreases in mean body weights (-2.3%; $p<0.05$), relative to controls (+4.9%) during gestation days 6-12 with only partial recovery by day 27 of gestation; and decreases in mean food consumption during treatment and post-treatment period (***see Table 1, p 4 of DER for data***) **LOAEL for maternal toxicity** = 300 mg/kg/day based on increased incidence of abortions and slight decreases in body weight and food consumption. **NOAEL for maternal toxicity** = 125 mg/kg/day	Probst and Adams 1980b MRID 00103302

Teratology Studies		
Species	**Exposure/Response**	**Reference**
	Developmental Toxicity: No dead fetuses at any dose level, and no effects observed on mean fetal body weights; treated caused abortions in 4/14 rabbits at 300 mg/kg/day and in 6/11 rabbits at 750 mg/kg/day; mean number of resorptions/litter increased 2 ½ fold at 300 mg/kg/day, relative to controls, but the difference was not considered statistically significant; at 750 mg/kg/day, the mean number of resorptions/litter was significantly increased ($p<0.05$), relative to controls. At 750 mg/kg/day, fetus observed to have exencephally, omphalocele, rudimentary ear, and rudimentary forelimbs without digits; there was an increased percentage of fetuses with 13 ribs, relative to controls, but considered comparable to historical controls; and there were increased incidences of unidentified thickened rib and sternebral variations; no visceral abnormalities were observed in control or treatment groups. **LOAEL for developmental toxicity** = 300 mg/kg/day based on increased incidences of abortions NOAEL for developmental toxicity = 125 mg/kg/day	
Rabbits, Dutch belted, pregnant, 5/sex/dose	***This is a pilot study for the reproduction study summarized above***. Daily gavage doses of 0, 250, 500, 750, or 1000 mg/kg/day fluridone (99.5% pure) in 10% acacia solution on days 6-18 of gestation. Maternal body weights were reduced at 750 and 1000 mg/kg/day; whereas, food consumption was reduced in all treatment groups; abortions increased among rabbits in the 500, 750, and 1000 mg/kg/day groups. No unusual fetal effects were reported; however, no internal examinations were made. ***DER indicates that study is adequate for dose-range finding***.	Probst et al. 1980b

Reproduction Studies

Species	Exposure/Response	Reference
Fischer 344 rats F_0 generation, 5-6 weeks old, mean body weights: 97.3 g (males) and 85.5 g (females) 25/sex/dose group	3-generation reproduction study involving dietary exposure to fluridone (99.5% pure). F_0 generation exposed to dietary levels of 0, 200, 650, or 2000 ppm for 2 months during growth (pre-mating) phase; calculated intake of fluridone during growth phases over the 3 generations were: 10.6-11.1, 35.5-36.6, or 111.9-112.3 mg/kg/day for males and 12.4-13.2, 40.4-44, or 128-131.4 mg/kg/day for females. Each generation produced to litters which were given the test or control diet continuously for at least 10 weeks prior to mating, throughout mating, gestation, lactation, and until necropsy. No mortalities attributed to treatment; no treatment-related effects on body weight or food consumption during growth phase in any of the 3 generations; and no treatment-related signs of toxicity in any of the 3 generations of treated rats. No adverse effects on maternal body weight gains during all generations; in teratology phase (F_{3c}), no dose-related differences observed in body weights at days 0, 7, 14, and 20 of gestation. NOAEL for maternal toxicity >2000 ppm (112 mg/kg/day, HDT). No statistically significant treatment-related effects observed on reproductive parameters. NOAEL for reproductive toxicity >2000 ppm (112 mg/kg/day, HDT). At 2000 ppm, body weights of F_2 pups were significantly depressed (90.7% of controls; $p<0.05$) on lactation day 21; in treated pups, there was a dose-related but not statistically significant decrease in weight gain from day 1 to day 21 of lactation. NOAEL for offspring toxicity = 650 ppm (36 mg/kg/day) LOAEL for offspring toxicity = 2000 ppm (112 mg/kg/day, HDT) During developmental phase, there was no evidence of embryo lethality, altered fetal growth, or developmental alteration. NOAEL for developmental toxicity >2000 ppm (112 mg/kg/day, HDT) ***Teratology phase of study is classified as unacceptable because the highest dietary level failed to produce maternal toxicity.***	Probst et al. 1980a MRID 00103304 Also summarized in U.S. EPA/OPP 2004d.

Chronic Studies

Species	Exposure/Response	Reference
Fischer 344 rats, 42-49 days old, average body weights: 120 g (males) and 92 g (females), 15/sex/dose group	Dietary levels of 0, 200, 650, or 2000 ppm a.i. (test material fluridone 97.2 or 97.8% purity) for 1 year. **Average daily intake of fluridone (males): 8.57, 27.90, or 86.58 mg/kg; and (females): 10.22, 33.86, or 104.58 mg/kg.** No mortality and no clinical signs of toxicity.	Probst 1980a MRID 00103305 Also summarized in U.S. EPA/OPP 2004d.
Fischer 344 rats, 42-49 days old, average body weights: 120 g (males) and 92 g (females), 60/sex/dose group	Dietary levels of 0, 200, 650, or 2000 ppm a.i. (test material fluridone 97.2 or 97.8% purity) for 2 years. **Average daily intake of fluridone 2-yr study (<u>males</u>): 7.64, 25.06, or 80.93 mg/kg; and (<u>females</u>): 9.15, 29.71, or 96.93 mg/kg. Average daily intake of fluridone 2-yr *replicate* study (<u>males</u>): 7.66, 25.24, or 80.68 mg/kg; and (<u>females</u>): 9.19, 30.51, or 97.08 mg/kg**. There was no treatment-related increase in tumor incidence. Mid Dose: decreased body weights (92% of controls; $p<0.05$), decreased eosinophil counts, and increased absolute and relative liver and kidney weights as compared to controls. High Dose: mortality increased 87% in males and 37% in females, relative to controls; clinical signs of toxicity included chromorhinorrhea, anorexia, cloudy eyes, and pale eyes; bodyweights decreased 59-66% in males and 81-89% in females; other toxic effects included decreased food consumption; decreased RBC counts Hb, hematocrit, mean corpuscular volume, and mean corpuscular hemoglobin; decreased lymphocyte and eosinophil counts; increased nucleated erythrocytes, leukocyte and neutrophil counts; increased total leukocyte count; increased BUN, creatinine, and bilirubin; increased incidences of small testes, dose-related trends in the numbers of enlarge, pale and/or granular kidneys; opaque, cloudy, pale, red, or ulcerated eyes; and skin nodules or masses; increases in absolute and relative liver and kidney increased incidences of atrophied testes, ocular keratitis, and epidermal inclusion cysts. **<u>NOTE</u>**: U.S. EPA/OPP 2004d indicates that the mg/kg/day doses are: Males: 0, 7.65, 25.15, or 80.8 mg/kg/day Females: 0, 9.17, 30.11, or 97.00 mg/kg/day. NOAEL = 7.65 mg/kg/day LOAEL 25.15 mg/kg/day	Probst 1980b MRID 103251 Also summarized in U.S. EPA/OPP 2004d and U.S. EPA/OPP 2004g.
Mice, ICR, 6-7 weeks old, males (22.4±0.2 g), females (19.3±0.2 g), 40 mice/sex/dose group, 60 mice/sex in	0, 33, 100, or 300 ppm fluridone, purity 97.2%, test material: Sonar pellets in diet for 2 years; (DER calculated mean test material concentrations: 30.0±5.4, 95.0±8.4, or 277.8±29.8 ppm) (equivalent doses based on conversion factor of 1 ppm = 0.15 mg/kg/day in ***TRED***: 0, 5, 15, or 50 mg/kg/day). No treatment related effects on mortality, clinical observations (protruding or irritated eyes, poor muscle tone, and abnormal	Probst 1981d,e (DERs) MRID 00103335 MRID 00103252 Also summarized in U.S. EPA/OPP

