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Control/Eradication Agents for the Gypsy Moth - Human Health and Ecological Risk Assessment for Diflubenzuron (Dimilin) FINAL REPORT

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Submitted to:
Dave Thomas, COTR
Forest Health Protection Staff
USDA Forest Service
Rosslyn Plaza Building C, Room 7129C
1601 North Kent Street
Arlington, VA 22209

Submitted by:
Patrick R. Durkin
Syracuse Environmental Research Associates, Inc.
5100 Highbridge St., 42C
Fayetteville, New York 13066-0950
Telephone: (315) 637-9560
Fax: (315) 637-0445
E-Mail: SERA_INC@msn.com
Home Page: www.sera-inc.com

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LIST OF WORKSHEETS

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AEL	adverse-effect level
a.i.	active ingredient
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
bw	body weight
CBI	confidential business information
CI	confidence interval
cm	centimeter
CNS	central nervous system
CPU	chlorophenylurea
DAA	days after application
DAT	days after treatment
d.f.	degrees of freedom
EC_x	concentration causing X% inhibition of a process
EC_{25}	concentration causing 25% inhibition of a process
EC_{50}	concentration causing 50% inhibition of a process
EXAMS	Exposure Analysis Modeling System
ExToxNet	Extension Toxicology Network
F	female
FH	Forest Health
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FOIA	Freedom of Information Act
FQPA	Food Quality Protection Act
g	gram
GLEAMS	Groundwater Loading Effects of Agricultural Management Systems
ha	hectare
Hb	hemoglobin
HQ	hazard quotient
IAA	indole-3-acetic acid
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
k_a	absorption coefficient
k_e	elimination coefficient
kg	kilogram
$K_{o/c}$	organic carbon partition coefficient
$K_{o/w}$	octanol-water partition coefficient
K_p	skin permeability coefficient
L	liter
lb	pound
LC_{50}	lethal concentration, 50% kill
LD_{50}	lethal dose, 50% kill

LOAEL	lowest-observed-adverse-effect level
LOC	level of concern
m	meter
M	male
MetHb	methemoglobinemia
mg	milligram
mg/kg/day	milligrams of agent per kilogram of body weight per day
mL	milliliter
mM	millimole
MOS	margin of safety
MRID	Master Record Identification Number
MSDS	material safety data sheet
MW	molecular weight
NCAP	Northwest Coalition for Alternatives to Pesticides
NCI	National Cancer Institute
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
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PRZM	Pesticide Root Zone Model
RBC	red blood cells
RED	re-registration eligibility decision
RfD	reference dose
SERA	Syracuse Environmental Research Associates
SRC	Syracuse Research Corporation
UF	uncertainty factor
U.S.	United States
USDA	U.S. Department of Agriculture
U.S. EPA	U.S. Environmental Protection Agency
USGS	U.S. Geological Survey
WCR	water contamination rate
WHO	World Health Organization
WP	wettable powder
µ	micron or micro-
4CA	4-chloroaniline

COMMON UNIT CONVERSIONS AND ABBREVIATIONS

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

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

CONVERSION OF SCIENTIFIC NOTATION

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

EXECUTIVE SUMMARY

OVERVIEW

While the data base supporting the risk assessment of diflubenzuron is large and somewhat complex, the risk characterization is relatively simple. Diflubenzuron is an effective insecticide. Consequently, application rates used to control the gypsy moth are likely to have effects on some nontarget terrestrial insects. Species at greatest risk include grasshoppers, various macrolepidoptera (including the gypsy moth), other herbivorous insects, and some beneficial predators of the gypsy moth. Some aquatic invertebrates may also be at risk; however, the risks appear to be less severe than risks to terrestrial insects. The risk characterization for aquatic invertebrates is highly dependant on site-specific conditions. In areas subject to minimal water contamination, the effects of diflubenzuron are expected to be marginally adverse or nonexistent. If diflubenzuron is applied when drift or direct deposition in water is not controlled well or in areas where soil losses from runoff and sediment to water are likely to occur, certain aquatic invertebrates are at risk of acute adverse effects, and exposure could cause longer-term effects on more sensitive species. Direct effects of diflubenzuron on humans and other groups of organisms—wildlife mammals, birds, amphibians, fish, terrestrial and aquatic plants, microorganisms, and non-arthropod invertebrates—do not appear to be plausible. Nontarget species that consume the gypsy moth or other invertebrates adversely affected by diflubenzuron may be at risk of secondary effects of exposure (for example, a change in the availability of prey). There is no indication that 4-chloroaniline formed from the degradation of diflubenzuron will have an adverse effect on any species.

PROGRAM DESCRIPTION

Diflubenzuron is an insecticide that inhibits chitin deposition in arthropods and is effective either as a stomach or contact insecticide. Two formulations of diflubenzuron are labeled for control of the gypsy moth: Dimilin 4L and Dimilin 25W. Other formulations of diflubenzuron are available but these are registered for agricultural uses which account for about 94% of the total amount of diflubenzuron applied each year. Both ground and aerial applications of Dimilin 4L and Dimilin 25W are permitted. The current risk assessment concerns the range of labeled application rates—i.e., 0.0078-0.0624 lbs a.i./acre. Virtually all use of diflubenzuron in USDA programs occurs in suppression programs (about 99% of the treated acres) with only about 1% of the use in slow the spread programs. The use of diflubenzuron in eradication programs is less than 0.001% of the total use.

HUMAN HEALTH RISK ASSESSMENT

Hazard Identification **–** There is no information regarding effects in humans exposed to diflubenzuron; however, the toxicity of this compound is well characterized in experimental mammals. In mammals, the most sensitive effect involves damage to hemoglobin, a component of blood involved in the transport of oxygen. Diflubenzuron causes the formation of methemoglobin, a form of hemoglobin that is not able to transport oxygen. Methemoglobinemia, an excessive formation of methemoglobin, is the primary toxic effect of diflubenzuron regardless of the route or duration of exposure in every species of animal tested. Diflubenzuron causes other effects on the blood; however, methemoglobinemia is the most sensitive effect—that is, the effect that occurs at the lowest dose. While effects on the blood are well documented, there is little indication that diflubenzuron causes other specific forms of toxicity. Diflubenzuron does not appear to be neurotoxic or immunotoxic, does not appear to affect endocrine function in laboratory mammals, and is not a carcinogen. In addition, diflubenzuron does not appear to cause birth defects or reproductive effects. Diflubenzuron is relatively nontoxic by oral administration, with reported single-dose LD_{50} values ranging from greater than 4640 to greater than10,000 mg/kg. There are numerous studies regarding the subchronic and chronic toxicity of diflubenzuron in laboratory animals, and these studies indicate that methemoglobinemia is the most consistent and sensitive sign of toxicity. Diflubenzuron can be absorbed from the skin in sufficient amounts to cause hematological effects—that is, methemoglobinemia and sulfhemoglobinemia. Nonetheless, the dermal exposure concentrations that are necessary to cause these hematological effects are higher than the oral exposure doses that are necessary to cause the same effects.

Exposure Assessment – Exposure assessments are conducted for both diflubenzuron and 4-chloroaniline. For diflubenzuron, a standard set of exposure scenarios are presented for both workers and members of the general public. Concern for 4-chloroaniline arises because it is an environmental metabolite of diflubenzuron and is classified as a carcinogen. 4-Chloroaniline is not a concern in worker exposure assessments because 4-chloroaniline will not be present at the time that diflubenzuron is applied. Also, 4-chloroaniline is not a concern in some acute exposure scenarios for the general public such as direct spray during the application of diflubenzuron. Consequently, only a subset of the standard exposure scenarios—those associated with exposure to vegetation or water contaminated with diflubenzuron—are presented for 4-chloroaniline. These scenarios, however, include all standard chronic exposure scenarios, which are of greatest concern because of the potential carcinogenicity of 4-chloroaniline.

All exposure assessments are conducted at the maximum single application rate for diflubenzuron of 0.0625 lb/acre (equivalent to 70 g/ha). This is also the maximum application rate for a single season. Assuming that diflubenzuron is applied in a single application at the maximum rate leads to the highest estimates of peak as well as longer-term exposures. The consequences of using lower application rates are discussed in the risk characterization.

For workers applying diflubenzuron, three types of application methods are considered: directed ground spray, broadcast ground spray, and aerial spray. Central estimates of exposure for workers are approximately 0.0009 mg/kg/day for aerial workers, 0.0008 mg/kg/day for backpack workers, and about 0.001 mg/kg/day for broadcast ground spray workers. Upper ranges of exposures are approximately 0.009 mg/kg/day for broadcast ground spray workers and 0.005 mg/kg/day for backpack and aerial workers. All of the accidental exposure scenarios for workers involve dermal exposures, and most of these accidental exposures lead to dose estimates that are either in the range of or substantially below the general exposure estimates for workers. The one exception involves wearing contaminated gloves for 1hour. The upper range of exposure for this scenario is about 0.4 mg/kg/day.

For the general public, estimates of acute exposure range from approximately 0.0000005 mg/kg, which is the lower range estimate for the consumption by a child of water from a stream contaminated by diflubenzuron, to 1.5 mg/kg, which represents the upper range for consumption of contaminated fish by subsistence populations—individuals who consume free-caught fish as a major proportion of their diet. Relatively high dose estimates are also associated with the consumption of contaminated water after an accidental spill (about 0.13 mg/kg at the upper range of exposure) and for the consumption of fish by members of the general public (0.3 mg/kg). Other acute exposures are lower by about an order of magnitude or more. For chronic or longer-term exposures, the modeled exposures are much lower than for acute exposures, ranging from approximately 0.00000002 mg/kg/day (2 in 10 millionths of a mg/kg/day), which is the lower range estimate for the consumption of contaminated water, to approximately 0.002 mg/kg/day, which is the upper range for consumption of contaminated fruit.

Estimates of exposure to 4-chloroaniline from contaminated vegetation are likely to be about 0.02 times less than corresponding estimates of exposure to diflubenzuron. The lower estimate of exposure to 4-chloroaniline is due to its expected rapid dissipation from diflubenzuron deposited on vegetation. In water, however, estimated concentrations of 4-chloroaniline are likely to be equal to or greater than anticipated water concentrations of diflubenzuron under certain circumstances. Finally, peak exposures to 4-chloroaniline differ from peak exposures to diflubenzuron in the environment, usually occurring at different times (later after the application of diflubenzuron) and under different conditions of precipitation. These differences are due to the relatively slow rate in the formation of 4-chloroaniline from diflubenzuron in soil.

Dose-Response Assessment – The dose-response assessment considers both diflubenzuron itself as well as 4-chloroaniline as an environmental metabolite of diflubenzuron. For systemic toxicity, the dose-response assessment involves the adoption or derivation of acute and chronic RfDs, doses that are considered to produce no adverse effects, even in sensitive individuals. RfDs are presented for both diflubenzuron and 4-chloroaniline. Cancer risk is considered quantitatively for 4-chloroaniline and is expressed as a dose associated with a risk of 1 in 1million. Following standard practices for USDA risk assessments, risk assessment values available from U.S. EPA are adopted directly unless there is a compelling basis for doing otherwise. When risk values are not available from U.S. EPA, the methods used by U.S. EPA are employed to derive surrogate values.

U.S. EPA derived a chronic RfD for diflubenzuron of 0.02 mg/kg/day. This chronic RfD is well documented and is used directly for all longer-term exposures to diflubenzuron. This value is based on a NOAEL in dogs and an uncertainty factor of 100. Because of the low acute toxicity of diflubenzuron, the U.S. EPA did not derive an acute RfD but identified an acute NOAEL of 10,000 mg/kg. While this NOAEL could be used to derive a surrogate acute RfD of 100 mg/kg, a more conservative approach is taken and a surrogate acute RfD of 11 mg/kg is derived based on a NOAEL of 1118 mg/kg from a study using a petroleum-based formulation of diflubenzuron. Since diflubenzuron is classified as a non-carcinogen by both U.S. EPA and WHO, there is no reason to conduct a quantitative cancer risk assessment for exposure to diflubenzuron.

The U.S. EPA derived a chronic RfD for 4-chloroaniline of 0.004 mg/kg/day, and this value is used in the current risk assessment to characterize risks from 4-chloroaniline for longer-term exposures. This RfD is based on a chronic oral LOAEL of 12.5 mg/kg/day using an uncertainty factor of 3000—three factors of 10 each for intraspecies extrapolation, sensitive subgroups, and the use of a LOAEL with an additional factor of 3 due to the lack of data reproductive toxicity data. As with diflubenzuron, the U.S. EPA did not derived an acute RfD for 4-chloroaniline. For this risk assessment a conservative approach is taken in which a surrogate acute RfD of 0.03 mg/kg is based on a subchronic (90-day) NOAEL of 8 mg/kg/day. Consistent with the approach taken by U.S. EPA for the chronic RfD, an uncertainty factor of 300 is used—a factor of 10 for interspecies extrapolation, 10 for intraspecies extrapolation, and 3 for the lack of data on reproductive toxicity. For cancer risk, the U.S. EPA proposes a human cancer potency factor for 4-chloroaniline of 0.0638 $(mg/kg/day)^{-1}$. This potency factor is used to calculate a dose of 1.6×10^{-5} mg/kg/day that would be associated with a cancer risk of 1 in 1million.

Risk Characterization – The risk characterization for potential human health effects associated with the use of diflubenzuron in USDA programs to control the gypsy moth is relatively unambiguous: none of the hazard quotients reach a level of concern at the highest application rate that could be used in USDA programs. In that many of the exposure assessments involve very conservative assumptions—that is, assumptions that tend to overestimate exposure—and because the dose-response assessment is based on similarly protective assumptions, there is no basis for asserting that this use of diflubenzuron poses a hazard to human health.

Notwithstanding the above assertion, it is worth noting that the greatest relative risk concerns the contamination of water with 4-chloroaniline rather than exposure to diflubenzuron itself. The highest hazard quotient for diflubenzuron is 0.1, a factor of 10 below a level of concern. Since this hazard quotient is based on toxicity, an endpoint that is considered to have a population threshold, the assertion can be made that risk associated with exposure to diflubenzuron is essentially zero.

This is not the case with 4-chloroaniline, which is classified as a probable human carcinogen and is an environmental metabolite of diflubenzuron. For 4-chloroaniline, the highest hazard quotient is 0.4, below the level of concern by a factor of only 2.5. The scenario of greatest concern involves cancer risk from drinking contaminated water. This risk would be most plausible in areas with sandy soil and annual rainfall rates ranging from about 50 to 250 inches. The central estimate of the hazard quotient for the consumption of water contaminated with 4-chloroaniline and based on a cancer risk of 1 in 1million is 0.09, which is 10 times lower than the level of concern.

ECOLOGICAL RISK ASSESSMENT

Hazard Identification – The toxicity of diflubenzuron is well characterized in most groups of animals, including mammals, birds, terrestrial invertebrates, fish, and aquatic invertebrates. In general, diflubenzuron is much more toxic to some invertebrates, specifically arthropods, than vertebrates or other groups of invertebrates. This differential toxicity appears to involve fundamentally different mechanisms of action. Toxicity to sensitive invertebrate species is based on the inhibition of chitin synthesis. In the more tolerant vertebrate species, the mechanism of action appears to be a specific effect on the blood that inhibits oxygen transport.

The species most sensitive to diflubenzuron are arthropods, a large group of invertebrates, including insects, crustaceans, spiders, mites, and centipedes. Most of these organisms use chitin, a polymer (repeating series of connected chemical subunits) of a glucose-based molecule, as a major component of their exoskeleton—that is, outer body shell. Diflubenzuron is an effective insecticide because it inhibits the the formation of chitin. This effect disrupts the normal growth and development of insects and other arthropods. Both terrestrial and aquatic arthropods are affected but some substantial differences in sensitivity are apparent. In terrestrial organisms, the most sensitive species include lepidopteran and beetle larvae, grasshoppers and other herbivorous insects. More tolerant species include bees, flies, parasitic wasps, adult beetles, and sucking insects. In aquatic organisms, small crustaceans that consume algae and serve as a food source for fish (e.g., *Daphnia* species) appear to be the most sensitive to diflubenzuron, while larger insect species such as backswimmers and scavenger beetles are much less sensitive. A wide range of other aquatic invertebrates, other crustaceans ,and small to medium sized aquatic insect larvae, appear to have intermediate sensitivities. Not all invertebrates use chitin and these invertebrates are much less sensitive to diflubenzuron than the arthropods. For terrestrial invertebrates, relatively tolerant species include earthworms and snails. For aquatic species, tolerant species include ostracods and non-arthropods such as rotifers, bivalves (clams), aquatic worms, and snails.

The most sensitive effect in vertebrate species concerns damage to blood cells involved in the transport of oxygen. This effect was demonstrated in laboratory mammals used in toxicity studies (for example, rats and mice) as well as in domestic animals and livestock. Although the effect was not studied in wildlife mammals, birds, or fish, it is reasonable to assume that hemoglobin in all vertebrate species could be affected by exposure to diflubenzuron. Acute exposures to diflubenzuron are relatively non-toxic to mammals and birds. The U.S. EPA places diflubenzuron in low toxicity categories (III or IV) for mammals and considers diflubenzuron to be virtually non-toxic to birds in acute exposures and only slightly toxic to birds in subchronic exposures. This assessment is supported by a numerous field studies in which no direct toxic effects in mammals or birds is reported. Effects, if any, on terrestrial vertebrates from the application of diflubenzuron are likely to be secondary to changes in food availability—that is, reduced numbers of insects—or changes in habitat— for example, the loss of protective vegetation, relative to areas not treated with diflubenzuron. Aquatic vertebrates also appear to be relatively tolerant to diflubenzuron ,and this compound is classified by U.S. EPA as practically non-toxic to fish. This classification appears to be appropriate and is supported by several longer-term toxicity studies and field studies. Changes in fish populations are reported in some studies; however, the changes appear to be secondary to changes in food supply. Although the data on amphibians is much more limited than the data onfish, a similar pattern is apparent—that is, although there are no direct toxic effects from exposure, changes in food consumption patterns appear secondary to direct effects on invertebrate species.

Data on plants and microorganisms are more limited than the data on invertebrates or vertebrates. Nonetheless, there does not appear to be any basis for asserting that diflubenzuron will have a substantial effect on these organisms.

Exposure Assessment – As in the human health risk assessment, exposures are estimated for both diflubenzuron and 4-chloroaniline. A full set of exposure assessments are developed for diflubenzuron but only a subset of exposure assessments are developed for 4-chloroaniline. This approach is taken, again as in the human health risk assessment, because 4-chloroaniline is assessed as an environmental metabolite of diflubenzuron. Thus, immediately after application, the amount of 4-chloroaniline as an environmental metabolite will be negligible. Consequently, the direct spray scenarios as well as the consumption of insects and the consumption of small mammals after a direct spray are not included for 4-chloroaniline. Also as in the human health risk assessment, all standard chronic exposure scenarios are included for 4-chloroaniline.

Terrestrial animals might be exposed to any applied pesticide from direct spray, the ingestion of contaminated media (vegetation, prey species, or water), grooming activities, or indirect contact with contaminated vegetation. For diflubenzuron, the highest acute exposures for small terrestrial vertebrates will occur after a direct spray and could reach up to about 10 mg/kg at an application rate of 70 g/ha. Exposures anticipated from the consumption of contaminated vegetation by terrestrial animals range from central estimates of about 0.08 mg/kg for a small mammal to 2 mg/kg for a large bird with upper ranges of about 0.2 mg/kg for a small mammal and 5 mg/kg for a large bird. The consumption of contaminated water leads to much lower levels of exposure. A similar pattern is seen for chronic exposures. Estimated longer-term daily doses for the a small mammal from the consumption of contaminated vegetation at the application site range from approximately 0.001 to 0.005 mg/kg. Large birds feeding on contaminated vegetation at the application site could be exposed to much higher concentrations, ranging from about 0.08 to 0.7 mg/kg/day. The upper ranges of exposure from contaminated vegetation far exceed doses anticipated from the consumption of contaminated water, which range from about 0.0000001 to 0.00001 mg/kg/day for a small mammal.

Exposures of terrestrial organisms to 4-chloroaniline tend to be much lower than those for diflubenzuron. The highest acute exposure is about 0.2 mg/kg, the approximate dose for the consumption of contaminated water by a small mammal and the consumption of contaminated fish by a predatory bird. The highest longer term exposure is 0.0002 mg/kg/day, the dose associated with the consumption of contaminated vegetation by a large bird.

Exposures to aquatic organisms are based on essentially the same information used to assess the exposure to terrestrial species from contaminated water. At the maximum application rate of 70 g/ha, the upper range of the expected peak concentration of diflubenzuron in surface water is taken as 16 µg/L. The lower range of the concentration in ambient water is estimated at 0.01 µg/L. The central estimate of concentration of diflubenzuron in surface water is taken as 0.4 µg/L.

Dose-Response Assessment **–** Diflubenzuron is relatively non-toxic to mammals and birds. For mammals, the toxicity values used in the ecological risk assessment are identical to those used in the human health risk assessments: an acute NOAEL of 1118 mg/kg and a chronic NOAEL of 2 mg/kg/day. A similar approach is taken for 4-chloroaniline for which an acute NOAEL is 8 mg/kg is used based on a subchronic study and a chronic NOAEL is estimated at 1.25 mg/kg/day based on the chronic LOAEL of 12.5 mg/kg/day. For birds, the acute NOAEL for diflubenzuron is taken as 2500 mg/kg from an acute gavage study and the longer-term NOAEL is taken as 110 mg/kg/day from a reproduction study. No data are available regarding the toxicity of 4-chloroaniline in birds and the available toxicity values for mammals are used as a surrogate.

For terrestrial invertebrates two general types of data could be used to assess dose-response relationships: laboratory toxicity studies and field studies. Field studies are used in the current risk assessment because the standard toxicity studies are extremely diverse and many are not directly applicable to a risk assessment. Despite the difficulty and uncertainty in interpreting some of the field studies, the relatively large number of field studies on diflubenzuron appear to present a reasonably coherent pattern that is at least qualitatively consistent with the available toxicity data and probably a more realistic basis on which to assess risk to nontarget species. The most sensitive species appear to be grasshoppers which may be adversely affected at an application rate of 22 g/ha. Somewhat high application rates—in the range of 30 to 35 g/ha—will adversely effect macrolepidoptera and some beneficial parasitic wasps. At the maximum application rate considered in this risk assessment— 70 g/ha—some herbivorous insects are likely to be affected. No adverse effects in several other groups of insects are expected at this or much higher application rates. Honeybees are among the most tolerant species and are not likely to be adversely affected at application rates of up to 400 g/ha.

Invertebrates that do not synthesize chitin are also relatively tolerant to diflubenzuron. The NOEC for a species of earthworm (*Eisenia fetida*) is 780 mg/kg soil and is used to represent tolerant species of soil invertebrates. Very little information is available on the toxicity of 4-chloroaniline to terrestrial invertebrates. As with diflubenzuron, the earthworm appears to be relatively tolerant to 4-chloroaniline with a reported LC_{50} value of 540 mg/kg dry soil. The toxicity of both diflubenzuron and 4-chloroaniline to soil microorganisms is also relatively low.

Toxicity values for aquatic species follow a pattern similar to that for terrestrial species: arthropods appear to be much more sensitive than fish or non-arthropod invertebrates. For diflubenzuron, LC_{50} values of 25-500 mg/L are used to characterize risks for sensitive and tolerant species of fish, respectively. 4-Chloroaniline appears to be more toxic to fish and an LC_{50} of 2.4 mg/L is used to characterize risks of peak exposures, while an LC_{50} of 0.2 mg/L is used to characterize risks of longer-term exposures.

There is substantial variability in the response of different groups of aquatic invertebrates to diflubenzuron. Very small arthropods appear to be among the most sensitive species—with acute NOEC values ranging from 0.3 to about 1 ppb (µg/L) and chronic NOEC values ranging from 0.04 to 0.25 ppb. Based on acute NOEC values, larger arthropods, including crabs and larger insects, appear to be more tolerant, with acute NOEC values ranging from 2 to 2000 ppb. For chronic effects, the differences between small and larger arthropods are less remarkable with stoneflies and mayflies (relatively large insects) having an NOEC value of 0.1 ppb, intermediate between *Daphnia* (0.04 ppb) and *Ceriodaphnia* (0.25 ppb). Molluscs (invertebrates including clams and snails) and worms (oligochaetes) appear to be much less sensitive to diflubenzuron.