Chronic Studies		
Species	**Exposure/Response**	**Reference**
control group	respiration), body weight; hematology, or absolute organ weights. **Clinical Blood Chemistry:** Combined data from the two 2-year studies indicated significant increase (157%) of controls in alkaline phosphatase activity in high-dose males, relative to controls (***see Table 2, p 6 of DER for data***). **Enzyme Induction**: Combined data from both studies indicate a significant increase in hepatic p-nitroanisole 0-demethylase activity in high-dose males, relative to controls. For females an increase was observed in 100 ppm group with no apparent dose-related trend (***see Table 3, p 8 of DER for data***). No gross pathology; slight, but significant (p=≤0.05)increase in hepatocellular hyperplasia in high-dose males (***see Table 4, p 9 of DER for data***); and slight increase in hepatic focal atypia (not defined in final report or pathologist's summary) in high dose females (***see Table 4, p 9 of DER for incidence data***). Data regarding statistically significant increase (as determined by DER reviewer using a Chi-square analysis) (p<0.05) of fibrosarcomas of the skin in high-dose females (***see Table 5, p 11 of DER for data***) was reviewed by HED Cancer Assessment Committee (TXR 007726, July 1985) and found to be insufficient evidence of the carcinogenicity of fluridone in mice. NOAEL = 100 ppm (15 mg/kg/day) for systemic toxicity LOAEL = 330 ppm (50 mg/kg/day) for systemic toxicity based on increased alkaline phosphatase activity (209% of controls) and increased incidence of hepatocellular hyperplasia DER indicates that three separate feeding studies conducted at the same dietary levels and initiated within one week or so of one another included a 1-year study and replicate 2-year oncogenic assays, which are reviewed as a single study.	2004d (TRED).
Beagle dogs, 16/sex, 8-23 months old, males (6.2-11.7 kg), females (6.1-11.0 kg), 4 dogs/sex/group	0, 75, 150, or 400 mg/kg/day fluridone (purity not specified) for 1 year. No mortality **DER Notes** NOEL = 75 mg/kg/day (no compound-related effects observed) LEL = 150 mg/kg/day (based on slight weight loss in males and trend toward increased alkaline phosphatase activity in females) Adverse effects: 400 mg/kg/day caused significant increases in serum alkaline phosphatase activity and absolute liver weight in females; 150 mg/kg/day caused a trend toward increased alkaline phosphatase levels in females. **TRED Notes**: NOAEL = 150 mg/kg/day LOAEL = 400 mg/kg/day Adverse effects: increased absolute liver weights; increased alkaline	Probst 1981c MRID 103336 (DER) Also summarized in U.S. EPA/OPP 2004b (TRED).

Chronic Studies		
Species	**Exposure/Response**	**Reference**
	phosphatase activity (female dogs) **NOTE**: DER classifies study as supplemental and argues that the ***tentative*** NOEL in this study can be conservatively estimated as 75 mg/kg/day, although the investigators suggest a NOEL of 150 mg/kg/day based on slight weight loss in males and the trend toward increased alkaline phosphatase activity in females and because similar changes were observed at the 400 mg/kg/day dose. The DER cites as deficiencies the use of considerable older dogs than specified in EPA guidelines; the fact the dogs were obtained from three separate and the method for assigning the dogs to test groups is not specified; appendices regarding study protocol and test material analysis are referred to in the study by were not included with the report; and complete histopathological tissue data were not presented for each dog.	

Species	Exposure	Effects	Reference
Single Dose Gavage/Capsules			
Bobwhite quail, adults	Single gavage administration of 2000 mg/kg fluridone (a.i. not specified) in 10% acacia solution	No mortality except one death of traumatic origin (NOS). LD_{50} >2000 mg/kg Treated and control birds appeared lethargic through day 6; no clinical signs of toxicity.	Kehr et al. 1978b
Acute Dietary			
Mallard ducks, 16-days old, 8 birds/concentration level (two replications of 4 birds/ concentration)	8-day acute dietary toxicity study. Dietary concentrations of 0, 1250, 2500, or 5000 ppm fluridone (a.i. not identified); highest assayed actual level = 4540 ppm. NOTE: Food consumption values not given in DER. In a similar study in mallards using aminopyralid (SERA 2007c), the food consumption values, as a proportion of body weight (kg food/kg bw) averaged about 0.3. Using this ratio, the daily doses correspond to about 0, 375, 750, and 1500 mg/kg bw/day.	8-day LC_{50} >5000 ppm No mortality, no overt signs of toxicity; statistically significant reduction in body weight at all treatment levels appeared to result from reduced food consumption due to apparent rejection.	Kehr et al. 1978a
Bobwhite quail	8-day acute dietary toxicity study. NOTE: Food consumption values not given in DER. In a similar study in quail using aminopyralid (SERA 2007c), the food consumption values, as a proportion of body weight (kg food/kg bw) averaged about 0.42.	LC_{50} >5000 ppm Based on a food consumption/body weight ratio of 0.42, the dietary LC50 corresponds to an LD50 of > 2100 mg/kg bw.	Summarized in Zucker et al. 1982 (EFB Review). No MRID number specified.

Reproduction Studies			
Mallard ducks, *Anas platyrhyncos*, adults, 4 males and 20 females/dose group	Continuous dietary exposure to 0, 100, 300, or 1000 ppm fluridone, 99.7% (EL-171) for one generation (NOS). NOTE: Food consumption values not given in DER. In a similar study in mallards using aminopyralid (SERA 2007c), the food consumption values, as a proportion of body weight (kg food/kg bw) averaged about 0.07. Using this ratio, the daily doses correspond to about 0, 7, 21, and 70 mg/kg bw/day.	NOEL = 1000 ppm No significant differences observed between treated and control ducks on the following reproductive parameters: % eggs set/laid; % visible embryo/eggs set; % 2-week-old survivors/viable embryos; % 2-week-old survivors/no. hatched; % no. hatched/no. laid. Treatment had no effects on food consumption or body weight; no clinical or pathological effects were attributed to treatment; feather loss, ataxia and limping were attributed to aggressive behavior and/or caging. 16 total adult deaths among treated and control ducks generally attributed to aggressive reproductive behavior as well as bacterial or fungal infections in one female from each dose group.	Ringer et al. 1981a
Bobwhite quail, *Colinus virginianus*, adults, 15/sex/dose group	Continuous dietary exposure to 0, 100, 300, or 1000 ppm fluridone, 99.7% (EL-171) for one generation (NOS). NOTE: Food consumption values not given in DER. In a similar study in bobwhite quail using aminopyralid (SERA 2007c), the food consumption values, as a proportion of body weight (kg food/kg bw) averaged about 0.068. Using this ratio, the daily doses correspond to about 0, 6.8, 20.4, and 68 mg/kg bw/day.	NOEL = 1000 ppm No significant differences observed between treated and control ducks on the following reproductive parameters: % eggs set/laid; % visible embryo/eggs set; % 2-week-old survivors/viable embryos; % 2-week-old survivors/no. hatched; % no. hatched/no. laid. 5 total adult deaths not attributed to treatment because there were no dose-related signs of toxicity. *DER states that submitted reproductive data from registrant are appended to the document, but those pages are not included. Evidently, egg production by control birds was poor and there was a high percentage of cracked eggs. The DER indicates that according to the study authors, none of the reproductive parameters tested were affected by treatment, including an unusually high percentage of cracked eggs, also observed in the control group. The DER reviewer suggests that the birds, treated and controlled, were stressed by poor husbandry (housing conditions) because eggshell thickness appeared to be normal.*	Ringer et al. 1981b

Note: All concentrations as a.i. unless otherwise specified.
Separate tables given for freshwater acute, freshwater chronic, and saltwater acute. Each table sorted by species and then author.

Note on Hamelink et al. 1986: These investigators conducted 31 static acute toxicity studies in fish using either the technical grade or a field formulation. They indicate in the discussion that differences in water hardness, temperature, and pH had no effect on the toxicity of fluridone to the fish. See Table 2 of the study for specifics. The data reported by Hamelink et al. (1986) are also reported in Mayer and Ellersieck 1986. Thus, entries for Mayer and Ellersieck (1986) that appear to correspond to the data reported in Hamelink et al. 1986 are not repeated in this appendix. The Hamelink paper species the use of: *a field formulation containing 48% active ingredient (479 g/L).* This corresponds to Sonar AS (4 lb/gal = 479.4 g/L) or 41.7% w/w.

Note on EC_{50}/NOEC Ratios: Where NOEC values are reported, ratios of EC_{50} to NOEC values (96-hour LC_{50}/NOEC) are calculated in this appendix. The use of these ratios is discussed in Section 4.3.3.1, Dose-Response Assessment for fish.