The data on the toxicity of 4-chloroaniline to aquatic invertebrates is sparse. An acute NOEC of 0.013 mg/L is used to characterize acute risks associated with peak exposures in aquatic invertebrates, and an NOEC of 0.01 mg/L from a reproduction study is used to characterize longer-term risks to aquatic invertebrates.

Risk Characterization – While the data base supporting the risk assessment of diflubenzuron is large and somewhat complex, the risk characterization is relatively simple. Diflubenzuron is an effective insecticide. Consequently, application rates used to control the gypsy moth are likely to have effects on some nontarget terrestrial insects. Species at greatest risk include grasshoppers, various macrolepidoptera (including the gypsy moth), other herbivorous insects, and some beneficial predators to the gypsy moth. These species are at risk because of the mode of action of diflubenzuron (i.e., inhibition of chitin) and the behavior of the sensitive insects (the consumption of contaminated vegetation or predation on the gypsy moth). Some aquatic invertebrates may also be at risk but the risks appear to be less than risks to terrestrial insects. The risk characterization for aquatic invertebrates is highly dependant on site-specific conditions. If diflubenzuron is applied when drift or direct deposition in water is not controlled well or in areas where soil losses from runoff and sediment to water are likely to occur, certain aquatic invertebrates are at risk of acute adverse effects, and exposure could cause longer-term effects on more sensitive species.

Direct effects of diflubenzuron on other groups of organisms—that is, mammals, birds, amphibians, fish, terrestrial and aquatic plants, microorganisms, and non-arthropod invertebrates—do not appear to be plausible. Nontarget species that consume the gypsy moth or other invertebrates adversely affected by diflubenzuron may be at risk of secondary effects of exposure (for example, a change in the availability of prey). There is no indication that 4-chloroaniline formed from the degradation of diflubenzuron will have an adverse effect on any species

There is no indication that 4-chloroaniline formed from the degradation of diflubenzuron will have an adverse effects on any species.

1. INTRODUCTION

This document provides updated risk assessments for human health effects and ecological effects to support an assessment of the environmental consequences of using diflubenzuron for the control or eradication of the gypsy moth (*Lymantria dispar*) in USDA/Forest Service and USDA/APHIS programs. This risk assessment is an update to the human health and ecological risk assessments prepared for the 1995 Final Environmental Impact Statement (FEIS) for the Cooperative Gypsy Moth Management Program (USDA 1995).

In the preparation of this risk assessment, literature searches on diflubenzuron were conducted using PubMed, TOXLINE, AGRICOLA, as well as the U.S. EPA CBI files. There is a very large body of literature on the environmental fate and toxicology of diflubenzuron. In addition to the previous risk assessments (USDA 1995), the toxicology, environmental fate, and other aspects associated with the use of diflubenzuron are the subject of relatively comprehensive reviews of human health and ecological effects by the World Health Organization (WHO 1996; WHO 2001). Several other reviews of various topics involving diflubenzuron have been published in the open literature (e.g. Cunningham 1986; Eisler 1992; Fisher and Hall 1992; Wilson 1997) and in materials submitted to U.S. EPA (Cardona 1999; Hobson 2001; Lengen, 1999; Wilcox and Coffey 1978).

In addition, a large number of studies have been submitted to the U.S. EPA/OPP in support of the registration of diflubenzuron and most of these studies have been reviewed by U.S. EPA (U.S. EPA/OPP 1997a, 1997b, 2000) and the derivation of food tolerances (EPA/OPP 1999, 2002a, 2003). The U.S. EPA (1997a) re-registration eligibility decision (RED) document and other reviews by U.S. EPA include summaries of the product chemistry, mammalian toxicology, and ecotoxicology studies that were submitted by industry to the U.S. EPA. Full text copies of the studies most relevant to this risk assessment (n=118) were kindly provided by the U.S. EPA Office of Pesticide Programs. The CBI studies were reviewed, and synopses of the information that can be disclosed from these studies are included in this document.

While this document discusses the studies required to support the risk assessments, it makes no attempt to re-summarize all of the information cited in the existing reviews. This is a general approach in all Forest Service risk assessments. For diflubenzuron in particular, an attempt to re-summarize all of the available information would tend to obscure rather than clarify the key studies that should and do impact the risk assessment.

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

For the most part, the risk assessment methods used in this document are similar to those used in risk assessments previously conducted for the Forest Service as well as risk assessments conducted by other government agencies. Details regarding the specific methods used to prepare the human health risk assessment are provided in SERA (2001). This document has four chapters, including the introduction, program description, risk assessment for human health effects, and risk assessment for ecological effects or effects on wildlife species. Each of the two risk assessment chapters has four major sections, including an identification of the hazards associated with diflubenzuron and its commercial formulations, an assessment of potential exposure to the product, an assessment of the dose-response relationships, and a characterization of the risks associated with plausible levels of exposure. These are the basic steps recommended by the National Research Council of the National Academy of Sciences (NRC 1983) for conducting and organizing risk assessments.

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

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

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

In considering different forms of variability, almost no risk estimate presented in this document is given as a single number. Usually, risk is expressed as a central estimate and a range, which is sometimes very large. Because of the need to encompass many different types of exposure as well as the need to express the uncertainties in the assessment, this risk assessment involves numerous calculations. Some of the calculations are relatively simple are included in the body of the document. Some sets of the calculations, however, are cumbersome. For those calculations, worksheets are included with this risk assessment. The worksheets provide the detail for the estimates cited in the body of the document. Documentation for these worksheets is provided in a separate document (SERA 2003). A set of worksheets is provided for diflubenzuron (Supplement 1) as well as 4-chloroaniline (Supplement 2). As discussed in this risk assessment, 4-chloroaniline is a metabolite of diflubenzuron that is quantitatively considered in this risk assessment. Both sets of worksheets are provided with the hard-text copy of this risk assessment as well as with the electronic version of the risk assessment.

This is a technical support document and it addresses some specialized technical areas. Nevertheless, an effort was made to ensure that the document can be understood by individuals who do not have specialized training in the chemical and biological sciences. Certain technical concepts, methods, and terms common to all parts of the risk assessment are described in plain language in a separate document (SERA 2001). General glossaries of environmental terms are widely available and a custom glossary designed to be used in conjunction with USDA risk assessments is available at www.sera-inc.com. Some of the more complicated terms that are specific to diflubenzuron are defined in the text of this risk assessment.

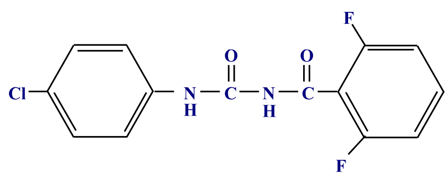
2. PROGRAM DESCRIPTION

2.1. Overview

Diflubenzuron is an insecticide that inhibits chitin deposition in arthropods and is effective either as a stomach or contact insecticide. Two formulations of diflubenzuron are labeled for control of the gypsy moth: Dimilin 4L and Dimilin 25W. Other formulations of diflubenzuron are available but these are registered for agricultural uses, which account for about 94% of the total amount of diflubenzuron applied each year. Both ground and aerial applications of Dimilin 4L and Dimilin 25W are permitted. For the current risk assessment, the range of labeled application rates – i.e., 0.0078 lb a.i./acre to 0.0624 lbs a.i./acre – are considered. Virtually all use of diflubenzuron in USDA programs occurs in suppression programs (about 99% of treated acres) with only about 1% of the use in slow the spread programs. The use of diflubenzuron in eradication programs is less than 0.001% of the total use.

2.2. Chemical Description and Commercial Formulations

Diflubenzuron is the common name for [1-(4-chlorophenyl) 3-(2,6-difluorobenzoyl)urea]:



Structurally, diflubenzuron consists of *p*-chloroanaline (the moiety on the left) linked to a 2,6-difluorobenzoic acid (the moiety on the right) by a ureido (carbon-nitrogen) bridge. Other synonyms for diflubenzuron as well as selected chemical and physical properties of diflubenzuron are summarized in Table 2-1. Additional information on the environmental fate and transport of diflubenzuron is summarized in the exposure assessments for the human health risk assessment (Section 3.2) and ecological risk assessment (Section 4.2).

Diflubenzuron is an insecticide that inhibits chitin deposition in arthropods and is effective either as a stomach or contact insecticide (Mabury and Crosby 1996). Chitin is a polymer (repeating series of connected chemical subunits) of a glucose-based molecule and comprises a substantial proportion of the exoskeleton (outer-shell) of arthropods. Consequently, the inhibition of chitin synthesis disrupts the growth and development (Baishya and Hazarika 1996; DeCleraq et al. 1995a,b; Griffith et al. 1996; Post and others 1974; Wright et al. 1996). Thus, diflubenzuron is not specific to the gypsy moth (Griffith et al. 1996; Horst and Walker 1995; Kadam et al. 1995) and is used to control a variety of pests on a variety of vegetation (Booth Riedl 1996; Boyle et al. 1996; McCasland et al. 1998). Because diflubenzuron can impact a number of invertebrate species, particularly aquatic species (e.g., Liber et al. 1996; O'Halloran et al. 1996), this compound is a restricted use pesticide that may only be applied by licenced applicators (C&P Press 2004).

Various formulations of diflubenzuron are labeled for forestry applications as well as other applications. All formulations of diflubenzuron are currently registered to Uniroyal Chemical (Table 2-2). Two formulations of diflubenzuron are labeled for control of the gypsy moth: Dimilin 4L and Dimilin 25W. As indicated in Table 2-2, an additional formulation, Micromite 25W, had been registered for gypsy moth but this formulation has been discontinued and the registration for this product has been canceled (U.S. EPA/OPP 2002b). Micromite 25WS and Micromite 25WGS are still available but these formulations are not used in USDA programs for the control of the gypsy moth.

Information on the impurities in and composition of these and other formulations of diflubenzuron have been submitted to U.S. EPA/OPP and this information (i.e., Drozdick 1998a,b,c,d,e; Van Kampen and Thus 1996; Vanstone 1998a,b,c; White 1998) has been reviewed as part of the current risk assessment. Specific information on inerts and contaminants in the diflubenzuron formulations is classified as CBI (confidential business Information) under Section 7(d) and Section (10) of FIFRA. This information cannot be specifically disclosed in this risk assessment. WHO (1996) has reported in the open literature that at least some processes in the synthesis diflubenzuron involve the reaction of 2,6-difluoro-benzamide with 4-chlorophenylisocyanate. Some inerts, however, must be disclosed on the material safety data sheet. Dimilin 4L contains petroleum oil [CAS No. 64742-46-7] and Dimilin 25W contains kaolin clay (C&P Press 2004). WHO (1996) indicated that kaolin is the only inert in some formulations of diflubenzuron. The potential risks associated with these inerts in the diflubenzuron formulations are discussed in Section 3.1.14.

2.3. Application Methods and Rates

Both ground and aerial applications of Dimilin 4L and Dimilin 25W are permitted (C&P Press 2004) and both methods are used in USDA programs. The most common methods for ground applications of diflubenzuron are hydraulic sprayers, mist blowers, or air blast sprayers (broadcast foliar). The spray equipment is typically mounted on tractors or trucks used to apply the insecticide on either side of the roadway. Usually, about 8 acres are treated in a 45-minute period (approximately 11 acres/hour). Special truck-mounted spray systems may be used to treat up to 12 acres in a 35-minute period with approximately 300 gallons of insecticide mixture (approximately 21 acres/hour and 510 gallons/hour) (USDA/FS89b, p 2-9 to 2-10).

In some instances, directed foliar applications may be used. In selective foliar applications, backpack applicators are used and the insecticide is applied to target vegetation. Application crews may treat up to shoulder high brush, which means that chemical contact with the arms, hands, or face is plausible. To reduce the likelihood of significant exposure, application crews are directed not to walk through treated vegetation. Usually, a worker treats approximately 0.5 acres/hour with a plausible range of 0.25-1.0 acre/hour.

In aerial applications, diflubenzuron formulations are applied under pressure through specially designed spray nozzles and booms. The nozzles are designed to minimize turbulence and maintain a large droplet size, both of which contribute to a reduction in spray drift. In aerial applications, approximately 40 to 100 acres may be treated per hour (USDA/FS89b, p 2-11). For Dimilin 25W, recommended droplet sizes are in the range of 150 to 200 microns (C&P Press 2004).

As indicated in Table 2-2, the application rate for Dimilin 4L ranges from 0.5 fluids ounces to 2 fluid ounces per acre. This corresponds to about 0.0039 to 0.0156 gallons [128 ounces per gallon] of Dimilin 4L per acre, which in turn corresponds to about 0.0156 to 0.0624 lbs diflubenzuron per acre [4 lbs diflubenzuron per gallon × 0.0039 to 0.0156] and 17 to 70 grams/ha. While multiple applications are permitted, the maximum single application rate is equal to the maximum annual application rate.

For Dimilin 25W, the range of labeled application rates is 0.5 ounces (avoirdupois) to 2 ounces per acre or 0.03125 to 0.125 pounds of Dimilin 25W per acre [i.e., 16 avoirdupois ounces per pound]. Since Dimilin 25W consists of 25% diflubenzuron, this range of application rates is equivalent to about 0.0078 to 0.03125 lb diflubenzuron per acre and 9 to 35 grams/ha. These rates for Dimilin 25W are about a factor of two below the corresponding rates for Dimilin 4L. The maximum application rate for Dimilin 25W in a single application is equivalent to the maximum annual application rate – i.e., multiple applications are allowed each year but the total amount applied in a single year cannot exceed 0.03125 lb a.i./acre [35 g/ha].

For the current risk assessment, the range of labeled application rates – i.e., 0.0078 lb a.i./acre to 0.0624 lbs a.i./acre – are considered. As calculated above, these rates are equivalent to 9 g/ha to 70 g/ha. All exposure assessments will be conducted at the maximum application rate. The consequences of using lesser rates are considered further in the risk characterization for human health (Section 3.4) and ecological effects (Section 4.4). These application rates are essentially the same as those used in the previous risk assessment (USDA 1995).

Recommended high volume ground sprays of Dimilin 4L and Dimilin 25W typically involve 100 to 400 gallons per acre but much concentrated solutions – i.e., 5 to 30 gallons per acre – are used in aerial applications. For the current risk assessment, the central value is taken as 30 gallons per acre and the range is taken as 5 to 400 gallons per acre. It should be noted that the selection of application rates and dilution volumes in this risk assessment is intended to simply reflect typical or central estimates as well as lower and upper ranges. In the assessment of specific program activities, the Forest Service will use program specific application rates in the worksheets that are included with this report to assess any potential risks for a proposed application.

The product label for Dimilin 25W specifically requires a 25 foot buffer for ground applications and a 150 foot buffer for aerial applications. These buffers indicate an area between the treated area and open bodies of water that may not be treated with diflubenzuron. The product label for Dimilin 4L does not specify a buffer but does indicate that the formulation cannot be applied to water or *"...to areas where surface water is present"* (C&P Press 2004). In the aerial or ground applications, the USDA will use at least a 100 foot buffer and will extend the buffer up to 500 feet in some instances (Cook 2004).

2.4. Use Statistics

In order to minimize the ecological effects and human health effects of gypsy moth infestations, the USDA has adopted various intervention strategies that are roughly categorized as suppression, eradication, and slow the spread (USDA 1995). Suppression efforts are conducted by the USDA Forest Service in areas of well established gypsy moth infestations to combat or interdict periodic gypsy moth population outbreaks. Eradication efforts are conducted by USDA/APHIS to completely eliminate gypsy moth populations in areas where new populations of the gypsy moth are found. Slow the spread, as the name implies, is a program to reduce the expansion of gypsy moth populations from areas of established populations to adjacent non-infested areas.

As indicated in Table 2-3, a total of 664,560 acres were treated with diflubenzuron formulations between 1995 and 2003, for an average annual treatment of about 73,840 acres per year. Virtually all (about 99%) of this use occurred in suppression programs with only about 1% of the use slow the spread programs. Very little diflubenzuron has been used in eradication programs – i.e., only 6 acres were treated in eradication programs accounting for <0.001% of the total acres treated for suppression, eradication, and slow the spread combined. Complete statistics for the amount of diflubenzuron applied in these applications has not been encountered. At the maximum labeled rate of 0.0624 lbs a.i./acre, the average annual treatment of about 73,840 acres per year would correspond to about 4608 pounds per year.

By comparison, the annual use of diflubenzuron on cotton for 1992 (the most recent year for which statistics are available) was 78,013 lbs (USGS 1998) or about a factor of 17 above the estimated average annul use by the Forest Service. The low use of the diflubenzuron by the USDA relative to agricultural applications – i.e., about 5.6% [4608 ÷ (78,013 + 4608) = 0.0558] – indicates that the use of diflubenzuron by the USDA will not contribute substantially to general levels of diflubenzuron in the environment. This 5.6% figure probably overestimates the use of diflubenzuron by the USDA relative to agricultural applications because USGS (1998) reports only use on cotton. Diflubenzuron is registered for application to a number of other agricultural crops. Nonetheless, localized release of diflubenzuron will occur and the consequences of this release is considered in the remainder of this risk assessment.

3. HUMAN RISK ASSESSMENT

3.1. HAZARD IDENTIFICATION

3.1.1. Overview

No information is available on the effects of diflubenzuron on humans but the toxicity of this compound has been well characterized in experimental mammals. In mammals, the most sensitive effect involves damage to hemoglobin, a component of blood involved in the transport of oxygen. Diflubenzuron causes the formation of methemoglobin, a form of hemoglobin that is not able to transport oxygen. Methemoglobinemia, an excessive formation of methemoglobin, is the primary toxic effect of diflubenzuron by all routes of exposure and for all durations of exposure in all species of animals that have been tested. Diflubenzuron causes other effects on the blood but methemoglobinemia is the most sensitive effect – i.e., the effect that occurs at the lowest dose. While effects on the blood are well documented, there is little indication that diflubenzuron causes other specific forms of toxicity. Diflubenzuron does not appear to be neurotoxic or immunotoxic, does not appear to affect endocrine function in laboratory mammals, and is not a carcinogen. In addition, diflubenzuron does not appear to cause birth defects or reproductive effects. Diflubenzuron is relatively nontoxic by oral administration, with single-dose LD_{50} values reported as > 4640 mg/kg to >10,000 mg/kg. A large number of studies on the subchronic and chronic toxicity of diflubenzuron are available. As with acute toxicity, methemoglobinemia is the most consistent and sensitive sign of toxicity in laboratory mammals. Diflubenzuron can be absorbed from the skin in sufficient amounts to cause hematologic effects – e.g., methemoglobinemia and sulfhemoglobinemia. Nonetheless, these effects occur at higher doses after dermal administration than after oral administration.

3.1.2. Mechanisms of Action

Some specific mechanisms of action for diflubenzuron are well understood in both mammals and invertebrates. As discussed in Section 4.1, diflubenzuron inhibits chitin synthesis in invertebrates and this in turn disrupts normal growth and development and can lead to death. Mammals, including humans, do not produce chitin and this mechanism thus has no relevance to the human health risk assessment. Another mechanism of diflubenzuron involves damage to hemoglobin, a key component of blood, through the development of methemoglobin and sulfhemoglobin. This is highly relevant to the human health risk assessment and the formation of methemoglobin is the basis for the U.S. EPA RfD for diflubenzuron (Section 3.3).

Hemoglobin is the component in red blood cells that is responsible for transporting oxygen throughout the body. If this function is impaired, either because of damage to hemoglobin (Hb) or lack of oxygen in the air, serious adverse effects (i.e., equivalent to suffocation) can occur. The formation of both methemoglobin and sulfhemoglobin can cause such impairment and lead to the formation of methemoglobinemia and sulfhemoglobinemia, respectively. Methemoglobin is formed by the oxidation of the heme iron in hemoglobin from the ferrous to the ferric state (Bradberry 2003; Smith 1996). Heme group oxidation occurs spontaneously and accounts for approximately 2% of the hemoglobin in normal individuals. Methemoglobin is reduced (restored to its natural state) by a set of enzymes referred to as methemoglobin reductases. The most common methemoglobin reductase is dependent on NADH, a molecule that is common in all living systems and is necessary for the proper function of many enzymes (Lo and Agar 1986). Some individuals are deficient in NADH-dependent methemoglobin reductase, in which case as much as 50% of their blood pigment may exist as methemoglobin. Newborns are also deficient in NADH-methemoglobin reductase. As discussed further in Section 3.1.15 (Impurities and Metabolites), 4-chloroaniline, a metabolite of diflubenzuron, has also been shown to induce methemoglobinemia (WHO 2003).

Sulfhemoglobinemia is characterized by the presence of abnormal pigments, other than methemoglobin, in red cells and can be regarded as a form of nonspecific oxidative damage (Smith 1996) and, in some cases, the differential diagnosis of sulfhemoglobinemia and methemoglobinemia may be difficult (Demedts et al. 1997). As with methemoglobinemia, sulfhemoglobinemia can be induced by aromatic amines and hydroxyamines. Unlike methemoglobinemia, sulfhemoglobinemia is irreversible. Sulfhemoglobinemia is associated with the formation of Heinz bodies, dark-staining granules found in red blood cells. The formation of Heinz bodies can lead to red cell dysfunction and hemolysis (breakdown of the cell membrane). The damaged cells are in turn captured by the spleen, which can lead to spleen enlargement. In general, cats, mice, dogs, and humans are more susceptible to Heinz body formation compared with rabbits, monkeys, chickens, and guinea pigs (Smith 1996). Studies on the effects of diflubenzuron on methemoglobin, sulfhemoglobin, Heinz body formation, and the spleen are summarized in Appendix 1. These data are discussed in further detail in Section 3.3 (Dose-Response Assessment).

While diflubenzuron displays other types of toxicity, as discussed in the following subsections, the formation of methemoglobin and sulfhemoglobin are the only mechanisms of toxicity that have been clearly identified.

3.1.3. Kinetics and Metabolism

3.1.3.1. Oral Absorption **–** Diflubenzuron appears to be readily absorbed after oral administration but the extent of absorption is dose-dependant. Cameron et al. (1990) conducted a standard pharmacokinetic study on diflubenzuron in rats. Diflubenzuron was rapidly absorbed and excreted in both the urine and feces. Urine showed significant levels of 2,6-difluorobenzoic acid, 2,6-difluorophippuric acid, 2,6-difluorobenzaimide, 4-chlorophenyl urea, and 2'-hydroxydiflubenzuron. Fecal excretion contained mostly unchanged parent compound. 4-Chloroaniline was not detected in urine or bile (limit of detection = 7.5 ng/mL). As discussed further below, 4-chloroaniline is a metabolite of diflubenzuron in some species (Section 3.1.3.3) and is an environmental metabolite of diflubenzuron formed by biodegradation in soil. The oral absorption of diflubenzuron appears to be dependent on dose (e.g., Willems et al. 1980). At relatively low doses, in the range of 1 mg/kg/day, a substantial fraction of administered diflubenzuron (about 50%) is absorbed. At much higher doses, in the range of 1000 mg/kg/day, much less diflubenzuron is absorbed (about 5%) (WHO 1996, 2001). While studies on the basis for this dose-dependent absorption have not been located for diflubenzuron, this is a relatively common pattern in many compounds that are highly lipophilic – i.e., tend to concentrate in fat tissue – and probably involves saturable transport by the lymphatic system (e.g., Rozman et al. 1979).

3.1.3.2. Dermal Absorption – No studies have been found on the dermal absorption of diflubenzuron in humans. Dermal absorption in rats has been studied by Andre (1996) and this study is summarized in Appendix 1. The dermal absorption of diflubenzuron appeared to be linear for doses of 0.005 or 0.05 mg/cm^2. This is unlike the pattern with oral absorption, as noted above, but the dermal doses are very low. In addition and unlike the case with oral absorption, there is no basis for asserting that dermal absorption is saturable. Andre (1996) does not provide a kinetic analysis of the absorption data. Andre (1996) does note that about 6% of the dose was bound to skin and that less than 1% of the dose was absorbed systemically over a 10 hour period. Taking 1% as an approximate measure of absorbed dose, the dermal absorption coefficient would be about 0.001 hour^{-1} [k = -ln(1-0.01)/10 hour = 0.001 hour^{-1}].

While several additional studies are available on the toxicity of diflubenzuron after dermal administration (Section 3.1.12.), these studies do not address the kinetics of dermal absorption. WHO (1996, 2001) summarizes an unpublished study conducted in the Netherlands indicating that 0.2% of a dermal dose of 150 mg/kg was absorbed by rabbits over a 6 hour exposure period. This corresponds to a dermal absorption rate of about 0.04 hour^{-1} [k = -ln(1-0.002)/6 hours = 0.000358 hour^{-1}], substantially less than the estimate in rats from the study by Andre (1996).

Estimates of first-order dermal absorption rates can also be made from structure activity relationships (SERA 2001). Based on these relationships, the estimated first-order dermal absorption rate for diflubenzuron is 0.0044 hour^{-1} with a 95% confidence interval of 0.0019 hour^{-1} to 0.01 hour^{-1} (Worksheet A09). These estimate first-order dermal absorption rates are somewhat higher than those based on experimental measurements. The higher dermal absorption rates from Worksheet A09 are used in the current risk assessment. While this is a somewhat conservative or protective approach, it has little impact on the risk characterization (Section 3.4) because none of the exposures based on these conservative estimates approach a level on concern.

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 (SERA 2001). Using the method recommended by U.S. EPA/ORD (1992), the estimated dermal permeability coefficient for diflubenzuron is 0.012 cm/hour with a 95% confidence interval of 0.0066 to 0.021 cm/hour. The application of this method to diflubenzuron is given in Worksheet A10.

Note that the first-order and zero-order absorption coefficients are summarized in Worksheet 03 but are rounded to two significant places. Links to these values are used in all of the exposure worksheets involving dermal absorption.

3.1.3.3. Metabolism – Two types of metabolites are considered in this risk assessment: metabolites that are formed *in vivo* by an animal after diflubenzuron has been absorbed and metabolites that the formed in the environment through the degradation of diflubenzuron in environmental media – i.e., soil, air, and water. The *in vivo* metabolism of diflubenzuron has been reviewed by WHO (1996, 2001) and additional unpublished studies have been submitted to the U.S. EPA on the metabolism of diflubenzuron in rats (Cameron et al. 1990; Gay et al. 1999) as well as the environmental metabolism of diflubenzuron (Dzialo and Maynard 1999; Thus et al. 1991; Walstra and Joustra, 1990).

An overview of the *in vivo* and environmental metabolism of diflubenzuron is given in Figure 3-1. Two basic pathways exist for the metabolism of diflubenzuron. In the environment as well as in sheep, pigs, and chickens, the major route of metabolism involves cleavage of the ureido bridge with the formation of 2,6-difluorobenzoic acid and 4-chlorophenyl urea. The latter compound is then metabolized to 4-chloroaniline. As discussed further in Section 3.1.15, the formation of 4-chloroaniline is important to the human health risk assessment because this compound is classified as a carcinogen. The other pathway for the metabolism of diflubenzuron predominates in rats and cows and involves hydroxylation rather than cleavage of the ureido bridge. Hydroxylation of the aromatic rings involves the addition of a hydrogen-oxygen or hydroxy (OH) group to one of the rings. Hydroxylation increases the water solubility of aromatic compounds. Particularly when followed by conjugation with other water soluble compounds in the body, such as sugars or amino acids, hydroxylation greatly facilitates the elimination of the compound in the urine or bile. As detailed further by WHO (2001), the ureido bridge may also be cleaved in rats but 4-chloroaniline does not appear to be a major metabolite. No information has been located on the metabolism of diflubenzuron in humans.

3.1.4. Acute Oral Toxicity

No information has been found on the acute toxicity of diflubenzuron in humans. Information regarding the acute toxicity of diflubenzuron and diflubenzuron formulations in laboratory mammals is summarized in Appendix 1. These data indicate that diflubenzuron is relatively nontoxic by oral administration, with single dose LD_{50} values in mice and rats reported as > 4640 mg/kg to >10,000 mg/kg. In other words, less than half of the animals died at these doses. Many of the exposure scenarios considered in the current risk assessment for the use of diflubenzuron for the control of the gypsy moth do involve very short term acute exposures and the use of acute oral toxicity values is considered further in Section 3.3.3.

3.1.5. Subchronic and Chronic Toxicity

No information has been found on the subchronic or chronic toxicity of diflubenzuron in humans. A large number of studies using experimental mammals are available on the subchronic and chronic toxicity of diflubenzuron. Studies most relevant to the current risk assessment as summarized in Appendix 1 and additional information, including unpublished studies conducted in Europe, are summarized by WHO (1996, 2000).

As with acute toxicity, methemoglobinemia is the most consistent and sensitive sign of toxicity in laboratory mammals and has been observed in all mammalian species on which bioassays have been conducted: cats (Keet et al. 1982), dogs (Chesterman et al. 1974; Keet et al. 1982; Greenough et al. 1985), mice (Colley et al. 1981; Colley et al. 1984; Keet et al. 1984b), rats (Berberian and Enan 1989; Burdock et al. 1980; Burdock 1984; Keet et al. 1984a), and sheep (Keet et al. 1982).

For the current risk assessment, the most relevant longer-term toxicity study is the one-year oral toxicity study in which dogs were administered diflubenzuron in gelatin capsules at doses of 0, 2, 10, 50, or 250 mg/kg/bw (Greenough et al. 1985). As indicated in Appendix 1 and discussed further in Section 3.3.2, this is the study on which the U.S. EPA (1988; 1997a; 2000) has based the chronic RfD. In this study, no clinical signs of toxicity or pathology attributable to treatment were observed. The only adverse effects that were observed included dose-related increases in methemoglobin and sulfhemoglobin accompanied by an increase in spleen weight. As noted in the previous section, the increased spleen weight is probably secondary to the hematologic effects of diflubenzuron. This study is also important in that a clear duration-response relationship is apparent, with no significant changes in methemoglobin and sulfhemoglobin concentrations at four weeks after the start of dosing.

3.1.6. Effects on Nervous System

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

Diflubenzuron, however, evidences few characteristics of a neurotoxicant even in terms of indirect effects. In an acute inhalation study involving a diflubenzuron formulation not used by the USDA (i.e, Dimilin 2L), excessive salivation and labored breathing were observed both during and after exposure (Hoffman 1997). While these can be signs of neurologic effects, they can be secondary to general irritation as well as other toxic effects. The only study on diflubenzuron that specifically assayed for neurotoxicity is the inhalation study by Newton (1999) in rats (details in Appendix 1). The neuro-behavioral battery included assays for autonomic effects, central nervous system effects (e.g., tremors and convulsions), general motor activity, movement and posture, reactivity to handling or sensory stimuli, grip strength, and observations for atypical behavior. Newton (1999) noted no treatment related effects of any endpoints assayed. The review of this study by WHO (2001) indicates that: “A reduction in ‘grid count’ was evident in the neuro-functional assessment of males and females exposed to 110 mg/m^3.” Here, grid count refers to the number of grids that both front feet simultaneously touched during a fixed observations period. Based on the data reported in Newton (1999) for males (summary in Table 3, p. 44 and individual data in Appendix pp. 150-151 in Newton 1999) and females (summary Table 3, p. 47 and individual data in Appendix pp. 168-169 in Newton 1999), a slight reduction in mean grid count is apparent for this response in study weeks 1, 2, and 3 but not in study week 4. There is, however, substantial scatter in the individual data in terms of the relationship of the response to concentration. The significance of the changes in grid count in the absence of any other sign of neurotoxicity is questionable.

3.1.7. Effects on Immune System

Immunotoxicants are chemical agents that disrupt the function of the immune system. Two general types of effects, suppression and enhancement, may be seen and both of these are generally regarded as adverse. Agents that impair immune responses (*immune suppression*) enhance susceptibility to infectious diseases or cancer. Enhancement or *hyperreactivity* can give rise to *allergy* or hypersensitivity, in which the immune system of genetically predisposed individuals inappropriately responds to chemical or biological agents (e.g., plant pollen, cat dander, flour gluten) that pose no threat to other individuals or *autoimmunity*, in which the immune system produces antibodies to self components leading to destruction of the organ or tissue involved.

There is very little direct information on which to assess the immunotoxic potential of diflubenzuron. The only studies specifically related to the effects of diflubenzuron on immune function are skin sensitization studies (Section 3.1.11). While the study by Blaszcak (1997e) indicates that diflubenzuron is not a skin sensitizer, this provides no information useful for directly assessing the potential for diflubenzuron to disrupt immune function.

Nonetheless, the toxicity of diflubenzuron has been examined in numerous acute, subchronic, and chronic bioassays. Although many of these studies did not focus on the immune system, changes in the immune system (which could potentially be manifest as increased susceptibility to infection compared to controls) were not observed in any of the available long-term animal studies (Appendix 1). Typical subchronic or chronic animal bioassays conduct morphological assessments of the major lymphoid tissues, including bone marrow, major lymph nodes, spleen and thymus (thymus weight is usually measured at autopsy 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 cellularity of lymphoid tissue and blood, indicative of a possible immune system stimulation or suppression, can also be detected (Durkin and Diamond 2002). None of these effects have been noted in any of the longer term toxicity studies on diflubenzuron (Appendix 1).

3.1.8. Effects on Endocrine Function

The *endocrine system* participates in the control of metabolism and body composition, growth and development, reproduction, and many of the numerous physiological adjustments needed to maintain constancy of the internal environment (*homeostasis*). The *endocrine system* consists of *endocrine glands*, *hormones*, and *hormone receptors*. *Endocrine glands* are specialized tissues that produce and export (*secrete*) *hormones* to the bloodstream and other tissues. The major endocrine glands in the body include the adrenal, hypothalamus, pancreas, parathyroid, pituitary, thyroid, ovary, and testis. Hormones are also produced in the gastrointestinal tract, kidney, liver, and placenta. *Hormones* are chemicals produced in endocrine glands that bind to *hormone receptors* in target tissues. Binding of a hormone to its receptor results in a process known as *postreceptor activation* which gives rise to a *hormone response* in the target tissue, usually an adjustment in metabolism or growth of the target tissue. Examples include the release of the hormone *testosterone* from the male testis, or *estrogen* from the female ovary, which act on receptors in various tissues to stimulate growth of sexual organs and development of male and female sexual characteristics. The target of a hormone can also be an endocrine gland, in which case, receptor binding may stimulate or inhibit hormone production and secretion. Adverse effects on the endocrine system can result in abnormalities in growth and development, reproduction, body composition, homeostasis (the ability to tolerate various types of stress), and behavior.

There is no indication that diflubenzuron causes endocrine disruption in experimental mammals. Standard subchronic, chronic and reproductive toxicity studies provide no basis for asserting that any signs of overt toxicity are related to changes in endocrine function. As discussed further in Section 4, however, a few studies do indicate a potential endocrine effects in sheep (Section 4.1.2.1), birds (Section 4.1.2.2) and terrestrial insects (Section 4.1.2.3) but the strength of the association is limited.

3.1.9. Reproductive and Teratogenic Effects

Diflubenzuron has been tested for its ability to cause birth defects (i.e., teratogenicity) as well as its ability to cause reproductive and developmental impairment. Teratogenicity studies typically entail gavage administration to pregnant rats or rabbits on specific days of gestation. Two such studies (each of which is detailed in Appendix 1) were conducted on diflubenzuron: one in rats (Kavanagh 1988a) and one in rabbits (Kavanagh 1988a). As discussed by U.S. EPA/OPP (1997a), both of these were screening studies conducted at one very high dose, 1000 mg/kg bw. Since no signs of maternal or fetal toxicity were observed, no additional testing was required.

Another type of reproduction study involves exposing more than one generation of the test animal to the compound. One such study has been conducted on diflubenzuron (Brooker 1995). As detailed in Appendix 1, this study involved dietary exposures at concentrations of 0, 500, 5000, or 50,000 ppm over two generations in rats. No effects on reproductive performance were noted even though effects were seen on body weight (F_0 only) and increases were noted in methemoglobin and spleen weight – i.e., effects that may be attributable to diflubenzuron.

3.1.10 Carcinogenicity and Mutagenicity

There are no epidemiology studies or case reports that demonstrate or suggest that exposure to diflubenzuron leads to cancer in humans.

The carcinogenicity of diflubenzuron has been tested in rats and mice and these studies are detailed in Appendix 1. No carcinogenic effects were observed in rats exposed to diflubenzuron in a 2-year feeding study (Keet et al. 1984a). Neither treated nor control rats had cancers of any type, although pathological changes were observed in the spleen of both male and female rats. In mice, no carcinogenic effects or changes in spleen pathology were observed in males or females in a 2-year feeding study (Colley et al. 1984).

In addition to its lack of carcinogenic activity in *in vivo* bioassays, several bioassays of diflubenzuron for mutagenicity or other damage to DNA have failed to detect adverse effects. A lack of mutagenic activity has been reported in a dominant lethal study in mice (Arnold 1974), cell transformation assays using BALB/3T3 cells (Brusick and Weir 1977a), the induction of unscheduled DNA synthesis (Brusick and Weir 1977b), transplacental transformation assays using hamster cells (Quarles et al. 1980), and Ames assays using various strains of Salmonella typhimurium with and without metabolic activation (Brusick and Weir 1977c). Diflubenzuron did induce cell transformations in BALB/c 3T3 cells in the absence of metabolic activation; however, the effect was not observed with metabolic activation (Perocco and others 1993).

Diflubenzuron has been shown to inhibit the uptake of uridine, adenosine, and cytidine in cultured melanoma cells (Mayer et al. 1984) and inhibit the in vivo growth of melanomas in mice (Jenkins et al. 1986). Since the inhibition was enhanced by mixed function oxidase induction with 3-methylcholanthrene or beta-napthaflavone, aromatic hydroxylation was suggested as a requisite to tumor inhibition.

Both the U.S. EPA/OPP (1996a) and the WHO (1996, 2001) have concluded that diflubenzuron is not a carcinogen. This is detailed further in Section 3.3.2.3. However, the potential carcinogenicity of 4-chloroaniline, an environmental metabolite of diflubenzuron, is of concern and this is discussed further in Section 3.1.15 (Impurities and Metabolites) and in the dose-response assessment (Section 3.3.3.3).

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

As summarized in Appendix 1, diflubenzuron and formulations of diflubenzuron do not appear to be skin irritants (Blaszcak 1997d;) or sensitizers (Blaszcak 1997e). When instilled directly into the eye, however, diflubenzuron does cause slight to moderate conjunctival irritation (Blaszcak 1997c).

3.1.12. Systemic Toxic Effects from Dermal Exposure

As noted in Section 3.1.3.2, diflubenzuron can be absorbed from the skin and many of the exposure scenarios considered in this risk assessment involve dermal contact (Section 3.2). The available toxicity studies clearly indicate that diflubenzuron can be absorbed in sufficient amounts to cause hematologic effects – e.g., methemoglobinemia and sulfhemoglobinemia (Goldenthal 1996). Nonetheless, these effects occur only at higher doses after dermal administration (i.e., 1000 mg/kg/day) than after oral administration (i.e., about 100 to 250 mg/kg/day). As with oral toxicity, severe signs of dermal toxicity are not observed even at doses that will induce methemoglobinemia and sulfhemoglobinemia (Blaszcak 1997b; Goldenthal 1996). This is an important relationship that impacts that characterization of risk, as detailed further in Section 3.4.

3.1.13. Inhalation Exposure

As with oral and dermal exposure, inhalation exposures appear to primarily effect the blood, causing increases in methemoglobin and sulfhemoglobin (Eyal 1999; Hoffman 1997; Berczy et al. 1975; Newton 1999). The threshold for these effects appears to be lower in nose only exposures – i.e., an NOEC of 30 mg/m^3 with an effect level of 100 mg/m^3 in the study by Eyal (1999) – compared to whole body exposures – i.e., an NOEC of 500 mg/m^3. It is unclear why this would be the case. In any event, as discussed further in Section 3.2, inhalation is not likely to be a significant route of exposure because of the low vapor pressure of diflubenzuron (Table 2-1) and ambient air will contain concentrations of diflubenzuron that are far below the NOEC values for nose-only exposure.

3.1.14. Inerts and Adjuvants

As noted in Section 2.2, Dimilin 4L contains petroleum oil [CAS No. 64742-46-7] and Dimilin 25W contains kaolin clay [CAS No. 1332-58-7] (C&P Press 2004). Kaolin clay is classified as a List 4a inert by the U.S. EPA (2004). This classification indicates that the product is considered as "Minimal risk inert ingredient". Petroleum oil with the CAS No. 64742-46-7 designation is classified as a List 2 inert which indicates a "Potentially Toxic Inert Ingredients/High Priority for Testing inerts". Details of these classifications may be found at: http://www.epa.gov/opprd001/inerts/lists.html. The toxicology of petroleum oil has been reviewed in some detail by ATSDR (2003). At sufficiently high doses, some petroleum oils can cause gastrointestinal, central nervous system (CNS), and renal effects. Petroleum oils however are highly variable and it is difficult to assess the potential contribution of the petroleum oil in Dimilin 4L to the overall toxicity of the formulation. No information on the toxicity of Dimilin 4L is included in the MSDS for this formulation (C&P Press 2004) or in the U.S. EPA RED (U.S. EPA/OPP 1997a) and no information on the toxicity of Dimilin 4L was encountered in the search of the U.S. EPA CBI files. The toxicity of Dimilin 2L (Blaszcak 1997a summarized in Appendix 1) appears to be comparable to that of Dimilin 25W (Koopman, 1977) as well as technical grade diflubenzuron (WHO 1996).

The identity of all inerts in both diflubenzuron formulations has been disclosed to the U.S. EPA (i.e., Drozdick 1998b,d; Vanstone 1998a,b,c) and this information has been reviewed as part of this risk assessment. This information, however, is protected under FIFRA (Section 10). Other than to state that no apparently hazardous materials have been identified, which is consistent with the MSDS for both Dimilin 4L and Dimilin 25W (C&P Press 2004), the information on the inerts in these formulations cannot be detailed.

3.1.15. Impurities and Metabolites

As with inerts, the impurities in formulations of diflubenzuron have been identified and disclosed to U.S. EPA (Drozdick 1998a,c,e; Van Kampen and Thus 1996; Vanstone 1998a,b,c; White 1998) and this information has been reviewed as part of this risk assessment. Again, this information is protected under FIFRA (Section 10) and cannot be disclosed in this risk assessment. Notwithstanding this limitation, the impurities that may be in diflubenzuron or formulations of diflubenzuron add relatively little uncertainty to this risk assessment. All toxicity studies summarized in Appendix 1 involved either technical grade diflubenzuron – i.e., diflubenzuron with any impurities – or the formulations which also contain the impurities. Thus, the available toxicity data should encompass the potential toxic effects of the impurities.

In terms of metabolites, the toxicity of most *in vivo* metabolites, as defined in Section 3.1.3.3, should also be encompassed by the available *in vivo* toxicity studies because these metabolites will be formed during the course of a standard *in vivo* toxicity study. This argument, however, does not hold for 4-chloroaniline for two reasons. First, as noted in Section 3.1.3.3, 4-chloroaniline does not appear to be metabolite in rodents, the species on which most toxicity studies have been conducted. Secondly, 4-chloroaniline is an environmental metabolite and is classified as a Group B2 carcinogen – i.e., indicating a probable human carcinogen following the classification of the U.S. EPA/OPP (1997a, 2000a) or a possible human carcinogen following the classification of the International Agency for Research on Cancer (IARC 1997). The carcinogenic activity of 4-chloroaniline has also been noted by WHO (2003). Consequently, potential exposures to 4-chloroaniline are quantitatively considered in the exposure assessment (Section 3.2), dose-response assessment (Section 3.3), and risk characterization (Section 3.4),

3.1.16. Toxicologic Interactions

There is no information on the interactions of diflubenzuron with other agents. Deleschuse et al. (1998) have investigated the cytotoxicity and induction of cytochromes P450 1A1/2 by insecticides in hepatic and epidermal cells. Diflubenzuron was one of the six pesticides studied and one of two that did not exert a cytotoxic effect in hepatocytes. In addition, de Sousa et al. (1997) noted a strong, dose-dependent, significant ($p<0.001$) induction of ethoxyresorufin O-deethylase (EROD) activity and or CYP1A1 mRNAs (5- to 7-fold greater than controls in human hepatocytes and approximately 7-fold greater than controls in rat hepatocytes). Any effect on hepatocytes and/or cytochrome P450 could impact how an organism would metabolize (either to toxicity or detoxify) a very large number of other compounds. The net effect of such interactions could be to enhance or inhibit toxicity and a more specific assessment would require data on specific combinations of other chemicals with diflubenzuron.

3.2. EXPOSURE ASSESSMENT

3.2.1. Overview.

Exposure assessments are conducted for both diflubenzuron and 4-chloroaniline. For diflubenzuron, a standard set of exposure scenarios are presented for both workers and members of the general public. As discussed in the hazard identification, concern for 4-chloroaniline arises because it is an environmental metabolite of diflubenzuron and is classified as a carcinogen. Thus, 4-chloroaniline is not a concern in worker exposure assessments because 4-chloroaniline will not be present at the time that diflubenzuron is applied. Nor is 4-chloroaniline a concern in some acute exposure scenarios for the general public such as direct spray during the application of diflubenzuron. Consequently, only a subset of the standard exposure scenarios – those associated with contaminated vegetation and contaminated water – are presented for 4-chloroaniline but these do include all standard chronic exposure scenarios, which are of greatest concern because of the potential carcinogenicity of 4-chloroaniline.

All exposure assessments are based on the maximum single application rate for diflubenzuron of 0.0625 lb/acre. This is also the maximum application rate for a single season. Assuming that diflubenzuron is applied in a single application at the maximum rate leads to the highest estimates of peak as well as longer term exposures. The consequences of using lower application rates are discussed in the risk characterization.

For workers applying diflubenzuron, three types of application methods are considered: directed ground spray, broadcast ground spray, and aerial spray. Central estimates of exposure for workers are approximately 0.0009 mg/kg/day for aerial workers, 0.0008 mg/kg/day for backpack workers and about 0.001 mg/kg/day for broadcast ground spray workers. Upper range of exposures are approximately 0.009 mg/kg/day for broadcast ground spray workers and 0.005 mg/kg/day for backpack and aerial workers. All of the accidental exposure scenarios for workers involve dermal exposures and most of these accidental exposures lead to estimates of dose that are either in the range of or substantially below the general exposure estimates for workers. The one exception involves wearing contaminated gloves for one-hour where the upper range of exposure is about 0.4 mg/kg/day.

For the general public, the range of acute exposures is from approximately 0.0000005 mg/kg associated with the lower range for the consumption of contaminated water from a stream by a child to 1.5 mg/kg associated with the upper range for consumption of contaminated fish by subsistence populations – individuals who consume free-caught fish as a major proportion of their diet. Relatively high dose estimates are also associated with the consumption of contaminated water after an accidental spill (about 0.13 mg/kg at the upper range of exposure) and for the consumption of fish by members of the general public (0.3 mg/kg). Other acute exposures are lower by about an order of magnitude or greater. For chronic or longer term exposures, the modeled exposures are much lower than for acute exposures, ranging from approximately 0.00000002 mg/kg/day (2 in 10 millionths of a mg/kg/day) associated with the lower range for the consumption of contaminated water to approximately 0.002 mg/kg/day associated with the upper range for consumption of contaminated fruit.