Freshwater Acute			
Species	**Exposure**	**Effects**	**Reference**
Bass, smallmouth (*Micropterus dolomieu*)	Sonar AS, toxicity values based on analytical measurements of fluridone.	24-hour LC_{50} = 19(17-24) ppm NOEC = 8.7 ppm LOEC = 18 ppm 48-hour LC_{50} = 11(9.7-13) ppm NOEC = 6.2 ppm LOEC = 8.7 ppm 72-hour LC_{50} = 9.5(8.5-11) ppm 96-hour LC_{50} = 7.6(6.9-8.7) ppm NOEC = 4.5 ppm LOEC = 6.2 ppm **96-hour LC_{50}/NOEC = 1.7**	Paul et al. 1994
Bass, largemouth (*Micropterus salmoides*)	Sonar AS, toxicity values based on analytical measurements of fluridone.	24-hour LC_{50} = 16 (N/A) ppm NOEC = 12 ppm LOEC = 21 ppm 48-hour LC_{50} = 16 (N/A) ppm NOEC = 12 ppm LOEC = 21 ppm 72-hour LC_{50} = 14 (13-16) ppm 96-hour LC_{50} = 13(12-15) ppm NOEC = 9.6 ppm LOEC = 12 ppm **96-hour LC_{50}/NOEC = 1.4**	Paul et al. 1994

Freshwater Acute			
Species	**Exposure**	**Effects**	**Reference**
Bluegill sunfish, *Lepomis macrochirus* 10/dose level	Nominal concentrations of 0 (control and solvent control), 1.25, 1.8, 2.5, 3.3, 4.5, 6.2, 9.0, or 12.5 ppm fluridone (a.i. not reported in study) under static conditions in aerated water for 96 hours; solvent: Tween 80; assayed test solutions contained 90-122% nominal values	96-hour LC_{50} = >9.0<12.5 ppm 90% mortality at 12.5 ppm; no mortality at lower concentrations except for incidental death at 1.8 ppm Hypoactivity observed at concentrations ≥2.5 ppm; no other signs of toxicity observed ***DER classifies study as invalid because water was aerated; mortality was 20% in water control but 0% in solvent control; fish (wt not provided for experimental fish) were much smaller than recommended; and LC_{50} value was not calculated.***	Karnak et al. 1978b
Bluegill sunfish, *Lepomis macrochirus*	Technical grade (98-99% a.i.) fluridone, hard water, static test	96-hour LC_{50} = 12.1 mg/L (95% CI = 11.3-17.7 mg/L) (assayed concentrations)	Hamelink et al. 1986
Bluegill sunfish, *Lepomis macrochirus*	Technical grade (98-99% a.i.) fluridone, soft water, static test	96-hour LC_{50} = 13.0 mg/L (95% CI = 9.9-17.1 mg/L) (nominal concentrations)	Hamelink et al. 1986
Bluegill sunfish, *Lepomis macrochirus*	Fluridone (field formulation containing 48% a.i.) or 479 g/L, soft water	96-hour LC_{50} = 12.0 mg/L (95% CI = 8.2-17.5 mg/L) (nominal concentrations)	Hamelink et al. 1986
Bluegill sunfish, *Lepomis macrochirus*, 10/dose level	96-hour static exposure to nominal concentrations of 0 (control), 0 (solvent = acetone total 500 ppm), 1.0, 1.4, 2.0, 2.75, 3.65, 5.0, 7.0, 9.0, 10.0, 11.0, 12.5, 14.0, 16.0 technical fluridone (purity not specified)	24-hour LC_{50} = 18.1 ppm fluridone (CL 13.7-24.1 ppm) 48-hour LC_{50} = 15.5 ppm fluridone (CL 13.9-17.2 ppm) 72-hour LC_{50} = 15.0 ppm fluridone (CL 13.8-16.3 ppm) 96-hour LC_{50} = 14.3 ppm fluridone (CL 13.4-15.3 ppm) NOEC = 2.0 ppm **96-hour LC_{50}/NOEC = 7.15** At concentrations of 2.75, 3.65, and 5 ppm, fish were hypoactive for 24 hours and then appeared normal for the rest of the study; at higher concentrations, fish exhibited dose-related stress patterns ranging from hypoactivity to irregular swimming.	Probst and Negilski 1981c

Freshwater Acute			
Species	**Exposure**	**Effects**	**Reference**
Bluegill sunfish, *Lepomis macrochirus*, 10/dose level	96-hour static exposure to nominal concentrations of 0 (water control), 18.0, 20.2, 22.5, 24.7, or 28.1 Sonar AS (equivalent to 0, 8.0, 9.0, 10.0, 11.0, or 12.5 ppm fluridone); actual assayed concentrations of fluridone: 0, 6.3, 6.9, 7.3, 7.8, or 8.3 ppm and 0, 5.4, 5.8, 6.0, 6.3, or 6.6 ppm	96-hour LC_{50} (based on nominal Sonar AS concentrations) >28.1 (highest test concentration) 96-hour LC_{50} (equivalent to assayed fluridone concentration) = 7.4 ppm NOEC = <18.0 ppm Sonar AS (equivalent to assayed fluridone concentration of <5.9 ppm) DER review indicates that although the study is scientifically sound, there were solubility problems and/or possible losses of test material due to aeration which means the formulated product cannot be quantified. Nevertheless, a.i. was measured during the assay, so the results provide supplemental information about the product's toxicity.	Probst and Negilski 1981d
Channel catfish, *Ictalurus punctatus*	Technical grade (98-99% a.i.) fluridone, soft water, static test	96-hour LC_{50} = 8.2-15.0 mg/L (nominal concentrations)	Hamelink et al. 1986
Channel catfish, *Ictalurus punctatus*	Technical grade (98-99% a.i.) fluridone, hard water, static test	96-hour LC_{50} = 14.0 mg/L (95% CI = 11.7-16.8 mg/L) (nominal concentrations)	Hamelink et al. 1986
Channel catfish, *Ictalurus punctatus*	Fluridone **formulation** containing 479 g a.i./L, soft water	96-hour LC_{50} = 13.2 mg/L (95% CI = 10.3-17.0 mg/L) (nominal concentrations)	Hamelink et al. 1986
Fathead minnow, *Pimephales promelas*	Technical grade (98-99% a.i.) fluridone, soft water, static test	96-hour LC_{50} = 22 mg/L (95% CI = 17-28 mg/L) (nominal concentrations)	Hamelink et al. 1986
Fathead minnow, *Pimephales promelas*	**Formulation** (479 g a.i./L). Consistent with Sonar AS. Soft water	LC_{50} >6.7<10.2 mg/L (measured concentrations)	Hamelink et al. 1986
Fathead minnow, *Pimephales promelas*	**Formulation** (41% a.i. w/w). Consistent with Sonar AS	96-hour LC_{50} = 41 (31-52) mg/L	Mayer and Ellersieck 1986
Rainbow trout, *Salmo gairdneri*	Technical grade (98-99% a.i.) fluridone, soft water, , pH 6.5 to 8.5, static test	96-hour LC_{50} values of ranging from 4.2 (pH 7.3) to 8.4 (pH 8.5) mg/L (nominal concentrations)	Hamelink et al. 1986
Rainbow trout, *Salmo gairdneri*	Technical grade (98-99% a.i.) fluridone, hard water, static test	96-hour LC_{50} = 7.6-11.7 mg/L (nominal concentrations)	Hamelink et al. 1986
Rainbow trout, *Salmo gairdneri*	Fluridone (**field formulation** containing 48% a.i.) or 479 g/L, soft water	96-hour LC_{50} = 8.1 mg/L (95% CI = 7.9-8.3 mg/L) (measured concentrations)	Hamelink et al. 1986

Freshwater Acute			
Species	**Exposure**	**Effects**	**Reference**
Rainbow trout, *Salmo gairdneri*	Fluridone (**field formulation** containing 48% a.i.) or 479 g/L, soft water	96-hour LC_{50} = 7.1 mg/L (95% CI = 5.6-9.1 mg/L) (nominal concentrations)	Hamelink et al. 1986
Rainbow trout, 10 fish/concentration level	Nominal concentrations of 0 (control and solvent control), 2.75, 3.65, 5.0, 7.0, 10.0, or 14 ppm technical grade fluridone (a.i. not specified) for 96 hours under static conditions; solvent: Tween 80; measured concentrations not reported.	96-hour LC_{50} = 11.7 ± 1.2 ppm (measured a.i.) 70% mortality at 14.0 ppm; no mortality at ≤5.0 ppm; signs of toxicity included hypoactivity and prostration (concentration levels not specified)	Kehr et al. 1978d
Rainbow trout, *Salmo gairdneri*, 10/vessel	96-hour static exposure to nominal concentrations of 0 (water control), 18.0, 20.2, 22.5, 24.7, 28.1, or 31.5 Sonar AS. Fluridone equivalents of 0, 8.0, 9.0, 10.0, 11.0, 12.5, or 14.0 fluridone. [**Actual assayed concentration of fluridone:** 0, 6.9, 7.4, 7.9, 8.3, 9.0, or 9.5 ppm and 0, 5.7, 5.9, 6.4, 6.9, 7.3, or 7.3 ppm]	96-hour LC_{50} = 8.2 ppm fluridone based on assayed concentrations (95% CL 7.9-8.3 ppm) Within 6.5 hours of exposure at all concentrations, fish displayed irregular swimming patterns or were prostate on bottom of test vessels; surviving fish were still severely stressed 96 hours later. **DER reviewer indicates that although the study is scientifically sound, there were solubility problems and/or possible losses of test material due to aeration, and the formulated product cannot be quantified. Nevertheless, a.i. was measured during the assay, so the results provide supplemental information about the toxicity of Sonar AS.**	Probst and Negilski 1981b
Walleye (*Stizostedion vitreum*)	Sonar AS, toxicity values based on analytical measurements of fluridone.	24-hour LC_{50} = 3.5 (3.2-4.1) ppm NOEC = 1.2 ppm LOEC = 2.0 ppm 48-hour LC_{50} = 2.8 (2.4-3.1) ppm NOEC = 1.2 ppm LOEC = 2.0 ppm 72-hour LC_{50} = 2.3 (2.0-2.6) ppm 96-hour LC_{50} = 1.8 (1.4-2.0) ppm NOEC = 0.78 ppm LOEC = 1.2 ppm **96-hour LC_{50}/NOEC = 2.3**	Paul et al. 1994

Freshwater Chronic Toxicity

Species	Exposure	Effects	Reference
Channel catfish, *Ictalurus punctarus*	Continuous exposure to 0.12, 0.25, 0.5, 1.0, or 2.0 mg/L technical fluridone (98-99% a.i.) for 60 days. Flow-through. Malfunction of equipment resulted in a 2.5 fold increase in the 2.0 mg/L concentration on Day 20.	No significant effects on growth or survival at ≤ 0.5 mg/L, compared with controls; growth was significantly ($p \leq 0.01$) reduced at test concentrations of 1.0 or 2.0 mg/L within the first 15 days and throughout the 60-day exposure period. Major metabolite: 4-hydroxy fluridone. NOEC: 0.5 mg/L	Hamelink et al. 1986
Fathead minnows, *Pimephales promelas*	Continuous exposure to mean measured concentrations of 0, 0.12 ± 0.02, 0.24 ± 0.02, 0.48 ± 0.03, 0.96 ± 0.6, or 1.9 ± 0.2 mg/L fluridone for three generations. Flow-through.	No adverse effects in fish observed at mean measured concentrations ≤ 0.48 mg/L; however survival of the second-generation fry decreased within 30 days after hatch at mean measured concentrations of 0.96 or 1.9 mg/L. Survival was the most sensitive endpoint. Growth was not adversely affected at any test concentrations. Although reproductive success did not appear to be affected by exposure; the investigators note that the effect could not be fully evaluated based on sparse spawning in all tanks during the study. (See Tables 8 and 9 of the study for details.) NOEC: 0.48 mg/L	Hamelink et al. 1986
Fathead minnow, *Pimephales promelas*, 30 eggs ≤ 48 hours old (F_0)	EL-171 (technical grade fluridone NOS). Duration of exposure: 35 days (full lifecycle) Nominal concentrations: 0.12, 0.25, 0.5, 1.0, or 2.0 mg/L . Measured concentrations: 0.12 ±0.02, 0.24±0.02, 0.48±0.03. 0.96±0.06, and 1.9±0.2 mg/L Separate water and solvent controls Solvent = DMSO (21 µg/L at highest concentration).	NOEC of 0.48 mg/L based on decreased survival of second generation fry exposed to 0.96 or 1.9 mg/L. ***DER indicates that the results of the pilot study show a significant decrease in the length of 30-day-old larvae exposed to 1.9 mg/L. Also, Table 12 (which is not included in the DER) shows that egg production was notably lower at the two highest concentration levels and that batches of eggs had to be transferred from tanks with lower concentration levels.*** Pages 7-17 are not included in copy of the DER. A note indicates that the information that is not included is generally considered confidential by the registrant.	Probst et al. 1981a [This appears to be identical to the above study by Hamelink et al. 1986]

Saltwater Acute			
Species	**Exposure**	**Effects**	**Reference**
Sheepshead minnow, *Cyprinodon variegates*, 9±1 mm, 13±4 mg, 10/jar	Nominal concentration of 0, 3.1, 5.8, 11.1, 24.0, or 48.0 ppm a.i. (assayed concentration of 0, 3.1, 5.8, 11.1, 24.0, 48.0 ppm a.i.) for 96 hours under flow-through conditions . Test material: technical grade fluridone (solvent = dimethyl formamide) .	NOEC (assayed) = 3.1 ppm Calculated 96-hour LC_{50}=11 ppm (95% CL 8-16 ppm) LC_{50} = **10.7** ppm (95% CL 8-14.3 ppm) based on measured concentrations. NOTE: Reported Results in DER indicate LC_{50} = 10.7 ppm (95% CL 8-14.3 ppm); Reviewer's Conclusions in DER indicate LC_{50} = 10.9 ppm (95% CL 8-14.8 ppm	Heitmuller 1981d
Sheepshead minnow, *Cyprinodon variegates*, average 9±1 mm, 13±4 mg, 10/jar	Nominal concentration of 0, 3, 6, 12, 25, or 50 ppm a.i. (measured concentration of 0, 2.8, 5.1, 8.1, 15.0, or 22.0 a.i.) for 96 hours under flow-through conditions. **Test material: Sonar AS** (43.16% fluridone).	Calculated LC_{50} for nominal concentrations = 83.6 mg/L (36.1 mg/L ÷ 0.432) NOEC = 25 ppm **NOTE: Exposure from the formulated product (Sonar AS) cannot be quantified because the test material precipitated out of solution, and only the a.i was measured. Also, there were possible losses of test material due to aeration.** **DER includes a table of mortality data.**	Heitmuller 1981h
Sheepshead minnow, Cyprinodon variegates	Technical grade (98-99% a.i.) fluridone, salinity 25%	96-hour LC50 = 10.7 mg/L (95% CI = 8-14.3 mg/L) (assayed concentrations)	Hamelink et al. 1986
Sheepshead minnow, Cyprinodon variegates	Fluridone (**field formulation** containing 48% a.i.) or 479 g/L, salinity 25%	96-hour LC50 = 16.7 mg/L (95% CI = 12.5-22.5 mg/L) (assayed concentrations)	Hamelink et al. 1986

Appendix 6: Toxicity to Aquatic Invertebrates

Note: Freshwater Acute followed by Freshwater Chronic, followed by Saltwater Acute in separate tables. Tables sorted by author. All concentrations as a.i. unless otherwise specified.

Note: Hamelink et al. 1986: Mayer and Ellersieck 1986 (a secondary compendia) duplicate many entries contained in Hamelink et al. 1986 (the primary publication). Obvious duplicates in Mayer and Ellersieck (1986) are not included below. The Hamelink paper species the use of: *a field formulation containing 48% active ingredient (479 g/L).* This corresponds to Sonar AS (4 lb/gal = 479.4 g/L) or 41.7% w/w.

Note on EC_{50}/NOEC Ratios: Where NOEC values are reported, ratios of EC_{50} to NOEC values (48-hour LC_{50}/NOEC) are calculated in this appendix. The use of these ratios is discussed in Section 4.3.4.1, Dose-Response Assessment for aquatic invertebrates.

Freshwater Acute

Species	Exposure	Effects	Reference
Amphipods, *Gammarus pseudolimnaeus*	Technical grade (98-99% a.i.) fluridone, acetone solvent, soft water	96-hour LC_{50} = 2.1 mg/L (95% CI = 0.9-5.0 mg/L) (nominal concentrations)	Hamelink et al. 1986
Amphipods, *Gammarus pseudolimnaeus*	Technical grade (98-99% a.i.) fluridone, acetone solvent, hard water	96-hour LC_{50} = 4.1 mg/L (95% CI = 2.9-5.7 mg/L) (nominal concentrations)	Hamelink et al. 1986
Amphipods, *Gammarus pseudolimnaeus*	Fluridone **formulation** soft water	96-hour LC_{50} >32 mg/L (nominal concentrations)	Hamelink et al. 1986
Amphipods, *Gammarus pseudolimnaeus*	Fluridone **formulation**, hard water	96-hour LC_{50} >32 mg/L (nominal concentrations)	Hamelink et al. 1986
Cladocera (*Alonella* sp.)	Fluridone 43.2% liquid formulation	48-hour LC_{50} 13 (11.5 to 14.1) mg/L	Naqvi and Hawkins 1989
Cladocera, *Daphnia magna*	Technical grade (98-99% a.i.) fluridone, acetone solvent, hard water	48-hour EC_{50} = 6.3 mg/L (95% CI = 5.4-7.4 mg/L) (nominal concentrations)	Hamelink et al. 1986
Cladocera, *Daphnia magna*	Fluridone **formulation**, soft water	48-hour EC_{50} = 3.6 mg/L (95% CI = 3.2-4.0 mg/L) (assayed concentrations)	Hamelink et al. 1986
Cladocera, *Daphnia magna*	Technical grade (98-99% a.i.) fluridone, acetone solvent, hard water	48-hour EC_{50} = 4.4 mg/L (95% CI = 3.0-6.4 mg/L) (nominal concentrations)	Hamelink et al. 1986
Cladocera, *Daphnia magna*	Technical grade (98-99% a.i.) fluridone, acetone solvent, soft water	48-hour EC_{50} = 3.9 mg/L (95% CI = 3.0-5.1 mg/L) (nominal concentrations)	Hamelink et al. 1986
Cladocera, *Daphnia magna*	Fluridone **formulation**, hard water	48-hour EC_{50} = 3.9 mg/L (95% CI = 2.9-5.0 mg/L) (nominal concentrations)	Hamelink et al. 1986