Exposures to 4-chloroaniline from contaminated vegetation are likely to be below corresponding exposures to diflubenzuron by a factor of about 0.02. This follows from the expected rapid dissipation of 4-chloroaniline that is derived from diflubenzuron which has been deposited on vegetation. Estimated concentrations of 4-chloroaniline in water, however, are likely to equal or exceed anticipated concentrations of diflubenzuron under some circumstances. The peak exposures to 4-chloroaniline will occur at different times (later after the application of diflubenzuron) and under different conditions of precipitation than those of diflubenzuron. These differences are due to the relatively slow rate in the formation of 4-chloroaniline from diflubenzuron in soil.

3.2.2. Workers.

The Forest Service uses a standard set of exposure assessments in all risk assessment documents. All of the exposure assessments for workers as well as members of the general public are detailed in the worksheets on diflubenzuron that accompany this risk assessment (Supplement 1) and documentation for these worksheets is given in SERA (2003). A copy of this documentation is available at www.sera-inc.com. This section on workers and the following section on the general public provide plain verbal descriptions of the worksheets and discuss diflubenzuron specific data that are used in the worksheets.

A summary of the exposure assessments for workers is presented in Worksheet E02 of the worksheets for diflubenzuron that accompany this risk assessment. Two types of exposure assessments are considered: general and accidental/incidental. The term *general* exposure assessment is used to designate those exposures that involve estimates of absorbed dose based on the handling of a specified amount of a chemical during specific types of applications. The accidental/incidental exposure scenarios involve specific types of events that could occur during any type of application. The exposure assessments developed in this section as well as other similar assessments for the general public (Section 3.2.3) are based on the maximum single and maximum annual application rate of 0.0624 lb/acre (Section 2). The consequences of using lower application rates are discussed further in the risk characterization (Section 3.4).

3.2.2.1. General Exposures – As described in SERA (2001), worker exposure rates are expressed in units of mg of absorbed dose per kilogram of body weight per pound of chemical handled. Based on analyses of several different pesticides using a variety of application methods, default exposure rates are estimated for three different types of applications: directed foliar (backpack), boom spray (hydraulic ground spray), and aerial.

The specific assumptions used for each application method are detailed in Worksheets C01a (directed foliar), C01b (broadcast foliar), and C01c (aerial). In the worksheets, the central estimate of the amount handled per day is calculated as the product of the central estimates of the acres treated per day and the application rate.

As described in SERA (2001), worker exposure rates are expressed in units of mg of absorbed dose per kilogram of body weight per pound of chemical handled. These exposure rates are based on worker exposure studies on nine different pesticides with molecular weights ranging from 221 to 416 and log K_{ow} values ranging from -0.75 to 6.50. The estimated exposure rates are based on estimated absorbed doses in workers as well as the amounts of the chemical handled by the workers. As summarized in Table 2-1 of this risk assessment, the molecular weight of diflubenzuron is 320 and the log K_{ow} is about 3.9. These values are within the range of the pesticides used in SERA (2001). As described in SERA (2001), the ranges of estimated occupational exposure rates vary substantially among individuals and groups, (i.e., by a factor of 50 for backpack applicators and a factor of 100 for mechanical ground sprayers). It seems that much of the variability can be attributed to the hygienic measures taken by individual workers (i.e., how careful the workers are to avoid unnecessary exposure); however, pharmacokinetic differences among individuals (i.e., how fast individuals absorb and excrete the compound) also may be important.

The number of acres treated per hour is taken from previous USDA risk assessments (USDA/FS 1989a,b,c). The number of hours worked per day is expressed as a range, the lower end of which is 6 hours based on an 8-hour work day with 1 hour at each end of the work day spent in activities that do not involve exposure to the compound. The upper end of the range, 8 hours per day, is based on an extended (10-hour) work day, allowing for 1 hour at each end of the work day to be spent in activities that do not involve exposure to the chemical.

It is recognized that the use of 6 hours as the lower range of time spent per day applying herbicides is not a true lower limit. It is conceivable and perhaps common for workers to spend much less time in the actual application of a herbicide if they are engaged in other activities. Thus, using 6 hours may overestimate exposure. In the absence of any published or otherwise documented work practice statistics to support the use of a lower limit, this approach is used as a protective assumption.

The range of acres treated per hour and hours worked per day is used to calculate a range for the number of acres treated per day. For this calculation as well as others in this section involving the multiplication of ranges, the lower end of the resulting range is the product of the lower end of one range and the lower end of the other range. Similarly, the upper end of the resulting range is the product of the upper end of one range and the upper end of the other range. This approach is taken to encompass as broadly as possible the range of potential exposures.

The central estimate of the acres treated per day is taken as the arithmetic average of the range. Because of the relatively narrow limits of the ranges for backpack and boom spray workers, the use of the arithmetic mean rather than some other measure of central tendency, like the geometric mean, has no marked effect on the risk assessment.

3.2.2.2. Accidental Exposures – Typical occupational exposures may involve multiple routes of exposure (i.e., oral, dermal, and inhalation); nonetheless, dermal exposure is generally the predominant route for herbicide applicators (Ecobichon 1998; van Hemmen 1992). Typical multi-route exposures are encompassed by the methods used in Section 3.2.2.1 on general exposures. Accidental exposures, on the other hand, are most likely to involve splashing a solution of herbicides into the eyes or various dermal exposure scenarios.

Diflubenzuron can cause slight to moderate eye irritation (Section 3.1.11). The available literature does not include quantitative methods for characterizing exposure or responses associated with splashing a solution of a chemical into the eyes; furthermore, there appear to be no reasonable approaches to modeling this type of exposure scenario quantitatively. Consequently, accidental exposure scenarios of this type are considered qualitatively in the risk characterization (section 3.4).

As detailed in Section 3.1.3, there are various methods for estimating absorbed doses associated with accidental dermal exposure (U.S. EPA 1992a, SERA 2001). Two general types of exposure are modeled: those involving direct contact with a solution of the herbicide and those associated with accidental spills of the herbicide onto the surface of the skin. Any number of specific exposure scenarios could be developed for direct contact or accidental spills by varying the amount or concentration of the chemical on or in contact with the surface of the skin and by varying the surface area of the skin that is contaminated.

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

Exposure scenarios involving direct contact with solutions of the chemical are characterized by immersion of the hands for 1 minute or wearing contaminated gloves for 1 hour. Generally, it is not reasonable to assume or postulate that the hands or any other part of a worker will be immersed in a solution of a herbicide for any period of time. On the other hand, contamination of gloves or other clothing is quite plausible. For these exposure scenarios, the key element is the assumption that wearing gloves grossly contaminated with a chemical solution is equivalent to immersing the hands in a solution. In either case, the concentration of the chemical in solution that is in contact with the surface of the skin and the resulting dermal absorption rate are essentially constant.

For both scenarios (the hand immersion and the contaminated glove), the assumption of zero-order absorption kinetics is appropriate. Following the general recommendations of U.S. EPA/ORD (1992), Fick's first law is used to estimate dermal exposure. As discussed in Section 3.1.3, an experimental dermal permeability coefficient (Kp) for diflubenzuron is not available. Thus, the Kp for diflubenzuron is estimated using the algorithm from U.S. EPA (1992a), which is detailed in Worksheet A10.

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

For both scenarios, it is assumed that the contaminated skin is effectively cleaned after 1 hour. As with the exposure assessments based on Fick's first law, this product (mg of absorbed dose) is divided by body weight (kg) to yield an estimated dose in units of mg chemical/kg body weight.

3.2.3. General Public.

3.2.3.1. General Considerations – Although some applications of diflubenzuron may be made in relatively remote areas involving limited exposure to the general public, both aerial and ground applications may be made in residential areas. In residential applications, members of the general public are more likely to be exposed to diflubenzuron. Any number of exposure scenarios can be constructed for the general public, depending on various assumptions regarding application rates, dispersion, canopy interception, and human activity. Several scenarios are developed for this risk assessment which should tend to over-estimate exposures in general.

The two types of exposure scenarios developed for the general public include acute exposure and longer-term or chronic exposure. All of the acute exposure scenarios are primarily accidental. They assume that an individual is exposed to the compound either during or shortly after its application. Specific scenarios are developed for direct spray, dermal contact with contaminated vegetation, as well as the consumption of contaminated fruit, water, and fish. Most of these scenarios should be regarded as extreme, some to the point of limited plausibility. The longer-term or chronic exposure scenarios parallel the acute exposure scenarios for the consumption of contaminated fruit, water, and fish but are based on estimated levels of exposure for longer periods after application.

The exposure scenarios developed for the general public are summarized in Worksheet E03. As with the worker exposure scenarios, details of the assumptions and calculations involved in these exposure assessments are given in the worksheets that accompany this risk assessment (Worksheets D01a to D09b). The remainder of this section focuses on a qualitative description of the rationale for and quality of the data supporting each of the assessments.

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

3.2.3.3. Dermal Exposure from Contaminated Vegetation – In this exposure scenario, it is assumed that the herbicide is sprayed at a given application rate and that an individual comes in contact with sprayed vegetation or other contaminated surfaces at some period after the spray operation. For these exposure scenarios, some estimates of dislodgeable residue and the rate of transfer from the contaminated vegetation to the surface of the skin must be available. No such data are available on dermal transfer rates for diflubenzuron and the estimation methods of Durkin et al. (1995) are used as defined in Worksheet D02. The exposure scenario assumes a contact period of one hour and assumes that the chemical is not effectively removed by washing for 24 hours. Other estimates used in this exposure scenario involve estimates of body weight, skin surface area, and first-order dermal absorption rates, as discussed in the previous section.

3.2.3.4. Contaminated Water – Water can be contaminated from runoff, as a result of leaching from contaminated soil, from a direct spill, or from unintentional contamination from aerial applications. For this risk assessment, three exposure scenarios are considered for the acute consumption of contaminated water: an accidental spill into a small pond (0.25 acres in surface area and 1 meter deep), accidental direct spray of or incidental drift into a pond and stream, and the contamination of a small stream and pond by runoff or percolation. In addition, longer-term estimates of concentrations in water are based on a combination of modeling and monitoring data. Each of these scenarios are considered in the following subsections.

3.2.3.4.1. Accidental Spill – The accidental spill scenario assumes that a young child consumes contaminated water shortly after an accidental spill into a small pond. The specifics of this scenarios are given in Worksheet D05. Because this scenario is based on the assumption that exposure occurs shortly after the spill, no dissipation or degradation of diflubenzuron 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 diflubenzuron in a small pond is estimated to range from about 0.014 mg/L to 1.1 mg/L with a central estimate of about 0.2 mg/L (Worksheet D05). This is and is intended to be an extreme accidental exposure scenario. The purpose of this scenario is simply to suggest the intensity of measures that would need to be taken in the event of a relatively large spill of diflubenzuron into a relatively small body of water.

3.2.3.4.2. Accidental Direct Spray/drift for a Pond or Stream – These scenarios are less severe but more plausible than the accidental spill scenario described above. The U.S. EPA typically uses a two meter deep pond to develop exposure assessments (SERA 2004). If such a pond is directly sprayed with diflubenzuron at the nominal application rate of 0.0624 lb/acre, the peak concentration in the pond would be about 0.0035 mg/L (3.5 µg/L or 3.5 ppb) (Worksheet D10a). This concentration is a factor of about 300 below the peak concentration of 1.1 mg/L after the accidental spill. Because the USDA will not directly spray open bodies of water but will use buffers of 100 to 500 feet (Section 2.3), the concentration of 0.0035 mg/L from direct spray would be an accidental exposure. Using the 100 to 500 foot buffers, drift of diflubenzuron from aerial applications would result in water concentrations between about 7.7×10^{-06} mg/L (about 0.008 ppb or 8 ppt – parts per trillion) to about 6.8×10^{-05} mg/L (0.07 ppb or 70 ppt) (Worksheet 10a).

Similar calculations can be made for the direct spray of a stream and the resulting water concentrations will be dependant on the surface area of the stream that is sprayed and the rate of water flow in the stream. The stream modeled using GLEAMS (see below) is about 6 feet wide and it is assumed that the pesticide is applied along a 1038 foot length of the stream with a flow rate of 710,000 L/day. The length of 1038 feet is based on the length of a side of a square 10 ha treatment plot. At an application rate of 0.0624 lb/acre, accidental direct spray onto the surface of the stream would deposit about 4047 mg and this would result in a downstream concentration of about 0.0057 mg/L. Using a buffer of 100 feet, the drift would be a fraction of 0.0195 of the application rate (Worksheet B24) and the concentration in the stream would be about 0.00011 mg/L. Details of these and additional calculations for concentrations in stream water are given in Worksheet 10b.

3.2.3.4.3. Gleams Modeling – For compounds such as diflubenzuron, which may be applied to an entire watershed, drift and even direct spray are not the only and may not be the greatest source of contamination of surface water. Water contamination may also occur from soil runoff or percolation and, depending on local conditions, can lead to substantial contamination of ponds or streams. Estimates of these concentrations can be based both on modeling and monitoring data.

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

For the current risk assessment, the application site was assumed to consist of a 10 hectare square area that drained directly into a small pond or stream. The chemical specific values as well as the details of the pond and stream scenarios used in the GLEAMS modeling are summarized in

Table 3-1. The GLEAMS modeling yielded estimates of runoff, sediment and percolation that were used to calculate concentrations in the stream adjacent to a treated plot, as detailed in Section 6.4 of SERA (2004). The results of the GLEAMS modeling for the small stream are summarized in Table 3-2 and the corresponding values for the small pond are summarized in Table 3-3. These estimates are expressed as both average and maximum concentrations in water. The top section of each table gives the contamination rates (WCR) – i.e., the concentration of the compound in water in units of ppb (µg/L) normalized for an application rate of 1 lb/acre. The bottom section of each table gives the estimated maximum and average concentrations adjusted for the application rate of 0.0624 lb/acre (Section 2.3).

As indicated in Table 3-2, no stream contamination is estimated in very arid regions – i.e., annual rainfall of 10 inches of less. For regions with annual rainfall rates of 15 inches or more, the modeled peak concentrations in streams range from less than 0.01 µg/L (sandy soil) to about 15 µg/L (clay soil at an annual rainfall rate of 250 inches per year). While not detailed in Table 3-2, the losses from clay are associated almost exclusively with sediment loss (about 94%), with the remaining amount due to runoff. No water contamination due to percolation is modeled. This is consistent with a large body of literature on diflubenzuron indicating that downward movement in the soil horizon is extremely limited (e.g., Sundaram and Nott 1989; WHO 1996). Even in sandy soils, where very little water contamination is anticipated, percolation accounts for only about 3% of the total loss at an annual rainfall rate of 250 inches.

Modeled concentrations in a small pond (Table 3-3) are lower than those modeled in the stream. As discussed further below, this is consistent with similar modeling conducted by Schocken et al. (2001) using PRZM/EXAMS. As with the stream modeling, no surface water contamination is expected in very arid regions. For regions with annual rainfall rates of 15 inches or more, the modeled peak concentrations in ponds range from less than 0.004 µg/L (sandy soil) to about 3 µg/L (clay soil at an annual rainfall rate of 250 inches per year).

The GLEAMS scenarios do not specifically consider the effects of accidental direct spray. As discussed above and detailed in Worksheet B06b, direct spray of a standard pond could result in peak concentrations of about 3.5 µg/L, comparable to the peak levels modeled in ponds adjacent to fields with clay soil.

As discussed in Section 3.1.15, this risk assessment is also concerned with concentrations of 4-chloroaniline that could occur in water after the application of diflubenzuron. This process was also modeled using GLEAMS as described above for diflubenzuron. As illustrated in Figure 3-1, diflubenzuron does not degrade directly to 4-chloroaniline. It is first degraded to 4-chlorophenylurea which is in turn degraded to 4-chloroaniline. For the GLEAMS modeling, however, the degradation was modeled as a one-step process, disregarding the formation of 4-chlorophenylurea. This is a conservative approach in that the formation of 4-chlorophenylurea will attenuate the formation of 4-chloroaniline. As discussed further in the risk characterization (Section 3.4), this conservative approach has no impact on the risk assessment.

The chemical specific properties for 4-chloroaniline used in the GLEAMS modeling are given in Table 3-4 and the results for the stream and pond are summarized in Tables 3-5 and 3-6, respectively. The pattern seen with 4-chloroaniline is somewhat more complex than that seen with the parent compound. For example, the average and peak concentrations of 4-chloroaniline in streams is not directly related to rainfall rates (Table 3-5). The highest peak concentration, about 2 µg/L, occurs at a rainfall rate of 100 inches per year. At a rainfall rate of 250 inches per year, the modeled peak concentration is only about 0.36 µg/L. This pattern occurs because the formation of 4-chloroaniline is more rapid in soil than in water – i.e., great microbial activity in soil. Thus, at higher rainfall rates, diflubenzuron is washed rapidly from soil and lesser amounts of 4-chloroaniline are formed. A similar pattern with respect to rainfall rates is seen in the modeling results for the pond (Table 3-6).

The temporal exposures to 4-chloroaniline will also differ from those of diflubenzuron. This is illustrated in Figure 3-2 for concentrations of diflubenzuron and 4-chloroaniline in ponds at an annual rainfall rate of 150 inches. In clay and loam soils, diflubenzuron concentrations peak after the first rainfall and then steadily decline. Concentrations of 4-chloroaniline, however, peak after about 30 to 70 days. While diflubenzuron concentrations are much higher from clay than loam because of higher runoff from clay, the peak concentrations for 4-chloroaniline are similar for both clay (0.42 µg/L) and loam (0.35 µg/L), with the peak concentration in loam soil occurring somewhat later than that in clay soil. The greatest difference between diflubenzuron and 4-chloroaniline occurs in sand. As discussed above, virtually no diflubenzuron is expected to occur in ponds with very sandy soils. This is illustrated in Figure 3-2 for an annual rainfall of 150 inches, in which the concentration of diflubenzuron in water for sand is estimated at zero over the one-year model run. Nonetheless, 4-chloroaniline as a breakdown product from diflubenzuron will form and will rapidly leach through sand. Thus, for 4-chloroaniline, the peak concentrations in the pond with sandy soil, about 1.4 µg/L, are substantially higher than the peak concentrations associated with either clay or loam soils.

3.2.3.4.4. Other Modeling Efforts – A summary of the GLEAMS modeling discussed above as well as modeling of diflubenzuron conducted for other analyses is given in Table 3-7. While some of these modeling efforts involved assumptions substantially different from the GLEAMS modeling (i.e., application rates, soil types, and rainfall patterns), the results are reasonably consistent with the above estimates of concentrations in surface waters based on GLEAMS. All of these modeling efforts used PRZM/EXAMS. As discussed in SERA (2004), PRZM (Pesticide Root Zone Model) is model used by U.S. EPA that is comparable to GLEAMS. PRZM is often linked with EXAMS (Exposure Analysis Modeling System) to estimate concentrations of pesticides in water (U.S. EPA/OPPTS 2004).

In the previous diflubenzuron risk assessment for the gypsy moth program (USDA 1995), maximum modeled concentrations at an application rate of 0.0624 lb/acre, identical to the rate used in the GLEAMS modeling, maximum concentrations in streams after direct spray were estimated at 16 ppb, very close to the estimate of 22 ppb made in the current risk assessment. Concentrations of diflubenzuron in streams associated with runoff were in the range of about 2 ppb to 13 ppb. These are very similar to the central and upper range of concentrations in streams based on the GLEAM modeling (2 ppb to 16 ppb). For open water, USDA (1995) estimated a maximum concentration of 1.22 ppb, which is only somewhat below the maximum of 3 ppb based on GLEAMS.

In the reregistration eligibility decision for diflubenzuron, U.S. EPA (1997a) modeled concentrations of diflubenzuron in surface water using Tier 2 computer models. These models are not otherwise specified in U.S. EPA (1997a). Typically, Tier 2 modeling by U.S. EPA involves PRZM/EXAMS. The U.S. EPA estimates much higher concentrations in water but this is largely due to differences in application rates. For example, at an application rate of 0.67 lb/acre, about a factor of 10 higher than the rate used with GLEAMS (0.0624 lb/acre), the U.S. EPA estimates a peak concentration of about 8.1 µg/L. Adjusting for the differences in application rate, the EPA estimate would be 0.8 µg/L [8.1 µg/L × 0.0624 lb/acre ÷ 0.67 lb/acre = 0.754 µg/L], similar to the estimates using GLEAMS with clay soil at rainfall rates of 100 to 150 inches. While the U.S. EPA (1997a) does not specify rainfall rates or soil types, Tier 2 modeling generally involves "worse case" assumptions which, in this case, would be based on high runoff soils (i.e., clay) and relatively high rainfall rates. The U.S. EPA (1997a) modeling for "Forestry" applications are specified as direct application. U.S. EPA (1997a) does not indicate the nature of the forestry application but direct spray of water does not correspond to applications for the control the gypsy moth. The concentrations modeled by U.S. EPA (1997a) of about 23 µg/L at an application rate of 0.07 lb/acre is consistent with the direct spray of a small stream modeled in this risk assessment (i.e., 22µg/L) but substantially higher than the direct spray of a pond (i.e., 3µg/L). In direct applications to shallow (1.3 to 1.7 m) ponds, Sundarum et al. (1991) monitored average day 1 concentrations in ponds of about 4 µg/L at an application rate of 70 g/ha (0.062 lb/acre), consistent with the peak concentrations in ponds discussed above (Section 3.2.3.4.3).

Harned and Relyea (1997) modeled diflubenzuron applications to a 10 ha plot after the application diflubenzuron at 350 g/ha, about a factor of 5 higher than the application rate used in the GLEAMS modeling. As with the EPA, Harned and Relyea (1997) used PRZM/EXAMS but combined these models with AgDrift. Harned and Relyea (1997) employed variable rainfall rates rather than fixed rates but the individual rainfall events varied from about 2.4 to 7.2 cm or about 1 to 2.8 inches. Based on their modeling, peak concentrations in the pond were estimated at about 1 µg/L. Correcting for the difference in application rates, their estimate of 1 µg/L would correspond to 0.2 µg/L in the GLEAMS modeling – i.e., higher by a factor of 5. As indicated in Table 3-3, concentrations estimated using GLEAMS at comparable daily rainfall events ranged from 0.2 to about 0.8 µg/L.

Schocken et al. (2001) also used AgDrift with PRZM/EXAMS to model diflubenzuron in streams and ponds beneath and adjacent to forests after an application of 0.125 lb/acre, about twice the application rate used in the GLEAMS modeling. Modeled estimates indicated that the initial concentration immediately after application should not exceed 0.255 µg/L in ponds and 0.938 µg/L in streams under the canopy. In adjacent areas, modeled estimates indicated that concentrations in ponds and streams should not exceed 0.260 µg/L and 0.856 µg/L, respectively.

The higher concentrations of diflubenzuron in streams compared to ponds is consistent with the GLEAMS modeling (Tables 3-2 and 3-3). The stream concentrations modeled by Schocken et al. (2001) of 1 µg/L are about a factor of 2 below the central estimates from GLEAMS – i.e., about 2 µg/L. This is probably due to the higher stream flow rate used by Schocken et al. (2001) – i.e., 58,320,000 L/day compared to 710,000 L/day used in the GLEAMS modeling. The peak concentrations in ponds modeled by Schocken et al. (2001), about 0.2 µg/L to 0.3 µg/L are very similar to the estimates from GLEAMS at rainfall rates of about 50 inches per year.

3.2.3.4.5. Monitoring Data – Several monitoring studies (Carr et al. 1991; Nigg and Stamper 1987; Van Den Berg 1986) are available that can be used to assess the plausibility of the modeling estimates summarized in Table 3-7. The common feature in each of these studies is that concentrations in pond and/or stream water are reported and these concentrations can be associated with a defined application rate. The study by Van Den Berg (1986) is probably the most directly relevant to this risk assessment. In this study, diflubenzuron was applied to a 10-acre mixed hardwood-conifer forested plot at an application rate of 0.0625 lb/acre. Initial concentrations of diflubenzuron in surface water (streams and stream pools) in treatment area ranged from 0.127-0.203 ppb and declined to 0.029-0.045 ppb after one day. These concentrations are in the range of concentrations modeled using GLEAMS for ponds (central range) and streams (lower range). Similar results are reported by Carr et al. (1991) who monitored concentrations in streams below 0.5 ppb after the application of diflubenzuron at rates of 13 g/ha or 26 g/ha. Adjusted for an application rate of 0.0624 lb/acre (70 g/ha), the concentration of 0.5 ppb would correspond to about 2.5 to 5 ppb, very close to the upper range of stream concentrations modeled using GLEAMS. The study by Nigg and Stamper (1987) involved a very high application rate, 560 g/ha (226 g/ac or 0.5 lb/acre) in a citrus grove. The maximum monitored concentration in an adjacent pond was 0.197 ppb. Adjusted to an application rate of 0.0624 lb/acre (70 g/ha), this corresponds to a concentration of about 0.02 ppb, in the lower range of pond concentrations modeled using GLEAMS.