Species	Exposure	Effects	Reference
Cladocera, *Daphnia magna*, first instars, 30-33/concentration	48-hour exposure under flow-through conditions to 0 (solvent control), 2.0, 3.3, 5.6, or 10 ppm fluridone (a.i. not specified); measured concentrations not reported; acetone used as diluents; water not aerated.	48-hour EC_{50} = 6.3 ppm (95% CI = 5.4-7.4 ppm) No mortality at 2.0 ppm; 70% mortality at 10 ppm Hypoactivity observed in varying degrees at all concentrations. **48-hour LC_{50}/NOEC:** **3.15 (for mortality)** **>3.15 (for sublethal effects)** Note: Study title indicates that the test was conducted as static; DER indicates flow-through conditions.	Kehr et al. 1978c
Cladocera, *Daphnia magna*, first instars (less than 24 hours old), 9-11/test vessel w/3 replicate vessels/dose level	48-hour static exposure to nominal concentrations of 0 (water control), 4.4, 6.2, 9.0, or 13.9 ppm Sonar AS (0, 1.8, 2.75, 4.0, or 10.0 ppm fluridone); assayed fluridone concentrations: 0, 2.0, 3.0, 4.0, or 6.5 ppm and 0, 2.0, 3.1, 4.4, or 6.9 ppm	24-hour EC_{50} (based on assayed fluridone concentrations) = 6.6 ppm (CL 4.8-9.1 ppm) 48-hour EC_{50} (based on assayed fluridone concentrations) = 3.6 ppm (CL 3.2-4.0 ppm) 24- and 48-hour NOEC = 4.4 ppm Sonar AS (equivalent to assayed fluridone concentration of 2.0 ppm). **48-hour LC_{50}/NOEC: 2.2** DER reviewer indicates that although the study is scientifically sound, there were solubility problems and/or possible losses of test material due to aeration which means the formulated product cannot be quantified. Nevertheless, a.i. was measured during the assay, so the results provide supplemental information about the product's toxicity.	Probst and Negilski 1981a
Copepod (*Diaptomus* sp.)	Fluridone 43.2% liquid formulation	48-hour LC_{50} 12 (10.6 to 13.5) mg/L	Naqvi and Hawkins 1989
Copepod (*Eucyclops* sp.)	Fluridone 43.2% liquid formulation	48-hour LC_{50} 8 (7.8 to 10.8) mg/L	Naqvi and Hawkins 1989
Crayfish, *Orconectes immunis*, juveniles, average rostrum to telson length: 49.4 mm; average wet weight: 4.96 g; 5 crayfish/dose group	Mean measured concentrations of 0 (freshwater and solvent controls), 1.1, 2.3, 4.4, 8.6, 16.9 ppm a.i. (test material technical grade fluridone (99.7% a.i.) with 0.2 ppm acetone solvent) for 14 days	No mortality or behavioral effects of toxicity observed at 1.1 mg/L; two or three deaths observed at ≥2.2 mg/L; behavioral effects of toxicity observed throughout the study only at the highest test concentration of 16.9 mg/L. 14-day LC_{50} >16.9 mg/L	Meyerhoff and Probst 1984 This appears to be identical to the data (see below) from Hamelink et al. 1986

Species	Exposure	Effects	Reference
Crayfish,*Orconetes immunis*	Technical grade (98-99% a.i.) fluridone, acetone solvent, hard water	14-day LC_{50} >16.9 mg/L (assayed concentrations)	Hamelink et al. 1986
Midges, *Chironomus plumosus*	Technical grade (98-99% a.i.) fluridone, acetone solvent, soft water	48-hour EC_{50} = 1.3 mg/L (95% CI = 0.8-2.2 mg/L) (nominal concentrations)	Hamelink et al. 1986
Midges, *Chironomus plumosus*	Fluridone **formulation**, soft water	48-hour EC_{50} = 1.3 mg/L (95% CI = 1.0-1.7 mg/L) (nominal concentrations)	Hamelink et al. 1986
Midges, *Chironomus plumosus*	Technical grade (98-99% a.i.) fluridone, acetone solvent, hard water	48-hour EC_{50} = 1.3 mg/L (95% CI = 0.8-2.0 mg/L) (nominal concentrations)	Hamelink et al. 1986
Midges, *Chironomus plumosus*	Fluridone **formulation**, hard water	48-hour EC_{50} = 1.3 mg/L (95% CI = 1.0-1.7 mg/L) (nominal concentrations)	Hamelink et al. 1986
Ostracod (*Cypria* sp.)	Fluridone 43.2% liquid formulation	48-hour LC_{50} 13 (10.9 to 14.1) mg/L	Naqvi and Hawkins 1989

Chronic Toxicity

Species	Exposure	Effects	Reference
Amphipods, *Gammarus pseudolimnaeus*	Continuous exposure to 0.1, 0.2, 0.3, 0.6, or 1.2 mg/L technical fluridone (98-99% a.i.) for 60 days	No significant effects on survival or reproduction at ≤ 0.6 mg/L, compared with controls; survival and mean length were significantly ($p \leq 0.01$) less than controls at the highest test concentration (1.2 mg/L)	Hamelink et al. 1986
Daphnia magna, adults	Continuous exposure to 0.1, 0.2, 0.4, 0.8, 1.6, or 3.4 mg/L technical fluridone (98-99% a.i.) for 21 days	No significant effects on survival or reproduction at ≤ 0.2 mg/L, compared with controls; total average number of offspring produced during 21-day exposure period was significantly ($p \leq 0.05$) less than controls at test concentrations ≥0.4 mg/L.	Hamelink et al. 1986
Midges, *Chironomus pulmosus*, larvae	Continuous exposure to 0.01, 0.03, 0.05, 0.15, 0.3, 0.6, or 1.2 mg/L technical fluridone (98-99% a.i.) for 30 days	Emergence of adults not significantly reduced at ≤ 0.6 mg/L, compared with controls; emergence of adults was significantly ($p \leq 0.01$) less than controls at the highest test concentration (1.2 mg/L)	Hamelink et al. 1986

Saltwater Acute

Species	Exposure	Effects	Reference
Pink Shrimp, *Penaeus duorarum*	Technical grade (98-99% a.i.) fluridone, DMF solvent	96-hour LC_{50} = 4.6 mg/L (95% CI = 3.3-6.7 mg/L) (assayed concentrations)	Hamelink et al. 1986

Species	Exposure	Effects	Reference
Pink Shrimp, *Penaeus duorarum*	Fluridone (field formulation containing 48% a.i.) or 479 g/L	96-hour LC_{50} = 2.4 mg/L (95% CI = 1.6-3.6 mg/L) (assayed concentrations)	Hamelink et al. 1986
Eastern oysters, *Crassoterea virginica*, embryos	Technical grade (98-99% a.i.) fluridone, DMF solvent	48-hour EC_{50} = 16.8 mg/L (95% CI = 15.7-18.1 mg/L) (assayed concentrations)	Hamelink et al. 1986
Eastern oysters, *Crassoterea virginica*, embryos	Fluridone (field formulation containing 48% a.i.) or 479 g/L	48-hour EC_{50} = 6.8 mg/L (95% CI = 6.5-7.1 mg/L) (assayed concentrations)	Hamelink et al. 1986
Blue crabs, *Callinectes sapidus*	Technical grade (98-99% a.i.) fluridone, DMF solvent	96-hour LC_{50} = 36.2 mg/L (95% CI = 22.5-58.1 mg/L) (assayed concentrations)	Hamelink et al. 1986
Blue crabs, *Callinectes sapidus*	Fluridone (field formulation containing 48% a.i.) or 479 g/L	96-hour LC_{50} = 34 mg/L (assayed concentrations)	Hamelink et al. 1986
Pink shrimp, *Penaeus duorarum*, juveniles, 34-48 mm, 0.41-0.94 g, 5/test jar	Nominal concentrations of 0, 0.6, 1.2, 2.5, 5.0, or 10 ppm a.i (measured or assayed concentrations of 0.6, 1.1, 2.3, 4.7, or 9.8 a.i. and 0.6, 1.0, 2.3, 4.9, or 9.8 a.i.) for 96 hours under flow-through conditions. Test material: technical grade fluridone (98.1%) (solvent: dimethyl formamide)	LC_{50} : 24 hours >5 <10 ppm 48 hours = 7.6 ppm (4.8-16.6 ppm) 72 hours = 6.1 ppm (4.8-8.1 ppm) 96 hours = 4.6 ppm (3.3-6.7 ppm)	Heitmuller 1981a

Species	Exposure	Effects	Reference
Pink shrimp, *Penaeus duorarum*, juveniles, 34-40 mm, 0.29-0.52 g (wet weight) 5/test jar	Nominal concentrations of 0, 0.6, 1.2, 2.5, 5.0, or 10 ppm a.i. (assayed fluridone concentrations of 0.6, 1.2, 2.4, 4.3, or 6.0 and 0.6, 1.2, 2.4, 4.1, or 6.4) for 96 hours under flow-through conditions Test material Sonar AS (43.16% fluridone) (no solvent)	**Calculated** 96-hour LC_{50} = 2.0 ppm (0.8-4.3 ppm) ***of nominal*** concentrations of formulated fluridone 96-hour LC_{50} = 2.4 ppm (1.6-3.6 ppm) of ***measured*** concentrations of fluridone NOEC(***measured fluridone***) = 0.6 ppm **48-hour LC_{50}/NOEC: 4** NOTE: Exposure from the formulated product (Sonar AS) cannot be quantified because the test material precipitated of solution, and only the a.i was measured. Also, there were possible losses of test material due to aeration. DER includes a table of mortality data for nominal concentrations of fluridone.	Heitmuller 1981f
Blue crab, *Callinectes sapidus*, juveniles, carapace width = 17-30 mm, wet weight = 0.39-1.98 g, 5/vessel	Nominal concentrations of 0, solvent control, 6, 12, 25, 50, or 100 ppm a.i. (average measured concentrations of 0, 0, 5.8, 9.4, 19.5, 38.0, or 37.8 ppm a.i. for 96 hours under flow-through condition Test material : technical grade fluridone (98.1%) (solvent: dimethyl formamide)	**Calculated** LC_{50} : 24 hours >100 ppm 48 hours = 85 ppm 72 hours = 71 ppm 96 hours = 71 ppm No mortality at 5.8 ppm. **48-hour LC_{50}/NOEC: 14.6** *The test chemical precipitated out of solution; consequently, the data are quite variable at some of the test concentrations, and a precise LC_{50} could not be derived.* DER includes a table of mortality data as well as details regarding the statistical analyses used to estimate the toxicity values.	Heitmuller 1981b

Species	Exposure	Effects	Reference
Blue crab, *Callinectes sapidus*, juveniles, carapace width = 17-22 mm, wet weight = 0.39-0.89 g, 5/jar	Nominal concentrations of 0, 6, 12, 25, 50, 100 ppm a.i. (average measured concentrations of 0, 5.35., 9.25, 13, 45, 34.0, 77.5 a.i. ppm). Test material, SONAR AS (43.16% fluridone) 96- hour exposure under flow-through conditions (no solvent)	**Estimated** 24 LC_{50} >100 ppm 48-, 72- and 96-hour LC_{50} = 50 ppm (***expressed as fluridone***). LC_{50} for nominal concentrations = 78.7 mg/L (34 mg/L ÷ 0.432) NOEC = 13.45 ppm **48-hour LC_{50}/NOEC: 5.9** NOTE: Exposure from the formulated product (Sonar AS) cannot be quantified because the test material precipitated out of solution, and only the a.i was measured. Also, there were possible losses of test material due to aeration. DER includes a table of mortality data.	Heitmuller 1981e
Eastern oyster, *Crassostrea virginica*, 25-31 mm, 3.5-6.0 g, 10/vessel	Nominal concentrations of 0, 0.12, 0.25, 0.50, 1.0, or 2.0 ppm a.i. (average measured concentrations of 0, 0.1, 0.2, 0.5, 0.93, or 1.4 mg/L a.i.) technical grade fluridone (solvent: dimethyl formamide) for 96 hours under flow-through conditions	Treatment levels not high enough to detect effects on shell deposition. Results indicate that ≤1.4 mg/L technical grade fluridone should not decrease oyster shell deposition. *The test material precipitated out of solution and accumulated in the mixing apparatus*. **DER includes a table of shell deposition data for duration of the study.**	Heitmuller 1981c
Eastern oyster, *Crassostrea virginica*, 25-31 mm (x=34±4mm), 4.5-9.9 g (x-7.1±0.8g), 10/vessel	Nominal concentrations of 0, 0.06, 0.12, 0.25, 0.5, 1.0 ppm a.i. (measured concentrations of ND, ND, ND, ND, 0.24, or 0.08 a.i. and ND, 0.04, 0.12, 0.08, 0.24, 0.62 a.i.) for 4 days under flow-through conditions. Test material, Sonar AS (43.16% fluridone)	No significant affect on new shell growth of oysters exposed to nominal concentrations ≤1.0 ppm a.i. (0.6 ppm a.i. measured concentrations); new shell growth in all treated oysters was equal to or greater than that of seawater controls. *The test material precipitated out of solution and accumulated in the mixing apparatus*.	Heitmuller 1981g

Species	Exposure	Effects	Reference
Eastern oyster, *Crassostrea virginica*, embryo larvae, 25,600/vessel	48-hour exposure to measured concentrations of 6.2, 9.2, 23.3., 29, or 32.7 a.i. under static conditions Test material: fluridone (98.1%) under static conditions. Solvent was dimethyl formamide.	48-hour EC_{50} =18 ppm (95% CL 3-100 ppm) of nominal concentrations; or 16.8 ppm (95% CL 15.7-18.1 ppm) of assayed concentrations. NOEC = 9.2 ppm (assayed concentration) **48-hour LC_{50}/NOEC: 1.96**	Hollister 1981a
Eastern oyster, *Crassostrea virginica*, embryo larvae, 25,600/vesse	48-hour exposure to nominal concentrations of 3, 6, 10, 32, 56, or 100 ppm a.i (measured concentrations of 3, 5.1, 6.13, 9.3, 12. 3, or 15 ppm a.i.)) under flow-through conditions. Test Material: Sonar AS (43.16% fluridone)	Calculated 48-hour EC_{50} = 13 ppm (95%CL 13-16 ppm) (expressed as nominal fluridone) Calculated 48-hour EC_{50} = 7 ppm (95%CL 6.4-7.10 ppm) (expressed as measured concentration of fluridone) Control mortality is not given in the DER. At the measured concentration of 5.1 ppb, mortality was 2/100. Even if control mortality was 1/100, 2/100 is not significant using the Fisher Exact Test (p=0.248). Thus, 5.1 ppb could be taken as a NOEC for mortality. **48-hour LC_{50}/NOEC: 1.4 [7 ppm/5.1 ppm]** *These values are from the statistical analysis pages appended to the DER because the reported results on page 1 of the DER do not include the EC_{50} value for the measured concentration; in addition, the 95% CL for the nominal concentration seems to be a typo.* Significant reduction of normal larvae was observed at concentrations ≥10 ppm fluridone. The study was flawed by solubility problems and possible losses of test material due to aeration.	Hollister 1981b

Separate tables for algae and macrophytes. Studies arranged by reference.
Genus and species designations are referenced as they are cited in the corresponding publication (e.g., for Sago pondweed, *Potamogeton pectinatus* is synonymous with *Stuckenia pectinata*.
Concentrations are expressed in the units used in the publication [1 ppm = 1 mg/L; 1 ppb = 1 µg/L]. Molar concentrations are converted to ppb as needed using a MW for 329.3.

Algae

Species	Exposure	Effects	Reference
Freshwater green alga (*Nitella furcata*), sporelings (oospores)	0.0 (control), 0.01, 0.1, 1.0, or 10.0 mg/L fluridone for up to 6 days.	Effects of fluridone increased with concentration and the duration of exposure. EC_{50} (bleaching of chlorophyll) = 0.02 mg/L. Duration for calculation not specified but it would appear to be for the end of the study (6 days).	Burkhart and Stross 1990
Freshwater green alga, *Chlamydomonas eugametos*	Concentrations of $1x10^{-7}$ M, $1x10^{-6}$ M, $1x10^{-5}$ M for 48 hours. Molar concentrations (1 M = 329.3 g/L) equivalent to 32.9 ppb, 329 ppb, and 3,290 ppb.	NOEC: 329 ppb LOEC: 3,290 ppb (98% growth inhibition)	Hess 1980
Freshwater blue-green alga, *Oscillatoria agardhii*	Fluridone (TGAI): 0, 20, 40, 60, 80, or 100 µg/L for 96 hours.	Carotenoids: NOEC: not defined LOEC: 20 µg/L Biomass: NOEC: 20 µg/L. LOEC: 40 µg/L. Significant inhibition of biomass 40 µg/L and higher. Inhibition (≈ 25% for biomass and 15% for chlorophyll *a*) observed at 20 µg/L but was not statistically significant. Carotenoids, however, were significantly reduced at 20 ppb. Chlorophyll a was a less sensitive endpoint with NOEC of 60 µg/L	Millie et al. 1990
Freshwater blue-green algae, *Anabaena cylindrica*	Fluridone (as 50% wettable powder), 0, 0.5, 1, 5, and 10 µg/mL (mg/L). Note that the next column expresses the concentration (correctly) in mg/L. Table 1 of the paper expresses concentration as µg/mL.	EC_{50} values based on nitrogen fixation: 4-hour EC_{50}: 70.2 (32.2-158.3) mg/L 24-hour EC_{50}: 3.3 (2.1 – 5.1) mg/L 96-hour EC_{50}: 5.6 (4.9 – 6.4) mg/L NOEC at 96 hours: 0.5 mg/L	Trevors and Vedelago 1985
Freshwater green alga, *Scenedesmus quadricauda*	Fluridone (as 50% wettable powder), 0, 0.5, 1, 5, and 10 µg/mL (mg/L).	Complete inhibition of growth when exposed at start of culturing. No marked inhibition when fluridone was added at 7 days after culturing.	Trevors and Vedelago 1985