This discussion of the monitoring data is not intended to imply a validation of the GLEAMS modeling or other modeling efforts. Model validation or calibration can only be done on a site-specific basis. Nonetheless, the monitoring data do suggest that estimates from GLEAMS as well as other comparable modeling efforts are at least plausible and may reasonably reflect the highly variable concentrations of diflubenzuron that may occur in surface water over a wide range of site-specific conditions.

3.2.3.4.6. Concentrations of Diflubenzuron in Water Used for Risk Assessment – A summary of the concentrations of diflubenzuron in water that are used for the current risk assessment is given in Table 3-8. The upper range of the expected peak concentration of diflubenzuron in surface water will be taken as 16 µg/L for an application rate of 0.0624 lb/acre. This is based on the upper range of concentrations estimated in streams from the GLEAMS modeling. This estimate is consistent with both the available monitoring data (Section 3.2.3.4.6) and other comparable modeling efforts (Section 3.2.3.4.5). This concentration also encompasses accidental direct sprays of both a small stream and small pond (Table 3-7). In most instances, concentrations in surface water are likely to be much lower. At the lower extreme, an argument may be made that concentrations of diflubenzuron are likely to be essentially zero – i.e., applications made at sites that are distant from open bodies of water and in areas in which runoff or percolation are not likely to occur. For this risk assessment, the lower concentration in ambient water will be set at 0.01 µg/L. This is in the lower range of non-zero concentrations modeled in streams and ponds in relatively arid regions. The central estimate of the concentration of diflubenzuron in surface water will be taken as 0.4 µg/L. This is the geometric mean of the range of 0.01 µg/L to 16 µg/L.

Longer term concentrations of diflubenzuron in surface water will be much lower than peak concentrations. At an application rate of 0.0624 lb/acre, the highest longer term concentration will be taken as 0.1 µg/L. This is near the maximum longer term concentration given by U.S. EPA (1997a) after adjusting for differences in application rate – i.e., 0.74 µg/L ÷ 6 applications at 0.06 lb/acre. This longer term maximum concentration is also near the upper range of the longer term concentrations modeled using GLEAMS – i.e., 0.06 µg/L in streams at an application rate of 0.0624 lb/acre. As with peak concentrations, the lower range of longer term concentrations will approach zero. For this risk assessment, the lower range of longer term concentrations is taken as 0.001 µg/L, the lowest non-zero value modeled for diflubenzuron in ponds. This lower range is somewhat arbitrary but has no impact on the risk assessment. The central value for longer term concentrations of diflubenzuron in water will be taken as 0.02 µg/L. This is adapted from the longer term concentrations modeled by Harned and Relyea (1997) but adjusted for differences in the application rate – i.e., 0.1 µg/L × (70 g/ha ÷ 350 g/ha) = 0.02 µg/L. This value is similar to the central estimates of longer term concentrations in streams modeled using GLEAMS – i.e., 0.01 µg/L in Table 3-7 – but is near the upper range of concentrations that would be expected in ponds – i.e., 0.06 µg/L in Table 3-7.

3.2.3.4.7. Concentrations of 4-Chloroaniline in Water Used for Risk Assessment – A summary of the concentrations of 4-chloroaniline in water that are used for the current risk assessment is given in Table 3-9. The upper range of the expected peak concentration of 4-chloroaniline in surface water will be taken as 3 µg/L for an application rate of 0.0624 lb/acre. This is based on the upper range of concentrations estimated in streams near application sites with sandy soil over a range of annual rainfall rates from about 25 to 250 inches (Table 3-5). This concentration is higher than concentrations that might be expected in ponds by about a factor of 3 (Table 3-6). As with diflubenzuron, the lower range of concentrations of 4-chloroaniline in water will approach zero. For this risk assessment, the lower range is taken as 0.00003 µg/L, the lowest non-zero concentration modeled in ponds (i.e., Table 3-6, peak concentration for loam at an annual rainfall rate of 15 inches). The central estimate is taken as 0.5 µg/L. This is about the concentration modeled in stream with loam soil over a range of annual rainfall rates of 100 to 250 inches.

Longer term concentrations of 4-chloroaniline are taken as 0.05 µg/L with a range of 0.0002 µg/L to 0.2 µg/L at an application rate of 0.0624 lb/acre. The lower range is based on the lowest non-zero concentration modeled in ponds – i.e., loam soil at an annual rainfall rate of 15 inches.

The upper range is taken as the highest concentration modeled in ponds – i.e., sandy soil at annual rainfall rate of about 25 to 100 inches. The central estimate is based on the relatively narrow range of concentrations modeled in ponds with loam soil over rainfall rates of 50 to 250 inches per year – i.e., about 0.04 to 0.06 µg/L in Table 3-6. Much lower concentrations are likely to be seen in streams.

3.2.3.5. Oral Exposure from Contaminated Fish – Many chemicals may be concentrated or partitioned from water into the tissues of animals or plants in the water. This process is referred to as bioconcentration. Generally, bioconcentration is measured as the ratio of the concentration in the organism to the concentration in the water. For example, if the concentration in the organism is 5 mg/kg and the concentration in the water is 1 mg/L, the bioconcentration factor (BCF) is 5 L/kg [5 mg/kg ÷ 1 mg/L]. As with most absorption processes, bioconcentration depends initially on the duration of exposure but eventually reaches steady state. Details regarding the relationship of bioconcentration factor to standard pharmacokinetic principles are provided in Calabrese and Baldwin (1993).

Burgess (1989) assayed the bioconcentration of diflubenzuron in Bluegill sunfish, *Lepomis macrochirus*, over a 28 day exposure using C^{14}-labeled diflubenzuron. In this study, concentrations in water, whole fish, fillet (muscle), and viscera were measured at day 0.17 (4 hours), as well as on days 1, 3, 7, 14, 21, and 28. In fillet, the fish muscle ,the BCF was 120 after 1 day and 170 after 28 days with a peak of 200 after 7 days. In whole fish, the BCF was 260 after 1 day and 350 after 28 days with a peak of 360 after 7 days. Similar BCF values have been noted for diflubenzuron by Schaefer et al. (1979, 1980).

For the human health risk assessment of diflubenzuron, the BCF in fillet of 120 after 1 day will be used for acute exposures and the maximum BCF in fillet of 200 will be used for longer term exposures. This approach is taken under the assumption that humans will consume only the fish muscle. In the ecological risk assessment, however, the assumption will be made a predatory consumes the entire fish. Thus, for the ecological risk assessment, the whole body BCF values will be used, 260 for acute exposures and 360 for longer term exposures. These values are entered into Worksheet A02 for diflubenzuron and used in the subsequent worksheets involving exposures to contaminated fish.

Less detailed information is available on the bioconcentration of 4-chloroaniline. Because 4-chloroaniline is much more water soluble than diflubenzuron and has a much lower octanol-water partition coefficient, very little bioconcentration is expected in fillet or whole fish (WHO 2003). In a 14-day exposure of carp to two concentrations of 4-chloroaniline, Tsuda et al. (1993) noted essentially no bioconcentration – i.e., the concentrations in water were essentially identical to those in the fish. Thus, in Worksheet A02 for 4-chloroaniline, values of 1 are used for all BCF values – acute and chronic, whole fish and muscle.

For all scenarios involving the consumption of contaminated fish, concentrations of diflubenzuron or 4-chloroaniline in water are identical to the concentrations used in the contaminated water scenarios (see Section 3.2.3.4). The acute exposure scenario is based on the assumption that an adult angler consumes fish taken from contaminated water shortly after an accidental spill of 200 gallons of a field solution into a pond that has an average depth of 1 m and a surface area of 1000 m^2 or about one-quarter acre. No dissipation or degradation is considered. Because of the available and well-documented information and substantial differences in the amount of caught fish consumed by the general public and native American subsistence populations, separate exposure estimates are made for these two groups (Worksheets D08a and D08b). The chronic exposure scenario is constructed in a similar way, as detailed in Worksheets D09a and D09b, except that estimates of concentrations in ambient water are based on the longer-term estimates summarized in Table 3-8 for diflubenzuron and Table 3-9 for 4-chloroaniline.

3.2.3.6. Oral Exposure from Contaminated Vegetation – Although Forest Service applications of diflubenzuron will not involve the intentional treatment of food crops, incidental exposure to vegetation that may be consumed by members of the general public is plausible during broadcast applications. Any number of scenarios could be developed involving either accidental spraying of crops or the spraying of edible wild vegetation, like berries. The two exposure scenarios developed for this exposure assessment include one scenario for acute exposure, as defined in Worksheet D03 and one scenario for longer-term exposure, as defined in Worksheet D04. In both scenarios, the concentration of diflubenzuron on contaminated vegetation is estimated using the empirical relationships between application rate and concentration on vegetation developed by Fletcher et al. (1994) which is in turn based on a re-analysis of data from Hoerger and Kenaga (1972). These relationships are defined in Worksheet B21. For the acute exposure scenario, the estimated residue level is taken as the product of the application rate and the residue rate (Worksheet D03).

For the longer-term exposure scenario (Worksheet D04), a duration of 90 days is used. The rate of decrease in the residues over time is taken from the vegetation half-time of 9.3 days (Table 2-1). Although the duration of exposure of 90 days is somewhat arbitrary, this duration is intended to represent the consumption of contaminated fruit that might be available over one season. Longer durations could be used for certain kinds of vegetation but would lower the estimated dose (i.e., would reduce the estimate of risk).

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

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

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

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

A somewhat different approach is required to assess exposures to 4-chloroaniline. Immediately after application, residues on vegetation will be comprised solely of diflubenzuron. As diflubenzuron degrades, 4-chloroaniline may be formed. Field studies, however, have indicated no residues of 4-chloroaniline on vegetation treated with diflubenzuron (Schroeder 1980). This may be due to the rapid atmospheric degradation of 4-chloroaniline in air – i.e., an estimated halftime of 3.9 hours or about 0.16 days. This is much less than the estimated vegetation halftime for diflubenzuron – i.e., 9.3 days (Sundaram 1986, 1996). Thus, the rate limiting step in the residues of 4-chloroaniline on vegetation will be the formation of 4-chloroaniline.

The approach for estimating concentrations of 4-chloroaniline on vegetation is conceptually similar to the approach taken with estimating concentrations in water. As a simplifying assumption, 4-chloroaniline generation will be estimated from the halftime of 9.3 days of diflubenzuron – i.e., direct breakdown from diflubenzuron to 4-chloroaniline. In addition, the dissipation of 4-chloroaniline from vegetation will be taken as the atmospheric halftime of 0.16 days, from WHO (2003). Under these conditions and at steady state, the ratio of 4-chloroaniline to diflubenzuron will be ratio of the these halftimes – i.e., 0.16 days ÷ 9.3 days = 0.017. In the scenario specific worksheets for 4-chloroaniline, all specific worksheets modeling exposure to contaminated vegetation are based on concentrations of diflubenzuron. The adjustment factor of 0.017 for 4-chloroaniline is incorporated into all worksheets involving exposure to contaminated vegetation (Worksheets D03, D04, F04a, F04b, F10, F11a, F11b, F12, F13a, F13b, F14a, and F14b).

3.3. DOSE-RESPONSE ASSESSMENT

3.3.1. Overview

The dose-response assessment considers both diflubenzuron itself as well as 4-chloroaniline as an environmental metabolite of diflubenzuron. For systemic toxicity, the dose-response assessment involves the adoption or derivation of acute and chronic RfDs, doses that are considered to produce no adverse effects, even in sensitive individuals. RfDs are presented for both diflubenzuron and 4-chloroaniline. Cancer risk is considered quantitatively for 4-chloroaniline and is expressed as a dose associated with a risk of 1 in 1-million. Following standard practices for USDA risk assessments, risk assessment values available from U.S. EPA are adopted directly unless there is a compelling basis for doing otherwise. When risk values are not available from U.S. EPA, the methods used by U.S. EPA are employed to derive surrogate values.

U.S. EPA has derived a chronic RfD for diflubenzuron of 0.02 mg/kg/day. This chronic RfD is well-documented and is used directly for all longer term exposures to diflubenzuron. This value is based on a NOAEL of 2 mg/kg/day in dogs and an uncertainty factor of 100 – a factor of 10 for interspecies differences and a factor of 10 for sensitive subgroups. Because of the low acute toxicity of diflubenzuron, the U.S. EPA has not derived an acute RfD but has identified an acute NOAEL of 10,000 mg/kg. While this NOAEL could be used to derive a surrogate acute RfD of 100 mg/kg, a more conservative approach is taken and a surrogate acute RfD of 11 mg/kg is derived based on a NOAEL of 1118 mg/kg from a study using a petroleum-based formulation of diflubenzuron. Diflubenzuron has been classified as a non-carcinogen by both U.S. EPA and WHO and no quantitative cancer risk assessment for exposures to diflubenzuron is conducted.

The U.S. EPA has derived a chronic RfD for 4-chloroaniline of 0.004 mg/kg/day and this value is used in the current risk assessment to characterize risks from 4-chloroaniline for longer term exposures. This RfD is based on a chronic oral LOAEL of 12.5 mg/kg/day using an uncertainty factor of 3000, three factors of 10 for interspecies extrapolation, sensitive subgroups, and the use of a LOAEL with an additional factor of 3 due to the lack of data reproductive toxicity data. As with diflubenzuron, the U.S. EPA has not derived an acute RfD for 4-chloroaniline. For this risk assessment a conservative approach is taken in which a surrogate acute RfD of 0.03 mg/kg is based on a subchronic (90-day) NOAEL of 8 mg/kg/day. Consistent with the approach taken by U.S. EPA for the chronic RfD, an uncertainty factor of 300 is used – a factor of 10 for interspecies extrapolation, 10 for intraspecies extrapolation, and 3 for the lack of data on reproductive toxicity. For cancer risk, the U.S. EPA proposes a human cancer potency factor for 4-chloroaniline of 0.0638 $(mg/kg/day)^{-1}$. This potency factor is used to calculate a dose of 1.6×10^{-5} mg/kg/day that would be associated with a cancer risk of 1 in 1-million.

3.3.2. Diflubenzuron

3.3.2.1. Chronic RfD – The most recent RfD for diflubenzuron is 0.02 mg/kg/day. This value is given on the U.S. EPA's agency-wide list of approved RfDs (i.e., IRIS) (U.S. EPA 1990) and has been adopted by the U.S. EPA's Office of Pesticides (U.S. EPA/OPP 1997a,b, 2001a).

The chronic RfD is based on a study by Greenough et al. (1985) in which technical grade diflubenzuron was administered daily in gelatin capsules to dogs at doses of 0, 2, 10, 50, or 250 mg/kg/day, 7 days/week, for 52 consecutive weeks. At the lowest dose, 2 mg/kg/day, no effects were noted on methemoglobin formation or other standard endpoints. This study is detailed further in Appendix 1. The RfD was calculated by dividing the NOAEL of 2 mg/kg/day by an uncertainty factor of 100, a factor of 10 for interspecies differences – i.e., extrapolation of animal data to humans – and a factor of 10 for intraspecies variability – i.e., individuals who might be most sensitive to diflubenzuron.

Under the Food Quality Protection Act (FQPA), the U.S. EPA is required to consider an additional uncertainty factor of 10 for the protection of infants and children. For diflubenzuron, the U.S. EPA (1997a) determined that the additional uncertainty factor is not required because of the information on the reproductive toxicity of diflubenzuron is adequate. As discussed in Section 3.1.9, diflubenzuron has been tested for and does not appear to cause birth defects or reproductive and developmental impairment.

For this risk assessment, the chronic RfD of 0.02 mg/kg/day is used to characterize risks for the general public as well as workers in longer term exposures. Because the RfD is intended to protect for lifetime exposures, it provides a conservative basis for comparing estimated exposure levels to an index of acceptable exposure.

3.3.2.2. Acute RfD – The U.S. EPA (1997a) did not specifically derive an acute RfD for diflubenzuron. In discussing the acute oral toxicity of diflubenzuron and referring specifically to the NOAEL of 10,000 mg diflubenzuron/kg bw from the single dose study in rats and mice by Koopman (1977) – i.e., a dose of 40,000 mg Dimilim/kg bw – the U.S. EPA/OPP (1996) concludes that:

> *One day single dose oral studies in rats and mice indicated only marginal effects on methemoglobin levels at a dose level of 10,000 mg/kg of a 25% wettable powder formulation. Sulfhemoglobin levels and Heinz bodies were not affected. Therefore, there is no acute dietary endpoint and a risk assessment for acute dietary exposure (1 day) is not necessary.* (U.S. EPA/OPP, 1996a, p. 16).

While this is a reasonable position, the current risk assessment is concerned with characterizing the risks of acute exposures as well as comparing the risks of acute exposures to diflubenzuron with risks associated with acute exposures other agents used to control the gypsy moth. A surrogate acute RfD of 100 mg/kg could be derived using the NOAEL of 10,000 mg/kg identified by U.S. EPA/OPP (1996a) and the uncertainty factor of 100 used by U.S. EPA/OPP (1996a) in deriving the chronic RfD (Section 3.3.2.1).

A more conservative approach, however, is taken for the current risk assessment. As noted in the hazard identification (Section 3.1.14), Dimilin 4L contains petroleum oil, a substance that is considered potentially toxic. While no acute toxicity studies have been encountered on Dimilin 4L, Blaszcak (1997a) has conducted a single dose gavage study in rats with Dimilin 2L, another petroleum based formulation of diflubenzuron. In this study, no signs of toxicity associated with treatment were noted at a dose of 5000 mg/kg as Dimilin 2L, equivalent to 1118 mg/kg as diflubenzuron. Thus, 1118 mg/kg rather than 10,000 mg/kg will be taken as the acute NOAEL. This value is used to calculate an acute RfD of 11 mg/kg by applying an uncertainty factor of 100, as in the chronic RfD, and rounding to the nearest integer.

3.3.2.3. Cancer Potency – The U.S. EPA/OPP (1996a) has determined that diflubenzuron itself does not pose a carcinogenic risk. Specifically, the U.S. EPA/OPP (1997a) has concluded that:

> *Based on the available evidence, which included adequate carcinogenicity studies in rats and mice and a battery of negative mutagenicity studies, diflubenzuron per se is classified as Group E (evidence of non-carcinogenicity for humans). –* (U.S. EPA 1997a, p. 18)

Thus, there is no basis for identifying carcinogenicity as and endpoint of concern and this effect is not treated quantitatively in the current risk assessment. This is consistent with the evaluation of the available data on carcinogenicity by WHO (1996, 2001).

3.3.3. 4-Chloroaniline

3.3.3.1. Chronic RfD – The chronic RfD for 4-chloroaniline is 0.004 mg/kg/day (U.S. EPA 1995). This RfD is based on a 2-year feeding study using rats in which the formation of non-neoplastic lesions of the splenic capsule was observed at 250 ppm in the diet (12.5 mg/kg/day) (NCI 1979). This dose is classified as a LOAEL and is divided by an uncertainty factor of 3,000 to derive the RfD. This uncertainty factor is intended to account for intra- and interspecies differences and the extrapolation from a LOAEL to a NOAEL. A value of ten is used for each of these three uncertainty factors is given – i.e., 10 × 10 × 10. An additional factor of 3 was incorporated into the uncertainty factor because of the lack of supporting reproductive toxicity data. This data gap has also been noted by WHO (2003). Confidence in the principal study, the database for toxic effects, and the RfD itself is low (U.S. EPA 1995).

For this risk assessment, the chronic RfD derived by U.S. EPA (1995) is used for characterizing longer-term risks for the general public. As with the RfD for diflubenzuron, this provides a conservative basis for assessing the risks of longer term exposures, which are typically over periods far less than lifetime.

3.3.3.2. Acute RfD – As with diflubenzuron, the U.S. EPA has not proposed an acute RfD for 4-chloroaniline. As noted in Section 3.1, acute exposures to 4-chloroaniline are likely to be minimal immediately after the application of diflubenzuron – i.e., prior to the environmental metabolism of diflubenzuron to 4-chloroaniline. Nonetheless, as detailed in Section 3.2.3.4 and illustrated in Figure 3-2, peak exposures to 4-chloroaniline in water may be higher than peak exposures to diflubenzuron in water, although the peak 4-chloroaniline exposures may occur weeks to months after the application of diflubenzuron. Consequently, this risk assessment will derive a surrogate acute RfD for 4-chloroaniline.

The toxicology of 4-chloroaniline has been reviewed in detail by WHO (2003) and the most relevant studies for the current risk assessment as summarized in Appendix 1. As a conservative approach, the surrogate acute RfD is based on the subchronic study by Scott and Eccleston (1967) in which rats were dosed daily with 4-chloroaniline at 0, 8.0, 20.0, or 50.0 mg/kg for 3 months. No hematologic or other adverse effects were observed at the lowest dose, 8 mg/kg/day. For the surrogate acute RfD, an uncertainty factor of 300 is used – a factor of 10 for interspecies extrapolation, 10 for intraspecies extrapolation, and 3 for the lack of data on reproductive toxicity. Thus, the surrogate acute RfD is taken as 0.03 mg/kg/day [8 mg/kg/day ÷ 300 = 0.02666 mg/kg/day which rounds to 0.03 mg/kg/day using one significant figure].

3.3.3.3. Cancer Potency – In the previous risk assessment for the use of diflubenzuron in gypsy moth programs (USDA 1995), a cancer potency factor of 0.013 $(mg/kg/day)^{-1}$ was used in the human health risk assessment. This was based on the NCI (1979) using the linearized multi-stage model. More recently, the U.S. EPA/OPP (1999, 2000a) has calculated a human cancer potency factor for 4-chloroaniline of 0.0638 $(mg/kg/day)^{-1}$, about a factor of 5 greater than the previous value used by USDA (1995).

In implementing the dietary risk assessment for the formation 4-chloroaniline from diflubenzuron, the U.S. EPA (2000a) has noted a potential cancer risk from 4-chlorophenylurea. As noted in Figure 3-1 and discussed in Section 3.1.3.3, 4-chlorophenylurea is structurally similar to 4-chloroaniline and is formed as an intermediate in the environmental breakdown of diflubenzuron to 4-chloroaniline. No specific information is available on the carcinogenicity of 4-chlorophenylurea. As a conservative approach in their dietary risk assessment of the degradation products of diflubenzuron, the U.S. EPA (2000a) elected to treat 4-chlorophenylurea as if it were a carcinogen with the same potency as 4-chloroaniline. This approach has been criticized by Cardona (1999, 2001) both because of the lack of information indicating that 4-chlorophenylurea is carcinogenic and because 4-chloroaniline does not appear to be an *in vivo* metabolite of 4-chlorophenylurea in rodents.

As detailed in Section 3.2.3.4.3 for drinking water and Section 3.2.3.6 for contaminated vegetation, the current risk assessment takes a somewhat different approach to the risks posed by 4-chlorophenylurea. There is no doubt that 4-chlorophenylurea is metabolized to 4-chloroaniline in the environment. Because the toxicity data on 4-chlorophenylurea are limited, the current risk assessment models the degradation of diflubenzuron to 4-chloroaniline as a one-step process, omitting the formation of 4-chlorophenylurea. While this is conceptually different from the equal potency assumption used by U.S. EPA (2000a), it is a conservative approach but avoids the use of a surrogate potency parameter for a compound, 4-chlorophenylurea, for which there is no evidence of carcinogenicity.