Algae			
Species	**Exposure**	**Effects**	**Reference**
Freshwater green alga, *Scenedesmus capricornutum*	Fluridone (technical grade, 95%). Concentrations of 10, 100, and 1,000 µM for 6 days. Concentrations equivalent to 3293 µg/L, 32,930 µg/L and 329,300 µg/L [1 µM/L = 329.3 µg/L].	1 µM/L (329 µg/L) at 2 days caused only a modest decrease in cell density. More pronounced effects as duration increased. No pronounced concentration-response relationship. No tabulation of data. See Figure 5 in publication. Cannot reliably calculate IC_{50}.	Schrader et al. 1997
Freshwater blue-green algae, *Oscillatoria chalybea*	Fluridone (technical grade, 95%). Concentrations of 10, 100, and 1,000 µM for 6 days. Concentrations equivalent to 3293 µg/L, 32,930 µg/L and 329,300 µg/L [1 µM/L = 329.3 µg/L].	Day 1 NOEC: 10 µM. Growth stimulation. LOEC: 100 µM Slight decrease in growth. Day 4 NOEC: 10 µM. Growth comparable to control. LOEC: 100 µM Substantial decrease in growth. Day 6 NOEC: 1 µM. Growth may be slightly inhibited. LOEC: 10 µM Growth appears to be significantly decreased from controls.	Schrader et al. 1997
Note on Schrader et al. 1997: See Figure 6 in publication. Very good concentration and duration data but authors do not provide data tabulation or statistical analyses. Above assessment based on visual interpretation of error bars in Figure 6 of publication.			

Toxicity studies in macrophytes start on next page.

Macrophytes			
Species, Stage	**Exposure**	**Effects**	**Reference**
American pondweed (*Potamogeton nodosus*), winter buds	Exposures of 1, 5, or 10 ppm for 14 days. No formulation specified. Exposures of up to 37 days to 1 ppm.	In 14-day exposures, an increase in length but a decrease in chlorophyll at all concentrations. At 1 ppm for 37 days, a 87% decrease in plant length.	Anderson 1981
Sago pondweed (*Potamogeton pectinatus*), winter buds	Exposures of 1, 5, or 10 ppm for 14 days. No formulation specified. Exposures of up to 37 days to 1 ppm.	In 14-day exposures, no significant change in length at any concentration but a decrease in chlorophyll at all concentrations. At 1 ppm for 37 days, a 50% decrease in plant length.	Anderson 1981
Hydrilla (*Hydrilla verticillata*), young and mature plants	Fluridone as 0.05, 0.5, 5.0, and 50 ppb of fluridone for up to 12 weeks.	NOEC: Not defined. LOEC: 0.05 ppb based on carotenoids, chlorophyll, and anthocyanin. Treatment decreased carotenoid and chlorophyll content in mature plants. Effects correlated with concentrations and durations. At 50 ppb, regardless of exposure duration, fluridone decreased the carotenoid and chlorophyll content of the plants by 80-95%. In young plants, 50 ppb fluridone reduced the content of carotenoids and chlorophyll by at least 50-65%.	Doong et al. 1993 *See entry below for MacDonald et al. 1993 for growth data.*
Duckweed (*Lemna gibba*), growth stage not characterized	Fluridone (technical grade) at $3.16x10^{-8}$M, 10^{-7}M, $3.16x10^{-7}$M, 10^{-6}M, $3.16x10^{-6}$M for up to 22 days. Concentrations correspond (MW=329.3 g/M) to about 10.4 µg/L, 32.93 µg/L, 104 µg/L, 329.3 µg/L, 1,040 µg/L	Little effect on growth on Day 3. Dose and duration related increase in growth thereafter. NOEC: not determined LOEC: 10.4 ppb, about a 10% decrease in frond number from controls on Day 16.	Lockhart et al. 1983
Hydrilla (*Hydrilla verticillata*), young and mature plants	Fluridone at 0.05, 0.5, 5.0, and 50 ppb of fluridone for up to 12 weeks.	*Young plants* NOEC: 0.5 ppb for young plants. LOEC: 5 ppb based on decreased growth (shoot dry weight) of young plants after 6 weeks. *Mature plants* NOEC: 50 ppb based on dry weight. LOEC: not established.	MacDonald et al. 1993 *See entry above for Dong et al. 1993 for biochemical endpoints.*
Hydrilla (*Hydrilla verticillata*), 2 months after planting	Sonar AS, 5 ppb for 84 days	Significant growth (as dry weight) by Day 21 though Day 84. Substantially enhanced toxicity with co-exposures to M*ycoleptodiscus terrestris*, a fungal plant pathogen.	Nelson et al. 1998
Eurasian watermilfoil (*Myriophyllum spicatum*) , 2 months after planting	Sonar AS, 5 ppb for 84 days	Significant growth (as dry weight) only by Day 84. With co-exposures to M*ycoleptodiscus terrestris*, a fungal plant pathogen, a significant decrease in growth by Day 42. No effect at Day 21.	Nelson et al. 1998

Macrophytes			
Species, Stage	**Exposure**	**Effects**	**Reference**
American pondweed (*Potamogeton nodosus*) , 2 months after planting	Sonar AS, 5 ppb for 84 days	Significant growth (as dry weight) only by Day 84. Mixed results with co-exposure to M*ycoleptodiscus terrestris*.	Nelson et al. 1998
Wild celery/ American eel grass (*Vallisneria americana*) , 2 months after planting	Sonar AS, 5 ppb for 84 days	No significant effects.	Nelson et al. 1998
Hydrilla (*Hydrilla verticillata*), 14 days	Sonar AS at target rates of 0.0, 0.25, 0.5, 0.75, 1.0, 2.0, 3.0, 4.0, and 25.0 µg/L for 90 days.	NOEC: 1 ppb based on decrease rate of biomass growth LOEC: 2 ppb based decrease rate of growth assayed as biomass Decreased chlorophyll at 0.75 ppb and higher by Day 90. At 4 ppb and above, decrease in absolute biomass.	Netherland and Getsinger 1995a
Eurasian watermilfoil (*Myriophyllum spicatum*), 14 days	Sonar AS at target rates of 0.0, 0.25, 0.5, 0.75, 1.0, 2.0, 3.0, 4.0, and 25.0 µg/L for 90 days.	NOEC: 1 ppb based on biomass LOEC: 2 ppb based on biomass Decrease in chlorophyll at 1 ppb and higher by Day 90. At 4 ppb and above, decrease in absolute biomass.	Netherland and Getsinger 1995a
Eurasian watermilfoil (*Myriophyllum spicatum*), 3 weeks	Sonar AS at target rates of 0, 12, 24, and 48 µg/L for 30, 60, and 90 days.	Regrowth of watermilfoil was apparent within 30 days at 12 and 24 ppb. Recovery much slower at higher concentrations and longer treatment periods.	Netherland et al. 1993
Hydrilla (Hydrilla verticillata) , 4 weeks	Sonar AS at target rates of 0, 12, 24, and 48 µg/L for 30, 60, and 90 days.	Similar to general pattern observed with milfoil. Compare Figure 1 and 2 in paper. No data tabulation.	Netherland et al. 1993
Eurasian watermilfoil (*Myriophyllum spicatum*), 21 days	Avast!, 0, 6, 12, 24 µg/L for 56 days	NOEC not defined LOEC: 6 µg/L based on decreased biomass.	Poovey et al. 2004
Wild celery (*Vallisneria americana*), 42 days	Avast!, 0, 6, 12, 24 µg/L for 56 days	NOEC: 24 µg/L LOEC: not defined based on biomass.	Poovey et al. 2004
Elodea (*Elodea canadensis*) , 42 days	Avast!, 0, 6, 12, 24 µg/L for 56 days	NOEC: 6 µg/L LOEC: 12 µg/L based on decreased biomass.	Poovey et al. 2004
Sago pondweed (*Stuckenia pectinata*), 42 days	Avast!, 0, 6, 12, 24 µg/L for 56 days	NOEC: 6 µg/L LOEC: 12 µg/L based on decreased biomass.	Poovey et al. 2004
Illinois pondweed (*Potamogeton illinoensis*), 42 days	Avast!, 0, 6, 12, 24 µg/L for 56 days	NOEC: 12 µg/L LOEC: 24 µg/L based on decreased biomass. Significant increase in biomass at 6 µg/L.	Poovey et al. 2004
Note on Poovey et al. (2004): Biomass illustrated in Figure 6, p. 14 of Poovey et al. 2004. Also in Table 3 of Poovey et al., (2004), a significant concentration-related reductions in β-carotene in all species. See Figure 4 in the current risk assessment for illustration of NOECs for biomass and *β*-carotene**.**			

Macrophytes			
Species, Stage	**Exposure**	**Effects**	**Reference**
Curlyleaf pondweed (*Potamogeton crispus*)	Sonar AS, 0, 3, 4, 5 µg/L for 56 days	LOEC for biomass: 3 µg/L Only modest decrease in tuber production without turbidity. Increasing turbidity enhanced the reduction in shoot biomass but increased tuber production.	Poovey et al. 2008

Appendix 8: Aquatic Field Studies

Studies sorted by author and date.