For this risk assessment, the human cancer potency factor for 4-chloroaniline of 0.0638 $(mg/kg/day)^{-1}$ proposed by U.S. EPA/OPP (1999, 2000a) is used to assess cancer risks for all longer term exposure scenarios. This potency factor is not applied directly to any acute exposure assessments. Nonetheless, it is worth noting that all of the longer term estimates of exposure are based on average values that include short-term peak exposures. Thus, these higher but transient acute exposures are incorporated into the cancer risk assessment.

In the risk characterization worksheet for 4-chloroaniline (Worksheet E04 in Supplement 2), cancer risk is expressed as the ratio of exposure (dose in mg/kg/day) to a dose with a risk of 1 in 1-million. In a linear cancer model, such as that used by U.S. EPA, risk is assumed to be linearly related to dose:

$$\text{Risk} = \text{dose} \times \text{potency}$$

Thus, taking the potency factor of 0.0638 $(mg/kg/day)^{-1}$ and a risk level of 1 in 1-million (1×10^{-6}), the dose associated with a risk of 1 in 1-million can be calculated as:

$$\text{dose} = 1\times10^{-6} \div 0.0638\ (\text{mg/kg/day})^{-1} = 0.000015673 \approx 1.6\times10^{-5}\ \text{mg/kg/day}$$

This dose is used in the Worksheet E04 for the risk characterization of cancer risks associated with exposure to 4-chloroaniline.

3.4. RISK CHARACTERIZATION

3.4.1. Overview

The risk characterization for potential human health effects associated with the use of diflubenzuron in USDA programs to control the gypsy moth is relatively unambiguous: none of the hazard quotients reach a level of concern at the highest application rate that could be used in USDA programs. In that many of the exposure assessments involve very conservative assumptions – i.e., assumptions that will tend to overestimate exposure – and because the dose-response assessment is based on similarly protective assumptions, there is no basis for asserting that this use of diflubenzuron poses a hazard to human health.

Notwithstanding the above assertion, it is worth noting that the greatest relative concern is with the contamination of water with 4-chloroaniline rather than with any exposures to diflubenzuron itself. The highest hazard quotient for diflubenzuron is 0.1, a factor of 10 below a level of concern. Since this hazard quotient is based on toxicity, an endpoint that is considered to have a population threshold, the assertion can be made that risk associated with exposure to diflubenzuron is essentially zero.

This is not the case with 4-chloroaniline, which is classified as a probable human carcinogen and is an environmental metabolite of diflubenzuron. For 4-chloroaniline, the highest hazard quotient is 0.4, below the level of concern by a factor of only 2.5. The scenario of greatest concern involves cancer risk from drinking contaminated water. This risk would be most plausible in areas with sandy soil and annual rainfall rates of about 50 to 250 inches. The central estimate of the hazard quotient for the consumption of water contaminated with 4-chloroaniline and based on a cancer risk of 1 in 1-million is 0.09, below the level of concern by a factor of 10.

3.4.2. Workers

A quantitative summary of the risk characterization for workers is presented in Worksheet E02 of the diflubenzuron worksheets (Supplement 1). The quantitative risk characterization is expressed as the hazard quotient, which is the ratio of the estimated exposure from Worksheet E01 to the RfD. For acute accidental/incidental exposures, the surrogate acute RfD of 11 mg/kg is used (Section 3.3.3.2). For longer term general exposures – i.e., exposures that could occur over the course of several days, weeks, or months during an application season – the chronic RfD of 0.02 mg/kg/day is used (Section 3.3.3.1).

The qualitative risk characterization for workers is reasonably unequivocal. None of the acute or longer term hazard quotients exceed 1, the level of concern. In the normal application of diflubenzuron over the course of a season or even several years, the hazard quotients range from 0.04 to 0.07 – i.e., below the level of concern by factors of about 14 to 25. At the upper ranges of exposure for workers, the hazard quotients approach but do not exceed a level of concern – i.e., 0.2 to 0.5. Similarly, the upper range of hazard quotients for accidental/incidental exposures range from 0.0001 to 0.03, below the level of concern by factors of about 33 to 10,000. As noted in Section 3.2.2.2, the only accidental/incidental exposure that exceeds general exposures involves wearing contaminated gloves for 1 hour. While the hazard quotient of 0.03 is substantially below a level of concern, the use of contaminated gloves appears to be the greatest source of concern in the handling of diflubenzuron.

Diflubenzuron can cause slight irritation to the eyes (section 3.1.11). Quantitative risk assessments for irritation are not derived; however, from a practical perspective, eye irritation is likely to be the only overt effect as a consequence of mishandling diflubenzuron. This effect can be minimized or avoided by prudent industrial hygiene practices during the handling of the compound.

3.4.3. General Public

3.4.3.1. Diflubenzuron – A quantitative summary of the risk characterization for members of the general public is presented in Worksheet E04 of the diflubenzuron worksheets (Supplement 1). As with the risk characterization for workers, risk is expressed quantitatively as the hazard quotient using the surrogate acute RfD of 11 mg/kg (Section 3.3.3.2) and the chronic RfD of 0.02 mg/kg/day is used (Section 3.3.3.1).

Also as with workers, the qualitative risk characterization for members of the general public is unambiguous, with none of the acute or longer term hazard quotients exceeding 1 even at the upper ranges of plausible exposure. The highest hazard quotient is 0.1, the upper range of risk for the consumption of contaminated fish by subsistence populations. Nonetheless, this extreme acute scenario is below the level of concern by a factor of 10. No other acute exposure scenarios, many of which involve extremely conservative assumptions, approach a level of concern at the upper range of exposure. Based on central estimates of acute exposure, which involve somewhat less conservative assumptions, the acute hazard quotients range from 0.000003 to 0.02 – i.e., below the level of concern by factors of 50 to over 300,000.

3.4.3.2. 4-Chloroaniline – A quantitative summary of the risk characterization for members of the general public is presented in Worksheet E04 of the 4-chloroaniline worksheets (Supplement 2). Risk is expressed quantitatively as the hazard quotient using the surrogate acute RfD of 0.03 mg/kg (Section 3.3.3.2) and the chronic RfD of 0.004 mg/kg/day is used (Section 3.3.3.1).

In terms of both toxicity and carcinogenicity, the hazard quotients for members of the general public are comparable to but somewhat higher than the corresponding hazard quotients for diflubenzuron – a maximum hazard of 0.4 for 4-chloroaniline compared to a maximum hazard quotient of 0.1 for diflubenzuron.

The hazard quotient of 0.4 for 4-chloroaniline is associated with contamination of water, the hazard quotient for toxicity for the consumption of contaminated fish by subsistence populations and the hazard quotient for the dose associated with a cancer risk of 1 in 1-million for the longer term consumption of contaminated water. As detailed in Section 3.2.3.4 and illustrated in Figure 3-2, these risks are associated with the application of diflubenzuron to sandy soils in areas with annual rainfall rates of about 50 to 250 inches. In areas with predominantly clay or loam soils, risks will be less by factors of about 3 to 10 (Table 3-6). Also, the relatively high hazard quotient of 0.4 is associated with standing bodies of water – i.e., ponds or lakes. Concentrations of 4-chloroaniline in streams even with sandy soil will be much less (Table 3-5).

Based on central estimates of exposure, acute hazard quotients range from 0.0004 to 0.01, below the level of concern by factors of 100 to 2500. Most chronic hazard quotients are in the range of 0.000002 to 0.0005, far below a level of concern. The only exception is the central estimate of the hazard quotient for the consumption of contaminated water based on a cancer risk of 1 in 1-million. This hazard quotient is 0.09, below the level of concern by a about a factor of 10. Nonetheless, the consumption of water that is contaminated with 4-chloroaniline as the greatest source of concern for members of the general public in the application of diflubenzuron to control the gypsy moth.

3.4.4. Sensitive Subgroups

Some individuals are born with a form of congenital methemoglobinemia and may be at increased risk of adverse effects to compounds that induce methemoglobinemia (Barretto et al. 1984). Infants less than 3 months old have lower levels of methemoglobin (cytochrome b5) reductase and higher levels of methemoglobin (1.32%), compared with older children or adults (Centa et al. 1985; Khakoo et al. 1993; Nilsson et al. 1990). A similar pattern is seen in many species of mammals (Lo and Agar 1986). Some infants with an intolerance to cow's milk or soy protein exhibit methemoglobinemia (Murray and Christie 1993; Wirth and Vogel 1988). These infants would be at increased risk if exposed to any materials contaminated with diflubenzuron or any compound that induces methemoglobinemia.

Individuals with poor diets may be at increased risk to some chemicals. Based on a study in rats (Hagler et al. 1981), iron deficiency leads to anemia but does not influence methemoglobin reductase activity. Thus, although individuals with poor nutritional status are generally a group for which there is particular concern, the available information does not support an increased concern for these individuals with respect to diflubenzuron exposure.

The RfDs used in the current risk assessment quantitatively consider sensitive subgroups. As noted in Section 3.3.2, the chronic RfD derived by U.S. EPA (1997a) incorporates a factor of 10 into overall uncertainty factor of 100 used for diflubenzuron to account for sensitive subgroups. Based on differences in methemoglobin reductase activity, a recovery mechanism for methemoglobinemia (Section 3.1.2), among different species, the factor of 10 for intraspecies variability appears adequate. The activity of this enzyme in humans appears to be about half of that in dogs (Calabrese 1991).

3.4.5. Connected Actions

The most sensitive effect for diflubenzuron, methemoglobinemia, is associated tebufenozide, another agent used for gypsy moth control. These two agents are likely to have an additive effect on methemoglobinemia but these agents are not used together. Thus, simultaneous exposures are unlikely. Exposure to other compounds in the environment that induce methemoglobinemia may also lead to an additive effect. Individuals exposed to combustion smoke or carbon monoxide (that is, agents that do oxidative damage to blood) may be at increased risk of developing methemoglobinemia (Hoffman and Sauter 1989; Laney and Hoffman 1992). In addition, individuals exposed to high levels of nitrates, either in air or in water, will have increased levels of methemoglobin (Woebkenberg et al. 1981) and may be at increased risks of exposure to compounds such as diflubenzuron.

3.4.6. Cumulative Effects

This risk assessment is based on single applications at the maximum allowable rate, 70 g/ha. This is also the maximum rate that can be applied in a single season. This approach is used to estimate maximum daily exposure and daily absorbed dose. Because the dispersal rate for diflubenzuron in the environment is relatively fast, multiple applications at lower rates per application will result in risks that are less than those associated with a single application at the maximum approved rate. Given the narrow range of application rates compared with the variability and uncertainties in the exposure assessments, the risks of toxic effects associated with a single application at less than the maximum rate will be related directly to the application rate. Thus, an application at 35 g/ha will entail risks that are approximately one half of those expected at the maximum application rate.

4. ECOLOGICAL RISK ASSESSMENT

4.1. HAZARD IDENTIFICATION

4.1.1. Overview

The toxicity of diflubenzuron is well characterized in most groups of animals including mammals, birds, terrestrial invertebrates, fish and aquatic invertebrates. In general, diflubenzuron is much more toxic to some invertebrates, specifically arthropods, than vertebrates or other groups of invertebrates. This differential toxicity appears to involve fundamentally different mechanisms of action. Toxicity to sensitive invertebrate species is based on the inhibition of chitin synthesis. In the more tolerant vertebrate species, the mechanism of action appears to be a specific effect on the blood that inhibits oxygen transport.

The species most sensitive to diflubenzuron are arthropods, a large group of invertebrates including insects, crustaceans, spiders, mites, and centipedes. Most of these organisms use chitin, a polymer (repeating series of connected chemical subunits) of a glucose-based molecule, as a major component of their exoskeleton – i.e., outer body shell. Diflubenzuron is an effective insecticide because it inhibits the the formation of chitin. This effect disrupts the normal growth and development of insects and other arthropods. Both terrestrial and aquatic arthropods are affected but some substantial differences in sensitivity are apparent. In terrestrial organisms, the most sensitive species include lepidopteran and beetle larvae, grasshoppers and other herbivorous insects. More tolerant species include bees, flies, parasitic wasps, adult beetles, and sucking insects. In aquatic organisms, small crustaceans that consume algae and serve as a food source for fish (e.g., *Daphnia* species) appear to be the most sensitive to diflubenzuron while larger insect species such as backswimmers and scavenger beetles are much less sensitive. A wide range of other aquatic invertebrates, other crustaceans and small to medium sized aquatic insect larvae, appear to have intermediate sensitivities. Not all invertebrates utilize chitin and these invertebrates are much less sensitive to diflubenzuron than the arthropods. For terrestrial invertebrates, relatively tolerant species include earthworms and snails. For aquatic species, tolerant species include ostracods (an arthropod) and non-arthropods such as rotifers, bivalves (clams), aquatic worms, and snails.

As detailed in the human health risk assessment, the most sensitive effect in vertebrate species appears to involve damage to blood cells involved in the transport of oxygen. This effect has been demonstrated in mammals that are often employed in toxicity studies (e.g., rats and mice) as well as domestic animals and livestock. The effect has not been demonstrated in wildlife mammals, birds, or fish but it seems reasonable to assume that hemoglobin in all vertebrate species could be affected by exposure to diflubenzuron. Acute exposures to diflubenzuron are relatively non-toxic to mammals and birds. The U.S. EPA places diflubenzuron in low toxicity categories (III or IV) for mammals and considers diflubenzuron to be virtually non-toxic to birds in acute exposures and only slightly toxic to birds in subchronic exposures. This assessment is supported by a large number of field studies in which no direct toxic effects in mammals or birds have been reported. Effects, if any, on terrestrial vertebrates from the application of diflubenzuron are likely to be secondary to changes in food availability (i.e., reduced numbers of insects) or changes in habitat (i.e., the protection of vegetation relative to untreated areas). Aquatic vertebrates also appear to be relatively tolerant to diflubenzuron and this compound is classified by U.S. EPA as practically non-toxic to fish. This classification appears to be appropriate and is supported by a relatively large number of longer term toxicity studies as well as field studies. Changes in fish populations have been noted in some studies but the changes appear to be secondary to changes in food supply. Although the data on amphibians are much more limited than the data in fish, a similar pattern is apparent – i.e., no direct toxic effects but changes in food consumption patterns secondary to effects on invertebrate species.

Data on plants and microorganisms are more limited than the data on invertebrates or vertebrates. Nonetheless, there does not appear to any basis for asserting that diflubenzuron will have a substantial effect on these organisms.

4.1.2. Toxicity to Terrestrial Organisms

4.1.2.1. Mammals – As summarized in Appendix 1 and discussed in the human health risk assessment (Section 3.1), there are a large number of toxicity studies on diflubenzuron in experimental mammals and these studies are relevant to the risk assessment for terrestrial mammals. Potential hazard to all wildlife mammals, however, may not be encompassed by the available data on experimental mammals – i.e., rats, mice, and dogs. As discussed in Section 3.1.3.1 and illustrated in Figure 3-1, some mammals such as sheep and pigs will metabolize diflubenzuron differently from rats. Specifically, metabolism in sheep, pigs, and perhaps other mammalian species, will result in cleavage of the ureido bridge with the formation of metabolites that are different from those seen in rats. There is little indication, however, that this difference in metabolism will lead to marked differences in toxicity. As summarized in Appendix 1, substantial differences in sensitivity among different species of mammals are not apparent. One possibly noteworthy difference, however, is a reduction in thyroid weight in sheep (Ross et al. 1977). As discussed in Section 3.1.8, the thyroid is an important organ in endocrine function. This effect, however, occurred in the absence of any signs of toxicity or changes in growth and may have been incidental.

The available field studies do not indicate any substantial impacts on mammalian wildlife from applications of diflubenzuron (Appendix 3a). As summarized in USDA (1995), applications of 60 to 280 g a.i./ha (0.85 to 4 oz a.i./ac) had no detectable adverse effects on the abundance of or reproduction in voles, field mice, and shrews (O'Connor and Moore 1975; Henderson et al. 1977). Small mammals increased in abundance on a plot receiving 280 g a.i./ha compared with a control plot (Henderson et al. 1977). The adverse effect that diflubenzuron might have on bot flies, a parasite of small as well as large mammals, was suggested as a possible explanation.

A more recent published field study by Seidel and Whitmore (1995) reports no effects on body measurements, weight, or fat content in populations of mice in areas treated with Dimilin 25 WP at a rate of rate of 140 g formulation/ha (35 g a.i./ha). Mice in the treated areas did consume less lepidopteran prey, secondary to the toxicity of diflubenzuron to lepidoptera, but total food consumption was not significantly different in treated and untreated plots.

4.1.2.2. Birds – A relatively large number of acute and subchronic toxicity studies are available in standard test species – i.e., mallard ducks and bobwhite quail – as well as other less commonly tested species – i.e., domestic hens and red-winged blackbirds (Appendix 4). Most of these studies were submitted to the U.S. EPA for the registration diflubenzuron (specified in Appendix 4 by MRID numbers) but some have been published in the open literature (e.g., Kubena 1981,1982, Kubena and Witzel 1980).

The acute toxicity of diflubenzuron to birds appears generally to be low and consistent with the gavage studies in rats in which gavage oral LD_{50} values are greater than 5000 mg/kg (Section 3.1 and Appendix 1). As summarized in Appendix 4, red-winged blackbirds appear to be somewhat more sensitive than mallard ducks – i.e., a gavage NOEL for red-winged blackbirds of 2500 mg/kg compared to a gavage NOEL for mallards of 5000 mg/kg. Nonetheless, diflubenzuron is classified a "virtually non-toxic" to both species as well as to bobwhite quail (U.S. EPA 1997a, p. 44). Based on the results of several standard reproduction studies, the the chronic dietary NOEC in birds is 500 ppm (U.S. EPA/OPP 1997a).

There is one atypical report of adverse reproductive effects in birds. Smalley (1976) reports that Dimilin (NOS), incorporated into the feed (dose not specified) of chicks (presumably chickens) for 13 weeks, resulted in an increased incidence of fat deposition in female chicks. The treated chicks weighed 6 ½ lbs, compared to normal weight of 3 lbs for controls (broilers) and males. In addition, Smalley (1976) reports a dose-related decrease in testosterone in treated males resulting in undeveloped combs, wattles, feathers, and voice. Very few experimental details are included in this study. Given the large number of other studies in birds in which no effects on reproduction were apparent, the report by Smalley (1976) appears to be an aberration.

The lack of direct effects on birds is supported by several field studies summarized in Appendix 3a. Some effects secondary to reduced lepidoptera prey may include increased foraging range (Cooper et al. 1990), relocation (Sample et al. 1993a,b) and lower body fat (Whitmore 1993).

4.1.2.3. Terrestrial Invertebrates – A large and relatively complex body of information is available on the toxicity of diflubenzuron to both target and non-target invertebrates. This information consists of both laboratory studies in which exposures are relatively well defined and controlled (Appendix 5) as well as field studies in which exposures are typically characterized as application rates (Appendix 3a).

A synopsis of the field studies in which exposures can be expressed in units of application rate (g/ha) are presented in Table 4-1. The first column in this table gives ranges of application rates spanning over an order of magnitude. The second and third columns provide species or groups of species in which no adverse effects (column 2) or adverse effects (column 3) were noted within the corresponding range of application rates. For each species or group the reference is given to a field study summarized in Appendix 3a. A similar summary table is not provided for the laboratory toxicity studies. As discussed further in the dose-response assessment

(Section 4.3.2.3), these studies were conducted using highly variable experimental designs and meaningful comparisons among the various toxicity assays summarized in Appendix 5 are difficult. Additional details of the comparisons among the various field studies are also provided in the dose-response assessment (see discussion of Table 4-5 in Section 4.3.2.3).

The insecticidal action of diflubenzuron is based on the inhibition of chitin synthesis. Chitin is a polymer (repeating series of connected chemical subunits) of a glucose-based molecule and comprises a substantial proportion of the exoskeleton (outer-shell) of insects. Consequently, the inhibition of chitin synthesis disrupts the growth and development of insects. Chitin is also contained in other arthropods (i.e., crustaceans, spiders, and centipedes) as well as some fungi. Thus, the mode of action of diflubenzuron as a insecticide to target species is also relevant to effects on non-target insects as well as other arthropods (Cardona 1999; Cunningham 1986; Eisler 1992; Fisher and Hall 1992; Hobson 2001; Lengen, 1999; Wilson 1997; Wilcox and Coffey 1978). Diflubenzuron also exerts ovicidal effects in several species (Ables et al. 1977; Büchi and Jossi, 1979; Kumar et al. 1994;) and has been shown to inhibit egg production in some species (Rumpf et al. 1998; Medina et al. 2002; Medina et al. 2003).

While the mechanism of action of diflubenzuron is not specific to target insects, there is ample data indicating substantial differences in sensitivity among various groups of terrestrial invertebrates. Invertebrates without exoskeletons, such as earthworms and snails, do not utilize chitin and diflubenzuron is relatively non-toxic to these species (Berends and Thus 1992; Berends et al. 1992). Even among different groups of arthropods, however, differences in sensitivity to diflubenzuron seem apparent. Species that are most sensitive to diflubenzuron include lepidopteran and beetle larvae, grasshoppers and other chewing herbivorous insects (Berry et al. 1993; Butler 1993; Butler et al. 1997; Elliott and Iyer 1982; Jepson and Yemane 1991; Jepson and Martinat et al. 1998, 1993; Kumar et al. 1994; McWhorter and Shapard 1971; Sample et al.1993b; Sinha et al. 1990; Redfern et al. 1980; Yemane 1991). Other species are relatively tolerant to diflubenzuron. These include flies, wasps that are parasites on insect eggs, adult beetles, and sucking insects (Ables et al. 1975; Broadbent and Pree, 1984a; Brown and Respicio, 1981; Bull and Coleman, 1985; De Clercq et al. 1995b; Deakle and Bradley 1981; Delbeke et al. 1997; Gordon and Cornect, 1986; Keever et al. 1977; Martinat et al., 1988; Webb et al. 1989; Zacarias et al. 1998; Zungoli et al. 1983).

The honey bee is a standard test species used by U.S. EPA to classify the toxicity of pesticides to non-target invertebrates. Based on early acute oral and contact toxicity studies in honey bees with LD_{50} values of >30 µg/bee and >114.8 µg/bee (Atkins et al. 1974; Stevenson 1978), the U.S. EPA (1997a) has classified diflubenzuron as *"practically non-toxic to honey bees"* (U.S. EPA 1997a, p. 81). As discussed further in the dose-response assessment (Section 4.3.2.3), several other laboratory toxicity studies also indicate that diflubenzuron is not highly toxic to bees (Chandel and Gupta 1992; Elliott and Iyer, 1982; Gijswijt, 1978; Kuijpers, 1989; Nation et al. 1986; Yu et al. 1984) and this is supported for several field studies conducted at application rates comparable to or substantially higher than those used to control the gypsy moth (Buckner et al. 1975; Emmett and Archer 1980; Matthenius, 1975; Schroeder 1978a; Schroeder 1980). In addition, no detectable amounts of diflubenzuron were found in honey bees in areas treated with diflubenzuron (Cochran and Poling 1995). Some studies have noted adverse effects in bees. As summarized in Appendix 5, Stoner and Wilson (1982) and (Thompson and Wilkins 2003) noted transient decreases in brood production at relatively high concentrations (10 ppm) in longer term exposures. At 1 ppm or less, however, no effects were noted. Barrows (1995) noted a decrease in the mean number of pollinating insects in watersheds during a year in which diflubenzuron was applied but not in the following year.

In addition to the acute toxic effects of diflubenzuron, mediated primarily through inhibition of chitin, adverse reproductive effects have been reported in several different orders of insects including moths (Beevi and Dale 1984; Tembhare and Shinde 1998), beetles (Büchi and Jossi 1979; Khebbeb et al. 1997; Mani et al. 1997; Soltani and Soltani-Mazouni 1994a,b,1995a,b,1997), grasshoppers (Mathur 1998), lacewings (Medina et al. 2002; Medina et al. 2003; Rumpf et al. 1998), and true bugs – i.e., Order Hemiptera including the suborder Heteroptera (Redfern et al. 1980; Sindhu and Muraleedharan 1997).

In Lepidoptera, reproductive effects were reported by Beevi and Dale (1984), who noted a high incidence of sterility in the rice swarming caterpillar (*Spodoptera mauritania*) after exposures to relatively high concentrations of Dimilin – 10 ppm and higher. The mechanism of this reproductive effect is unclear but may involve the endocrine system – i.e., hormone release by neurosecretory cells. This has been noted in larvae of the fruit-sucking moth, *Othreis materna* (Tembhare and Shinde 1998) and in the cotton bug (*Dysdercus cingzrlattis*) (Sindhu and Muraleedharan 1997). In some other species of Lepidoptera – i.e., tufted apple bud moth – pupae are sensitive to diflubenzuron but no effects are apparent on reproduction (Biddinger and Hull 1999).

In beetles (Coleoptera), effects on larvae, eggs, and reproductive performance have been noted (Büchi and Jossi1979; Mani et al. 1997). In the mealworm, diflubenzuron impacts lipid metabolism in fat bodies and ovaries (Khebbeb et al. 1997). A series of studies in this species (Soltani and Soltani-Mazouni 1997; Soltani-Mazouni and Soltani1994a,b, 1995b) suggest that the decreased fecundity observed in this and other insect species may be associated with the effect of diflubenzuron on oogenesis, possibly due to changes vitellogenic precursors, the production of ecdysteroid by follicle cells, and/or the inhibition of ovarian DNA synthesis. Direct damage to ovary tissue has also been observed in one species of Orthoptera, a grasshopper, but the mechanism of action in this species has not been studied (Mathur 1998).

Reproductive effects in lacewings (Neuroptera) have been noted by Rumpf et al. (1998) and Medina et al. (2002, 2003). As detailed in Appendix 5, contact exposures to diflubenzuron at 0.07 $\mu g/cm^2$ resulted in a substantial decrease in egg production and complete infertility in 13% of the exposed animals. No effects on egg production or hatching in this species have been observed after direct topical applications at doses as low as 0.5 ng/insect. At a substantially higher dose, 75 ng/insect, egg hatching was reduced by 32%. (Medina et al. 2002, 2003).

4.1.2.4. Terrestrial Plants (Macrophytes) – As noted in U.S. EPA/OPP (1997a), no terrestrial plant toxicity studies had been submitted to the U.S. EPA at the time of the reregistration of diflubenzuron. In the literature search conducted for the current risk assessment, no bioassays for herbicidal activity of diflubenzuron were encountered in either the published literature or in the more recent U.S. EPA/OPP files.

There are a large number of terrestrial field studies regarding the efficacy of diflubenzuron applied to terrestrial vegetation for the control of various insect pests including the gypsy moth (Appendix 3a). If diflubenzuron were toxic to terrestrial plants at application rates that are used in the field, it is plausible that adverse effects would have been reported in this literature. No such reports were encountered. Thus, there is no basis for asserting that diflubenzuron will cause adverse effects in terrestrial plants and such effects will not be considered quantitatively in this risk assessment.

4.1.2.5. Terrestrial Microorganisms – As discussed in Section 3.2 and summarized in Appendix 2 (Environmental Fate) and Appendix 3a (Terrestrial Field Studies), diflubenzuron is readily degraded by terrestrial microorganisms. The degradation of diflubenzuron by soil microorganisms suggests that this compound is not toxic to soil microorganisms and this presumption may account for the relatively few studies on microbial toxicity. Fungi, however, do contain chitin in cell walls and thus could be a potential target. Booth (1978) found no inhibition of fungal growth in several species of fungi (*Aspergillus*, *Fusarium*, *Rhizopus*, *Trichoderma*) at concentrations of up to 100 ppm in growth media – i.e. mg diflubenzuron per kg of soil. Some growth inhibition, however, was noted in a species of *Pythium* at a concentration of 50 ppm. Inhibition of *Rhizoctonia solani*, another terrestrial fungus, has been noted at 300 ppm (Townshend et al. 1983).

The lack of microbial toxicity was also specifically noted in one field study in which no effects on soil or litter populations of bacteria, actynomycetes or fungi were noted after applications of diflubenzuron at a rate of 67.26 g/ha (Kurczewski et al. 1975; Wang 1975), field and laboratory studies on molds and leaf litter or soil bacteria (Landolt and Stephenson 1995), and studies on mycorrhizal or debris decomposing fungi (Iskra et al. 1995; Gundrum et al. 1995).

One study has noted minor and transient changes in microbial activity. Sexstone (1995) conducted a laboratory study in which soil cores were treated at 4.418µg/44.2 cm^2, roughly equivalent to an application rate of 10 g/ha [4.418µg/44.2 $cm^2 \times 10{,}000\ cm^2/m^2 \times 10{,}000\ m^2/ha$ = 9,995,475 µg/ha ≈ 10 g/ha]. Only transient and sporadic decreases were noted in microbial biomass [Figure 14-1 in Sexton 1995]. These changes in microbial activity were apparent up to day 35 after treatment but there were no changes by 64 days after treatment. Changes in respiration [Figure 14-2 in Sexton 1995] and nitrification [Figures 14-3 to 14-6 in Sexton 1995] and appear to insubstantial. While some of the differences were statistically significant at some time points, Sexstone (1995) characterizes the effects a "minor" and this assessment appears reasonable.

4.1.3. Aquatic Organisms.

4.1.3.1. Fish – The toxicity of diflubenzuron to fish is well characterized in terms of both acute and chronic toxicity and one mesocosm study is available (Appendix 6). In addition, several of the aquatic field studies (Appendix 3b) involve observations on fish populations. Diflubenzuron has a low order of acute toxicity to fish, with 96-hour LC_{50} values in the range of over 25 mg/L(the value for yellow perch reported by Johnson and Finley 1980) to over 500 mg/L (the value for fathead minnow reported by Reiner and Parke 1975). In addition to data on technical grade diflubenzuron, some studies have also been conducted on Dimilin 25W (Julin and Sanders 1978 with additional studies summarized in U.S. EPA 1997a) and these studies indicate that the toxicity of Dimilin 25W is not greater than the toxicity of technical grade diflubenzuron. No studies have been encountered on the acute toxicity of Dimilin 4L to fish. Based on the available information, the U.S. EPA (1997a, p. 47) has classified diflubenzuron as *"practically non-toxic"* to fish in terms of risks from acute exposures.

Diflubenzuron also appears to be relatively non-toxic to fish in longer term exposures. One standard assay for longer term toxicity in fish involves exposing fish eggs to a compound and maintaining the exposure through to the fry stage. In this type of assay, concentrations up to 45 ppb has no effect on egg or fry of steelhead trout, fathead minnows, or guppies (Hansen and Garton 1982a). In addition, no effects were seen in longer-term studies at concentrations up to 100 ppb (Cannon and Krize 1976) or in 2-generation reproduction studies at concentrations of up to 50 ppb (Livingston and Koenig 1977).

As discussed in Section 4.1.3.2, diflubenzuron is much more toxic to invertebrates than to fish and indirect effects on fish are plausible based on a decrease in invertebrate populations. Such effects have been demonstrated in mesocosm studies (Moffett and Tanner 1995; Tanner and Moffett 1995) in which concentrations as low as 2.5 ppb resulted in decreased growth of fish in littoral enclosures – i.e., populations of fish placed and monitored in enclosures along the shore of a body of water. The reduced growth observed in these studies was attributed to a reduction in macroinvertebrates that serve as a food source for the fish.

It is unclear, however, that secondary effects on fish growth or populations will be observed in the field. None of the field studies summarized in Appendix 3b note any adverse effects on fish in applications comparable to or greater than those used in the control of the gypsy moth. For example, Farlow et al. (1978) conducted a relatively large field study in a marsh area treated with six applications of diflubenzuron at 28 g a.i./ha – i.e., a cumulative application of 168 g/ha. While substantial shifts were noted in various invertebrates (Appendix 3a and Section 4.1.3.2), populations of mosquito fish (*Gambusia affinis*) and American flag fish (*Jordanella floridae*) increased. Similarly, no effects on the growth of fish were noted in ponds directly treated with diflubenzuron at a concentration of 5 ppb (Apperson et al. 1977, 1978) or 13 ppb (Colwell and Schaefer 1980). The study by Colwell and Schaefer (1980) did note a shift in diet of fish (secondary to changes in food availability) but no effect on growth rates or general condition of the fish.

4.1.3.2. Amphibians – Amphibians are not standard test organisms for toxicity studies and no standard bioassays on amphibians have been encountered in the open literature or U.S. EPA/OPP files. Two field studies (Pauley 1995a,b), however, are available on salamanders. Both of these studies were conducted as part of a large study on the effects of spraying diflubenzuron in the northeast for control of the gypsy moth (Reardon 1995a). In this study, two watersheds were treated with Dimilin 4L in 1992 at a rate of 80g/ha (0.03 lb/acre) (Reardon 1995b). Pauley (1995a,b) conducted field studies to assess effects on both aquatic (Pauley 1995a) and terrestrial salamanders (Pauley 1995b). While all salamanders are amphibians, some species spend most of their time on land while others spend most of their time in water. In aquatic salamanders, diflubenzuron treatment was associated with a shift in dietary consumption to more hard-bodied prey secondary to a reduction in the availability of soft-bodied prey. This is similar to the pattern with fish as noted above. No effects in salamanders, however, were noted based on body size or population (Pauley 1995). In terrestrial salamanders, similar results were observed with no change in body size or body fat associated with treatment but a shift was seen in food consumption to hard-bodied prey (Pauley 1995b).

4.1.3.3. Aquatic Invertebrates – As summarized in Appendix 7, there is a very large and diverse body of literature indicating that diflubenzuron is highly toxic to many aquatic invertebrates. Because diflubenzuron inhibits the synthesis of chitin, crustaceans (arthropods which rely on chitin synthesis for the formation of the exoskeleton) are the aquatic invertebrates that are most sensitive to diflubenzuron.

One of the most common crustacean species used in freshwater invertebrate toxicity studies is *Daphnia magna*, a member of Daphnidae in the order Cladocera. These and other zooplankton feed on aquatic algae and are a source of food for fish. Many bioassays, both acute and chronic, have been conducted on *Daphnia magna* (Hansen and Garton 1982a; Kuijpers 1988; Majori et al. 1984; Surprenant 1988) as well as a related species, *Ceriodaphnia dubia* (Hall 1986). As detailed further in the dose-response assessment, these organisms are among the most sensitive to diflubenzuron, with acute LC_{50} values of about 2 μg/L (Hall 1986; Hansen and Garton 1982a). Several other crustacean species appear to be about as sensitive or only somewhat less sensitive to diflubenzuron as daphnids (Appendix 7).

Broad generalizations are somewhat difficult to make, however, because of the diversity of the studies that have been conducted. Nonetheless, large insects appear to be much more tolerant to diflubenzuron than crustaceans, with acute LC_{50} values on the order of 2123 μg/L for backswimmers (Lahr et al. 2001) and an NOEC of 250 μg/L for scavenger beetles (Miura and Takahashi 1974).

Organisms that do not rely on chitin for an exoskeleton are much less sensitive to diflubenzuron. In the microcosm study by Corry et al. (1995) concentrations of diflubenzuron that caused adverse effects in cladocerans caused no adverse effects in rotifers – an aquatic invertebrate that lacks an exoskeleton. Similar tolerance in rotifers have been observed in littoral enclosure studies at diflubenzuron concentrations of up to 30 μg/L (Liber and O'Halloran 1995). At about the same concentration, 30 µg/L, two species of snails and aquatic worms were not affected by exposures to diflubenzuron (Hansen and Garton 1982a,b). One common genus of snail, *Physa*, had a reported LC_{50} value of greater than 125 mg/L – i.e., 125,000 µg/L. Ostracods (small bivalve crustaceans) were not affected by diflubenzuron at concentrations up to 2.5 µg/L (Liber and O'Halloran 1995) and much larger Quahog clams (*Mercinaria mercinaria*) were unaffected at concentrations up to 320 µg/L (Surprenant 1989).

As with fish, no data have been located on the toxicity of Dimilin 4L. Lahr (2000, 2001) used a "solvent based" formulation of diflubenzuron but did not specify the formulation as Dimilin 4L. The 48-hour EC_{50} of 0.74 µg/L (0.60-0.88 µg/L) of the solvent based formulation in fairy shrimp, *Streptocephalus sudanicus* reported by Lahr (2001) is comparable to EC_{50} value of 0.65 µg/L for technical grade diflubenzuron reported in grass shrimp, *Palaemonetes pugio* (Tourat and Rao 1987). Toxicity studies are available on Dimilin 25W and, as with fish, the toxicity of Dimilin 25W appears to be the same as technical grade diflubenzuron when exposures are expressed in units of active ingredient (Wilson and Costlow 1986). Thus, there does not appear to be a basis for asserting that the formulated products containing diflubenzuron are more hazardous than diflubenzuron itself.

The available field studies on the effects of diflubenzuron on aquatic invertebrates reenforce the standard toxicity studies, indicating that diflubenzuron will impact invertebrate populations. Several of these studies, however, were conducted at application rates substantially higher than those used to control the gypsy moth. As noted in the program description (Section 2), the maximum application rate that will be used in USDA programs is about 70 g/ha. Many of the studies in which severe adverse effects were observed in aquatic invertebrate populations involved multiple applications at rates between about 110 g/ha and 560 g/ha (e.g., Ali and Mulla 1978a,b; Ali et al. 1988; McAlonan 1975). Similarly, other field studies involve direct applications to open water, a treatment method that is not part of USDA program activities, and which resulted in water concentrations that are in the range of 10 ppb (e.g., Apperson et al. 1977; Boyle et al. 1996; Colwell and Schaefer 1980; Lahr et al. 2000; Sundaram et al. 1991). As discussed further in Section 4.2, concentrations of 10 ppb or greater are in the range of peak concentrations that are likely to be encountered in USDA programs. Concentrations in the range of 10 ppb, however, are substantially higher than average concentrations of diflubenzuron in water that are likely to be encountered in USDA programs.

Those field studies that used lower application rates more typical of USDA programs (e.g., Farlow 1976; Griffith et al. 1996; Griffith et al. 2000; Hurd et al. 1996; Jones and Kochenderfer 1987; Reardon 1995a) have noted some effects on freshwater invertebrates, particularly smaller crustaceans, but the effects were much less severe than those seen in the higher application rate studies. This is discussed further in Section 4.4 (Risk Characterization).

4.1.3.4. Aquatic Plants – Data on the toxicity of diflubenzuron to aquatic plants is summarized in Appendix 8. Most studies report no direct toxic effects of diflubenzuron on aquatic plants (algae or macrophytes) at concentrations of 100 µg/L or higher (Booth and Ferrell 1977;

Thompson and Swigert 1993a,b,c) and no indirect effects on aquatic macrophytes (Moffett 1995). A decrease in periphyton in littoral enclosures, however, was noted by Moffett (1995) at 7.0, or 30 µg/L but not at 0.7 or 2.5 µg/L. This effect was attributed not to a direct toxic effect on the periphyton but to the loss of grazers (e.g., cladocera) that may have induced premature senescence in periphyton secondary to a decrement in water quality.

4.1.3.5. Aquatic Microorganisms – There is very little information suggesting that diflubenzuron will adversely affect aquatic microorganisms. No marked differences in numbers of fungal taxa in treated and untreated watersheds were noted by Dubey (1995) in a survey of watersheds treated with diflubenzuron for the control of the gypsy moth. In an aquatic mesocosm, Kreutzweiser et al. (2001) did note a slight but significant effect of diflubenzuron (50 µg/L and 50,000 µg/L) on microbial decomposition and respiration. Changes at 50 µg/L, however, were only marginally significant and variable over the 21-day period.

In the Kreutzweiser et al. (2001) study, Dimilin 4L was used. This is the only laboratory study involving Dimilin 4L. Because no corresponding studies are available on Dimilin 25W or technical grade diflubenzuron, inferences concerning the potential effect of the petroleum solvent in Dimilin 4L cannot be made.

4.2. EXPOSURE ASSESSMENT

4.2.1. Overview

As in the human health risk assessment (Section 3.2), exposures are estimated for both diflubenzuron and 4-chloroaniline. A full set of exposure assessments are developed for diflubenzuron but only a subset of exposure assessments are developed for 4-chloroaniline. This approach is taken, again as in the human health risk assessment, because 4-chloroaniline is assessed as an environmental metabolite of diflubenzuron. Thus, immediately after application, the amount of 4-chloroaniline as an environmental metabolite will be negligible. Consequently, the direct spray scenarios as well as the consumption of insects and the consumption of small mammals after a direct spray are not included for 4-chloroaniline. Also as in the human health risk assessment, all standard chronic exposure scenarios are included for 4-chloroaniline. Details of the exposure assessments for diflubenzuron and 4-chloroaniline are given in the two sets of worksheets that accompany this risk assessment: Supplement 1for diflubenzuron and Supplement 2 for 4-chloroaniline. All exposure assessments are based on the maximum application rate of 70 g/ha.

Terrestrial animals might be exposed to any applied pesticide from direct spray, the ingestion of contaminated media (vegetation, prey species, or water), grooming activities, or indirect contact with contaminated vegetation. For diflubenzuron, the highest acute exposures for small terrestrial vertebrates will occur after a direct spray and could reach up to about 10 mg/kg at an application rate of 70 g/ha. Exposures anticipated from the consumption of contaminated vegetation by terrestrial animals range from central estimates of about 0.08 mg/kg for a small mammal to 2 mg/kg for a large bird with upper ranges of about 0.2 mg/kg for a small mammal and 5 mg/kg for a large bird. The consumption of contaminated water leads to much lower levels of exposure. A similar pattern is seen for chronic exposures. Estimated longer-term daily doses for a small mammal from the consumption of contaminated vegetation at the application site are in the range of about 0.001 mg/kg to 0.005 mg/kg. Large birds feeding on contaminated vegetation at the application site could be exposed to much higher concentrations, ranging from about 0.08 mg/kg/day to 0.7 mg/kg/day. The upper ranges of exposure from contaminated vegetation far exceed doses that are anticipated from the consumption of contaminated water, which range from about 0.0000001 mg/kg/day to 0.00001 mg/kg/day for a small mammal.

Exposures of terrestrial organisms to 4-chloroaniline tend to be much lower than those for diflubenzuron. The highest acute exposure is about 0.2 mg/kg, the approximate dose for the consumption of contaminated water by a small mammal and the consumption of contaminated fish by a predatory bird. The highest longer term exposure is 0.0002 mg/kg/day, the dose associated with the consumption of contaminated vegetation by a large bird.

Exposures to aquatic organisms are based on the same information used to assess the exposures of terrestrial species from contaminated water. At the maximum application rate of 70 g/ha, the upper range of the expected peak concentration of diflubenzuron in surface water is taken as 16 µg/L. The lower range of the concentration in ambient water is estimated at 0.01 µg/L. The central estimate of concentration of diflubenzuron in surface water is taken as 0.4 µg/L.

4.2.2. Terrestrial Animals

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

In this exposure assessment, estimates of oral exposure are expressed in the same units as the available toxicity data. As in the human health risk assessment, these units are usually expressed as mg of agent per kg of body weight and abbreviated as mg/kg for terrestrial animals. One exception in this risk assessment involves terrestrial invertebrates. As detailed in the dose-response assessment (Section 4.3), toxicity data in units of mg/kg bw are available for some terrestrial invertebrates and these data are used in a manner similar to that for terrestrial vertebrates. For other species, however, standard toxicity studies report units that are not directly useful in a quantitative risk assessments – e.g., contact toxicity based on petri dish exposures. As an alternative, some dose response assessments are based on field studies in which the dose metameter is simply the application rate in units of mass per area such as g a.i./ha.

For dermal exposures to terrestrial animals, the units of measure usually are expressed in mg of agent per cm^2 of surface area of the organism and abbreviated as mg/cm^2. In estimating dose, however, a distinction is made between the exposure dose and the absorbed dose. The *exposure dose* is the amount of material on the organism (i.e., the product of the residue level in mg/cm^2 and the amount of surface area exposed), which can be expressed either as mg/organism or mg/kg body weight. The *absorbed dose* is the proportion of the exposure dose that is actually taken in or absorbed by the animal.

The exposure assessments for terrestrial animals are summarized in Worksheet G01. As with the human health exposure assessment, the computational details for each exposure assessment presented in this section are provided scenario specific worksheets (Worksheets F01 through F16b). Given the large number of species that could be exposed to insecticides and the varied diets in each of these species, a very large number of different exposure scenarios could be generated. For this generic risk assessment, an attempt is made to limit the number of exposure scenarios.

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

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

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

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

Other, perhaps more substantial, uncertainties affect the estimates for absorbed dose. For example, the estimate based on first-order dermal absorption does not consider fugitive losses from the surface of the animal and may overestimate the absorbed dose. Conversely, some animals, particularly birds and mammals, groom frequently, and grooming may contribute to the total absorbed dose by direct ingestion of the compound residing on fur or feathers. Furthermore, other vertebrates, particularly amphibians, may have skin that is far more permeable than the skin of most mammals. Quantitative methods for considering the effects of grooming or increased dermal permeability are not available. As a conservative upper limit, the second exposure scenario, detailed in Worksheet F02a, is developed in which complete absorption over day 1 of exposure is assumed.

Because of the relationship of body size to surface area, very small organisms, like bees and other terrestrial invertebrates, might be exposed to much greater amounts of a pesticide per unit body weight compared with small mammals. Consequently, a third exposure assessment is developed using a body weight of 0.093 g for the honey bee (USDA/APHIS 1993) and the equation above for body surface area proposed by Boxenbaum and D'Souza (1990). Because there is no information regarding the dermal absorption rate of diflubenzuron by bees or other invertebrates, this exposure scenario, detailed in Worksheet F02b, also assumes complete absorption over the first day of exposure. As noted above, exposures for other terrestrial invertebrates are based on field studies in which application rate is the most relevant expression of exposure. This is discussed further in Section 3.3 (Dose-Response Assessment) and Section 3.4 (Risk Characterization).

Direct spray scenarios are not given for large mammals. As noted above, allometric relationships dictate that large mammals will be exposed to lesser amounts of a compound in any direct spray scenario than smaller mammals.

4.2.2.2. Indirect Contact – As in the human health risk assessment (see Section 3.2.3.3), the only approach for estimating the potential significance of indirect dermal contact is to assume a relationship between the application rate and dislodgeable foliar residue. Unlike the human health risk assessment in which transfer rates for humans are available, there are no transfer rates available for wildlife species. As discussed in Durkin et al. (1995), the transfer rates for humans are based on brief (e.g., 0.5 to 1-hour) exposures that measure the transfer from contaminated soil to uncontaminated skin. Wildlife, compared with humans, are likely to spend longer periods of time in contact with contaminated vegetation. It is reasonable to assume that for prolonged exposures a steady state may be reached between levels on the skin, rates of absorption, and levels on contaminated vegetation, although there are no data regarding the kinetics of such a process. The bioconcentration data on diflubenzuron indicates that this compound will accumulate in the tissue of the fish. Thus, it is plausible that absorbed dose resulting from contact with contaminated vegetation will be as great as those associated with comparable direct spray scenarios.

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

For the consumption of contaminated vegetation, a small mammal is used because allometric relationships indicate that small mammals will ingest greater amounts of food per unit body weight, compared with large mammals. The amount of food consumed per day by a small mammal (i.e., an animal weighing approximately 20 g) is equal to about 15% of the mammal's total body weight (U.S. EPA/ORD 1989). When applied generally, this value may overestimate or underestimate exposure in some circumstances. For example, a 20 g herbivore has a caloric requirement of about 13.5 kcal/day. If the diet of the herbivore consists largely of seeds (4.92 kcal/g), the animal would have to consume a daily amount of food equivalent to approximately 14% of its body weight [(13.5 kcal/day ÷ 4.92 kcal/g)÷20g = 0.137]. Conversely, if the diet of the herbivore consists largely of vegetation (2.46 kcal/g), the animal would have to consume a daily amount of food equivalent to approximately 27% of its body weight [(13.5 kcal/day ÷ 2.46 kcal/g)÷20g = 0.274] (U.S. EPA/ORD 1993, pp.3-5 to 3-6). For this exposure assessment (Worksheet F03), the amount of food consumed per day by a small mammal weighing 20 g is estimated at about 3.6 g/day or about 18% of body weight per day from the general allometric relationship for food consumption in rodents (U.S. EPA/ORD 1993, p. 3-6).