Application	Observations	Reference
Ponds of varying sizes treated with fluridone at rates specified as 0.28 kg/ha to 1.68 kg/ha. *[Note: Difficult to extract data based on fluridone concentrations.]*	Transient decrease in algae at fluridone concentrations of 1 ppm. Little impact on benthic organisms at 0.3 ppm but a decrease at 1 ppm. Appears to have a minor impact on rotifers, copepods, cladocerans, and ostracods based on serial observations. No data for control ponds.	Arnold 1979
Ponds in Washington State treated with a Sonar (NOS) formulation resulting in fluridone concentrations of about 30 ppb for 6 to 8 weeks.	Growth inhibition and reduced biomass of Eurasian watermilfoil (*Myriophyllum spicatum*). Based on aerial surveys, minimal impact on most nontarget plant communities, except for floating-leaved vegetation.	Farone and McNabb 1993
Ponds in Florida for the control of hydrilla (*Hydrilla verticillata*) based on nominal application rates of 10 to 12 ppb for 13 weeks using an AS formulation (presumably Sonar).	Suggests that the product of concentration (ppb) and duration (days) may be used as a predictor of efficacy, with long term control (up to 12 months) as 500 ppb days. 250 ppb days resulted in control but also in a more rapid recovery of hydrilla.	Fox et al. 1994
Applications of Sonar AS to lakes (55 to 220 ha) in Michigan for the control of Eurasian watermilfoil. Initial target applications of 5 ppb dropping to 2 ppb	Treatment at 5 ppb with longer term concentrations of 2 ppb effectively controlled watermilfoil.	Getsinger et al. 2002

Application	Observations	Reference
A man-made pond (8 m wide x 70 m long x 1 m deep) in Northern Greece was treated with an aqueous suspension of formulated fluridone (Sonar 4AS) sprayed over the water surface to produce a concentration of 0.042 mg/L a.i. in the pond water. The pond, which was populated with carp, *Cyprinus carpio*. Samples were taken from the lake for the sake of comparison. Observation period of 80 days.	No mortality or clinical signs of toxicity were observed in the fish; treatment had no adverse effects on the general body condition or behavior of the fish. No remarkable effects on rotifers, copepods, and cladocerans. Treatment drastically reduced the phytoplankton species (*Cyanophyceae, Diatomaceae, Chorophyceae, Dinophyceae, and Euglenineae*) shortly after fluridone was applied to the pond. *Cyanophyceae* disappeared within about 2 months; however the percentage of epiphytic and benthic species increased substantially, probably because they were released from the decomposed aquatic vegetation affected by treatment with fluridone.	Kamarianos et al. 1989
Formulations specified as 4AS, 5P, and SRP applied for control of Watermeal (*Wolffia columbiana*). Average application rate (as a.i.) of 94 ppb for 4AS, 91 ppb for 5P, and 82 ppb for SRP.	Early-season applications of 4AS and 5P formulations were effective. SRP gave less satisfactory control. Late winter applications evidenced effects in early summer. The rates of uptake and dissipation, as well as the time required to elicit a physiological response were probably inhibited by cooler water temperatures in the late winter.	Kay 1991

Application	Observations	Reference
Sonar AS applications to control hydrilla (*Hydrilla verticillata*) were monitored in several shallow lakes in 1985 and 1987. Table 1 of the study provides a detailed description of the area treated (ha), the fluridone application (kg/ha) and formulation, and the adjuvants applied with respect to each of the lakes.	The fluridone residues peaked (>200 µg/L) within 6 hours after application, but could not be detected (detection limit = 1 µg/L) at 36-48 hours post treatment. Seven days after treatment, fluridone was detected moving out of the treated lakes at concentrations of 11-26 µg/L in 1985 and concentrations of 1-9 µg/L in 1987. By 14 days post treatment in 1985, 7µg/L fluridone was detected at the potable water intake 8 km downstream from the treatment areas, and the finished water did not contain detectable residues. In 1987, 1-4 µg/L fluridone were detected at the potable water intake, and the finished water contained 1-2 µg/L fluridone. Fluridone residues were detected within the river system downstream from the treated plots for 50 days in 1985 and 28 days in 1987. Water flow was induced by increased rainfall in 1987 which likely accounted for the greater persistence of fluridone in 1985. Treatment reduced the hydrilla by 40-90% in treated lakes in 1985, and the reduction lasted 4 months to 1 year. In 1987, however, there was little reduction in aquatic vegetation.	Leslie et al. 1993
Two applications (separated by about 2 to 3 weeks) of Sonar AS to 8 lakes in Michigan at a rate of 5 ppb in the top 10 feet of water.	Excellent control of Eurasian watermilfoil in 7 of 8 lakes. Control of curlyleaf pondweed varied with application timing. Overall increase in plant diversity in treated lakes. No change in species diversity considering only native plants.	Madsen et al. 2002
Ponds in Washington State treated with a Sonar (NOS) formulation resulting in fluridone concentrations of about 12 ppb to 48 ppb for 30 to 90 days.	Growth inhibition and reduced biomass of and hydrilla (*Hydrilla verticillata*).	Netherland et al. 1993

Application	Observations	Reference
Mesocosm containing milfoil and the native species elodea, American pondweed, *Chara* sp, *Najas* sp, sago pondweed, and Vallisneria. Target concentrations of 5, 10, and 20 ppb using Sonar AS.	5 ppb: Significant biomass reduction in milfoil with only a transient reduction in Elodea. Increased biomass of other species. 10 ppb: Significant biomass reduction in all species except *Chara* sp, *Najas* sp. 20 ppb: As with 10 ppb but more pronounced.	Netherland et al. 1997
Fluridone (Sonar AS or Sonar 5P) applied to 18 hydrilla test plots (0.65 to 1 ha). Application rates expressed as kg/ha to the bottom 1 foot of the water column: 0.84, 1.70, 3.36, 6.72 kg a.i./ha.	Significant reductions in biomass over 84 days at 1.7 kg/ha but not at 0.84 kg/ha. No difference in efficacy between the two formulations tested. Initial concentrations in water at 1.7 kg/ha were in the range of about 10 ppb to 40 ppb in the different test plots. At 6.72 kg/ha, the initial concentrations were in the range of about 20 ppb to 50 ppb (see Table 2 of study). No concentrations given for 0.84 kg/ha. Phytoplankton: No consistent impact. Zooplankton: No significant differences between treated and control plots. Mollusks (NOS): Declines in populations observed in both test plots and control plots. No impact attributable to fluridone.	Sanders et al. 1980

Application	Observations	Reference
Several applications of Sonar AS to lakes in Michigan between 1990 and 1996 for the control Eurasian watermilfoil (*Myriophyllum spicatum*) and/ or curly leaf pondweed (*Potamogeton crispus*). Application rates ranging from 5 to 20 ppb. All application rates based on the top 10 feet of lake water.	Semi-quantitative assessments of species sensitivity: *Highly sensitive*: Eurasian watermilfoil, curly leaf pondweed, elodea (*Elodea canadensis*), naiads (*Najas* sp.), and coontail (*Ceratophyllum demersum*). *Intermediate sensitivity*: various pondweeds (*Potamogeton* sp.), wild celery (*Vallisneria americana*), and flatstem pondweed (*Potamogeton zosterifonnis*) *Highly tolerant*: bladderwort (*Utricularia* sp.) and water stargrass (*Heteranthera dubia*) Dose-response curves illustrated in Figure 2 but tabulation of data not give. Appears to be consistent with semi-quantitative categories given above. Elodea appears to be the most sensitive species with about 60% inhibition at ≤5 ppb. The high sensitivity of elodea consistent with bioassay data in Poovey et al. (2004) as summarized in Appendix 7.	Smith and Pullman 1997
Fluridone as unspecified Sonar formulation at a target concentration of 125 ppb, two applications made at a 25 day interval to isolated water columns in two fish ponds, designated as S1 and S3. Observations to 2 weeks after last application.	Pond S1: Significant decrease in phytoplankton density and chlorophyll-*a*. Pond S3: Transient and less substantial decreases in phytoplankton and chlorophyll-*a*. No remarkable effect by about 2 weeks after the last application.	Struve 1991
Treatment of a reservoir in Mississippi with granular fluridone formulations (Sonar Q, Sonar PR, and Sonar SRP) for the control of hydrilla (*Hydrilla verticillata*). Application rate not specified.	At 30 and 60 days after application, fluridone concentrations ranged from non-detectable to 1.6 ppb. Use of granular formulation *...accounts for low concentrations of fluridone*. Decrease in tuber numbers of hydrilla with fluridone treatment. Leaf necrosis noted in many hydrilla samples, presumably due to fluridone exposure.	Wersal et al. 2007