A large herbivorous mammal is included because empirical relationships of concentrations of pesticides in vegetation, discussed below, indicate that grasses may have substantially higher pesticide residues than other types of vegetation such as forage crops or fruits (Worksheet B21). Grasses are an important part of the diet for some large herbivores, but most small mammals do not consume grasses as a substantial proportion of their diet. Thus, even though using residues from grass to model exposure for a small mammal is the most conservative approach, it is not generally applicable to the assessment of potential adverse effects. Hence, in the exposure scenarios for large mammals, the consumption of contaminated range grass is modeled for a 70 kg herbivore, such as a deer. Caloric requirements for herbivores and the caloric content of vegetation are used to estimate food consumption based on data from U.S. EPA/ORD (1993). Details of these exposure scenarios are given in Worksheet F10 for acute exposures as well as Worksheets F11a and F11b for longer-term exposures.

For the acute exposures, the assumption is made that the vegetation is sprayed directly – i.e., the animal grazes on site – and that100% of the animals diet is contaminated. While appropriately conservative for acute exposures, neither of these assumptions are plausible for longer-term exposures. Thus, for the longer-term exposure scenarios for the large mammal, two sub-scenarios are given. The first is an on-site scenario that assumes that a 70 kg herbivore consumes short grass for a 90 day period after application of the chemical. In the worksheets, the contaminated vegetation is assumed to account for 30% of the diet with a range of 10% to 100% of the diet. These are essentially arbitrary assumptions reflecting grazing time at the application site by the animal. Because the animal is assumed to be feeding at the application site, drift is set to unity - i.e., direct spray. This scenario is detailed in Worksheet 11a. The second sub-scenario is similar except the assumption is made that the animal is grazing at distances of 25 to 100 feet from the application site (lowering risk) but that the animal consumes 100% of the diet from the contaminated area (increasing risk). For this scenario, detailed in Worksheet F12b, AgDRIFT is used to estimate deposition on the off-site vegetation. Drift estimates from AgDrift are summarized in Worksheet B24 and this model is discussed further in Section 4.2.3.2.

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

For this component of the exposure assessment, the estimated amounts of pesticide residue on vegetation are based on the relationship between application rate and residue rates on different types of vegetation. As summarized in Worksheet B21, these residue rates are based on estimated residue rates from Fletcher et al. (1994).

Similarly, the consumption of contaminated insects is modeled for a small (10g) bird and a small (20g) mammal. No monitoring data have been encountered on the concentrations of diflubenzuron in insects after applications of diflubenzuron. The empirical relationships recommended by Fletcher et al. (1994) are used as surrogates as detailed in Worksheets F14a and F14b. To be conservative, the residue rates from small insects are used – i.e., 45 to 135 ppm per lb/ac – rather than the residue rates from large insects – i.e., 7 to 15 ppm per lb/ac.

A similar set of scenarios is provided for the consumption of small mammals by either a predatory mammal (Worksheet F16a) or a predatory bird (Worksheet F16b). Each of these scenarios assumes that the small mammal is directly sprayed at the specified application rate and the concentration of the compound in the small mammal is taken from the worksheet for direct spray of a small mammal under the assumption of 100% absorption (Worksheet F02a).

In addition to the consumption of contaminated vegetation and insects, diflubenzuron may reach ambient water and fish. Thus, a separate exposure scenario is developed for the consumption of contaminated fish by a predatory bird in both acute (Worksheet F08) and chronic (Worksheet F09) exposures. Because predatory birds usually consume more food per unit body weight than do predatory mammals (U.S. EPA 1993, pp. 3-4 to 3-6), separate exposure scenarios for the consumption of contaminated fish by predatory mammals are not developed.

4.2.2.4. Ingestion of Contaminated Water – Estimated concentrations of diflubenzuron in water are identical to those used in the human health risk assessment (Worksheet A04). The only major differences involve the weight of the animal and the amount of water consumed. There are well-established relationships between body weight and water consumption across a wide range of mammalian species (e.g., U.S. EPA 1989). Mice, weighing about 0.02 kg, consume approximately 0.005 L of water/day (i.e., 0.25 L/kg body weight/day). These values are used in the exposure assessment for the small (20 g) mammal. Unlike the human health risk assessment, estimates of the variability of water consumption are not available. Thus, for the acute scenario, the only factors affecting the variability of the ingested dose estimates include the field dilution rates (i.e., the concentration of the chemical in the solution that is spilled) and the amount of solution that is spilled. As in the acute exposure scenario for the human health risk assessment, the amount of the spilled solution is taken as 200 gallons. In the exposure scenario involving contaminated ponds or streams due to contamination by runoff or percolation, the factors that affect the variability are the water contamination rate, (see Section 3.2.3.4.2) and the application rate. Details regarding these calculations are summarized in Worksheets F06 and Worksheet F07.

4.2.3. Terrestrial Plants

Terrestrial plants will certainly be exposed to diflubenzuron. A large number of different exposure assessments could be made for terrestrial plants – i.e., direct spray, spray drift, runoff, wind erosion and the use of contaminated irrigation water. Such exposure assessments are typically conducted for herbicides. For diflubenzuron, however, the development of such exposure assessments would serve no purpose. As discussed in Section 4.1.2.4 (Hazard Identification for Terrestrial Plants), there is no basis for asserting that diflubenzuron will cause adverse effects in terrestrial plants. Thus, no formal exposure assessment is conducted for terrestrial plants.

4.2.4. Soil Organisms

For both soil microorganisms and soil invertebrates, the toxicity data are typically expressed in units of soil concentration – i.e., mg agent/kg soil which is equivalent to parts per million (ppm) concentrations in soil. The GLEAMS modeling, discussed in Section 3.2.3.4, provides estimates of concentration in soil as well as estimates of off-site movement (runoff, sediment, and percolation). Based on the GLEAMS modeling, concentrations in clay, loam, and sand over a wide range of rainfall rates are summarized in Table 4-2. As indicated in this table, peak soil concentrations at an application rate of 70 g/ha are in a relatively narrow range: about 0.003 to 0.009 mg/kg (ppm) over all soil types and rainfall rates. Longer term concentrations in soil are all low and are on the order of 0.00005 to 0.0005 mg/kg – i.e., 0.05 ppb to 0.5 ppb. Modeled concentrations of 4-chloroaniline in soil are summarized in Table 4-3. As would be expected of any environmental metabolite, peak concentrations are lower than those of the parent compound. For 4-chloroaniline these range from about 0.0007 to 0.003 mg/kg, about a factor of three lower than the corresponding concentrations of diflubenzuron.

4.2.5. Aquatic Organisms

The potential for effects on aquatic species are based on estimated concentrations of diflubenzuron and 4-chloroaniline in water that are identical to those used in the human health risk assessment. As summarized in Table 3-8, the peak estimated concentration of diflubenzuron in ambient water is 0.4 (0.01 to 16) µg/L at an application rate of 70 g/ha. For longer-term exposures, the corresponding longer term concentrations in ambient water are estimated at 0.02 (0.001 to 0.1) µg/L. The corresponding estimates for 4-chloroaniline are summarized in Table 3-9: 0.5 (0.00003 to 2) µg/L for acute exposures and 0.05 (0.0002 to 0.2) µg/L for longer term exposures.

4.3. DOSE-RESPONSE ASSESSMENT

4.3.1. Overview

As in the human health risk assessment, toxicity values are derived for both diflubenzuron and 4-chloroaniline. Several of the toxicity values used in the ecological risk assessment for diflubenzuron are summarized in Table 4-4. For two groups of organisms, terrestrial arthropods and aquatic invertebrates, detailed dose-response assessments can be made for several different subgroups. These toxicity values are summarized in Table 4-5 for terrestrial arthropods and Table 4-6 for aquatic invertebrates. The values for 4-chloroaniline are summarized in Table 4-7.

Diflubenzuron is relatively non-toxic to mammals and birds. For mammals, the toxicity values used in the ecological risk assessment are identical to those used in the human health risk assessments: an acute NOAEL of 1118 mg/kg and a chronic NOAEL of 2 mg/kg/day. A similar approach is taken for 4-chloroaniline for which an acute NOAEL of 8 mg/kg is used based on a subchronic study and a chronic NOAEL is estimated at 1.25 mg/kg/day based on the chronic LOAEL of 12.5 mg/kg/day. For birds, the acute NOAEL for diflubenzuron is taken as 2500 mg/kg from an acute gavage study and the longer term NOAEL is taken as 110 mg/kg/day from a reproduction study. No data are available on toxicity of 4-chloroaniline in birds and the available toxicity values for mammals are used as a surrogate.

For terrestrial invertebrates two general types of data could be used to assess dose-response relationships: laboratory toxicity studies and field studies. Field studies are used in the current risk assessment because the standard toxicity studies are extremely diverse and many are not directly applicable to a risk assessment. Despite the difficulty and uncertainty in interpreting some of the field studies, the relatively large number of field studies on diflubenzuron appear to present a reasonably coherent pattern that is at least qualitatively consistent with the available toxicity data and probably a more realistic basis on which to assess risk to nontarget species. The most sensitive species appear to be grasshoppers which may be adversely affected at an application rate of 22 g/ha. Somewhat high application rates – in the range of 30 to 35 g/ha – will adversely affect macrolepidoptera and some beneficial parasitic wasps. At the maximum application rate considered in this risk assessment – i.e., 70 g/ha – some herbivorous insects are likely to be affected. No adverse effects in several other groups of insects are expected at this or much higher application rates. Honeybees are among the most tolerant species and are not likely to be adversely affected at application rates of up to 400 g/ha.

Invertebrates that do not utilize chitin are also relatively insensitive to diflubenzuron. The NOEC for a species of earthworm (*Eisenia fetida*) is 780 mg/kg soil and is used to represent tolerant species of soil invertebrates. Very little information is available on the toxicity of 4-chloroaniline to terrestrial invertebrates. As with diflubenzuron, the earthworm appears to be relatively tolerant to 4-chloroaniline with a reported LC_{50} value of 540 mg/kg dry soil. The toxicity of both diflubenzuron and 4-chloroaniline to soil microorganisms is also relatively low.

Toxicity values for aquatic species follow a pattern similar to that for terrestrial species: arthropods appear to be much more sensitive than fish or non-arthropod invertebrates. For diflubenzuron, LC_{50} values of 25 mg/L to 500 mg/L are used to characterize risks for sensitive and tolerant species of fish, respectively. 4-Chloroaniline appears to be more toxic to fish and an LC_{50} value of 2.4 mg/L is used to characterize risks of peak exposures and 0.2 mg/L is used to characterize risks of longer term exposures.

Substantial variability in the response of different groups of aquatic invertebrates to diflubenzuron is apparent. Very small arthropods appear to be among the most sensitive species – with acute NOEC values in the range of 0.3 to about 1 ppb (µg/L) and chronic NOEC values in the range of 0.04 to 0.25 ppb. Based on acute NOEC values, larger arthropods, including crabs and larger insects, appear to be more tolerant, with acute NOEC values in the range of 2 to 2000 ppb. For chronic effects, the differences between small and larger arthropods are less remarkable, a stoneflies and mayflies (relatively large insects) having an NOEC value of 0.1 ppb, intermediate between *Daphnia* (0.04 ppb) and *Ceriodaphnia* (0.25 ppb). Molluscs (invertebrates including clams and snails) and worms (oligochaetes) appear to be much less sensitive to diflubenzuron.

The data on the toxicity of 4-chloroaniline to aquatic invertebrates is sparse. An acute NOEC of 0.013 mg/L is used to characterize acute risks associated with peak exposures in aquatic invertebrates and an NOEC of 0.01 mg/L from a reproduction study is used to characterize longer term risks to aquatic invertebrates.

4.3.2. Toxicity to Terrestrial Organisms

4.3.2.1. Mammals – The dose-response assessment for mammalian wildlife species is based on the same set of studies used in the human health risk assessment for diflubenzuron (Section 3.3.2) and 4-chloroaniline (Section 3.3.3).

For diflubenzuron, the most sensitive effect in experimental mammals involves toxic effects in red blood cells. The NOAEL for this endpoint in experimental mammals is 2 mg/kg/day (U.S. EPA 1997a) and is based on a study in which dogs were administered doses of 0, 2, 10, 50, or 250 mg/kg/day, 7 days/week, for 52 consecutive weeks in gelatin capsules (Greenough et al. 1985). No adverse effects, including changes in methemoglobin formation, were noted at 2 mg/kg/day. This dose will be used to characterize longer term risks to mammals. For acute exposures, the acute NOAEL of 1118 mg/kg is used. As discussed in Section 3.3.2.2, this is based on a study using a petroleum based formulation of diflubenzuron, Dimilin 2L. Because none of the estimated exposures approach a level of concern, no elaboration of the dose-response assessment is needed.

A similar approach is taken for 4-chloroaniline. The acute NOAEL is taken as 8 mg/kg. This is a very conservative approach – i.e., likely to be overly protective – because this NOAEL is from a 90 day study (Scott and Eccleston 1967). The chronic value is based on a LOAEL of 12.5 mg/kg/day from a 2-year feeding study using rats (NCI 1979). Because a NOAEL was not identified in this study, the LOAEL of 12. 5 mg/kg/day is divided by 10 to estimate a chronic

NOAEL of 1.25 mg/kg/day. This is essentially the same estimate used by U.S. EPA (1997a) in the derivation of the RfD based on the LOAEL of 12.5 mg/kg/day (Section 3.3.3.1).

4.3.2.2. Birds

4.3.2.2.1. Diflubenzuron – There appears to be relatively little difference in the acute toxicity of diflubenzuron to birds and mammals. As summarized above, the lowest acute NOAEL for mammals is 1118 mg/kg (rats dosed with Dimilin 2L in the study by Blaszcak (1997a). For birds, the lowest acute NOAEL is 2500 mg/kg from the study by Alsager and Cook (1975) in red-winged blackbirds. As detailed in Appendix 1 for mammals and Appendix 8 for birds, higher NOAEL values have been reported in other studies – i.e., up to 10,000 mg/kg for mammals (rats and mice in the study by Koopman 1977) and 5,000 mg/kg for birds (mallard ducks in the study by Roberts and Parke 1976). Analogous to the approach taken with rats, the lowest NOAEL is taken as the toxicity value for acute exposures in bird – i.e., the NOAEL of 2500 mg/kg in red-winged blackbirds from the study by Alsager and Cook 1975.

It should be noted that the variability in the acute NOAEL values does not imply any systematic differences among species but simply reflects the highest dose tested in the different experiments. Thus, the use of the lowest NOAEL rather than the highest NOAEL may be viewed as somewhat conservative. As discussed in Section 4.3.2.1, the use of the 1118 mg/kg dose for mammals is justified based on the use of a petroleum based formulation in the study by Blaszcak (1997a). The use of the lowest NOAEL for birds based on the conservative assumption that somewhat higher doses in the study by Alsager and Cook (1975) could have resulted in effects. Notwithstanding this assumption, the data are not sufficient to derive separate NOAEL values for tolerant and sensitive species because none of the available data actually demonstrated differences in sensitivity – i.e., differences in LOAEL values.

In terms of chronic toxicity, however, birds appear to be somewhat more tolerant to diflubenzuron than mammals. Based on reproduction studies, the NOEC for reproductive toxicity in birds is greater than 500 ppm – i.e., at the highest dietary concentration, no effects were noted – in mallard ducks (Beavers et al. 1990a) and bobwhite quail (Beavers et al. 1990b). Based on differences in food consumption (Appendix 4), the lowest dose in terms of mg/kg bw/day is 110 mg/kg/day from the study in quail (Beavers et al. 1990b). This is substantially above for the mammalian NOAEL of 2 mg/kg/day and the corresponding mammalian LOAEL of 10 mg/kg/day. While this suggests a difference in sensitivity between mammals and birds, the toxicity endpoints are different – i.e., effects on blood from chronic exposure in mammals and reproductive effects in birds. As noted in Appendix 1, doses as high as about 4000 mg/kg/day were not associated with reproductive effects in rats (Brooker 1995). In any event, the chronic NOAEL of 110 mg/kg/day in quail from the study by Beavers et al. (1990b) is used to characterize the risks associated with longer term exposures of birds to diflubenzuron.

4.3.2.2.2. 4-Chloroaniline – No data have been encountered on the toxicity of 4-chloroaniline to birds. For the current risk assessment, the toxicity values for 4-chloroaniline in mammals are used as surrogates for birds. This adds uncertainty to the risk assessment for birds and this is discussed further in Section 4.4 (Risk Characterization).

4.3.2.3. Terrestrial Invertebrates

4.3.2.3.1. Diflubenzuron – Two general types of data could be used to assess dose-response relationships for terrestrial invertebrates: laboratory toxicity studies (Appendix 5) and field studies (Appendix 3a). In most risk assessments conducted by U.S. EPA (e.g. U.S. EPA/OPP 1997a) as well as risk assessments conducted for the USDA/Forest Service, dose-response assessments for terrestrial invertebrates are based on controlled laboratory studies that are commonly conducted on the honey bee using relatively standard protocols. As indicated in Table 4-5, a different approach is used in the current risk assessment: the large number of field studies on diflubenzuron that report either effect or no effect levels are used directly for characterizing risk with exposures expressed in units of application rate.

One reason for this approach involves the disparity in experimental designs among the toxicity studies that are available which confounds quantitative comparisons of relative sensitivities among species. As discussed in Section 4.1.2.3, there is an apparently wide range of sensitivities to diflubenzuron among different invertebrate species. Based on standard toxicity tests, the honey bee is among the more tolerant species. The U.S. EPA used an LD_{50} of greater than 30 μg/bee to classify diflubenzuron as practically non-toxic to the honey bee. Taking an average weight of 0.093 g/bee or 0.000093 kg/bee (USDA/APHIS 1993) and making the very conservative assumption of 100% absorption, this would correspond to an LD_{50} greater than 322 mg/kg bw [0.03 mg/bee ÷ 0.000093 kg bw/bee = 322.58 mg/kg]. As summarized in Appendix 5, somewhat lower LD_{50} values have been reported by Chandel and Gupta (1992) – i.e., about 22 mg/kg for pupae and 53 mg/kg for third instar larvae. The gypsy moth is obviously a sensitive species, with a topical LD_{50} value of about 4 to 9 mg/kg, based on residues on vegetation (Berry et al. 1993), about a factor of 2 to 5 below the lowest LD_{50} value for the honey bee. A similar topical LD_{50} of 1.07 mg/kg has been reported by Sinha et al. (1990) for the butterfly, *Pieris brassicae*. Somewhat lower LD_{50} values have been reported for an orthopteran – i.e., 0.31 mg/kg in *Oxya japonica* from the study by Lim and Lee (1982). Based on topical LD_{50} values, the most sensitive species appears to be lacewing, *Chysoperla carnea*, with a reported topical LD_{50} values of 2.26 ng/insect or about 0.00226 μg/insect (Medina et al. 2003). Based on a mean body weight of 7.53 mg reported by Medina et al. (2003), this corresponds to a dose of 0.0003 μg/mg, which in turn corresponds to a dose of 0.0003 mg/g or 0.0000003 mg/kg bw. Thus, based on this LD_{50}, the lacewing would appear to be more sensitive than the gypsy moth by a factor of 13 to 30 million [4 to 9 mg/kg ÷ 0.0000003 mg/kg]. The LD_{50} value from Medina et al. (2003), however, is not really comparable to the value for the gypsy moth because the topical application to the lacewing involved direct application of diflubenzuron (in acetone) rather than a spray or contact with a contaminated surface. Thus, while the various laboratory toxicity studies could be used to construct a standard dose-response assessment for tolerant and sensitive species, there would be substantial uncertainty in the comparisons because of the diversity in experimental designs.

An alternative approach may be based on the available field studies. A summary of these studies is presented in Table 4-1 and additional details are provided in Appendix 3a. Field studies, like epidemiology studies, can be difficult to interpret because of differences in the treated site versus the control site. For example, the study by Van Den Berg (1986) on mites and collembolans is noted in Table 4-1 as providing a NOAEL in which transient or equivocal effects were noted. As detailed in Appendix 3a, Van Den Berg (1986) concluded that the effects on the mites and collembolans were insubstantial. The data, however, indicate generally fewer species over time in the treated site versus the untreated site. The author's conclusion that the effects were insubstantial is based on the fact that the populations of mites and collembolans were different at the control and treated sites prior to treatment and that the capture patterns over time for mites were highly erratic. In other words, compared to pre-treatment populations as well as the time course of population changes, the effect of diflubenzuron in this study appeared to be marginal and insubstantial. An examination of the data presented by Van Den Berg (1986) supports the conclusion that the application of diflubenzuron in this study should be classified as a NOAEL. A similar assessment may be made of the study by Martinat et al. (1993) in which changes in populations of spiders and orthopteroids (i.e., cockroaches, mantises, locusts, and crickets) were only sporadically noted over time and no consistent effect is apparent.

Despite the difficulty and uncertainty in interpreting some of the fields, the relatively large number of field studies on diflubenzuron appear to present a reasonably coherent pattern that is at least qualitatively consistent with the available toxicity data and probably a more realistic basis on which to assess risk to nontarget species. Consistent with the laboratory studies, the field studies clearly indicate that honey bees are relatively insensitive to diflubenzuron: application rates of up to 400 g/ha are not likely to affect honeybees (Table 4-5). The most sensitive species appear to be grasshoppers which may be adversely affected at an application rate of 22 g/ha. Somewhat high application rates – in the range of 30 to 35 g/ha – will adversely effect macrolepidoptera and some beneficial parasitic wasps. At the maximum application rate of considered in this risk assessment – i.e., 70 g/ha – some herbivorous insects are likely to be affected. No adverse effects in several other groups of insects are expected at this or much higher application rates, as detailed in Table 4-5.

As also noted in Section 4.1.2.3, invertebrates that do not utilize chitin are relatively insensitive to diflubenzuron. Based on soil toxicity studies, the NOEC 780 mg/kg soil for the earthworm (*Eisenia fetida*) from the study by Berends et al. (1992) is used to represent tolerant species of soil invertebrates.

4.3.2.3.2. 4-Chloroaniline – Very little information is available on the toxicity of 4-chloroaniline to terrestrial invertebrates (WHO 2003). This is not uncommon for compounds that are not used or registered as insecticides. WHO (2003) summarizes a standard OECD study on earthworms in which the 28-day LC_{50} value was 540 mg/kg dry soil. As noted in Section 3.2, this is far higher than any concentrations of 4-chloroaniline that are likely to be found in soil.

4.3.2.4. Terrestrial Plants (Macrophytes) – As discussed in 4.1.2.4 (Hazard Identification for Terrestrial Plants), no toxicity studies have been conducted on terrestrial plants and there is no basis for asserting that adverse effects on terrestrial plants are likely from exposures to either diflubenzuron or 4-chloroaniline. Consequently, no dose-response assessments for terrestrial plants are presented in this risk assessment.

4.3.2.5. Soil Microorganisms

4.3.2.5.1. Diflubenzuron – Diflubenzuron does not appear to be very toxic to soil microorganisms (Section 4.1.2.5). While one study (Sexstone 1995) has noted transient changes in gross microbial biomass and activity at one exposure rate (roughly equivalent to 10 g/ha), no dose-response relationship is demonstrated and the effects, if any, appear to be very minor. Consequently, this study is not used quantitatively in the dose-response assessment for soil microorganisms. For the current risk assessment, bioassays on fungi are used to identify tolerant and sensitive species – a LOEC of 50 ppm in *Pythium* for sensitive species and an NOEC of 100 ppm for tolerant species (*Aspergillus*, *Fusarium*, *Rhizopus*, *Trichoderma*) from the study by (Townshend et al. 1983). If any species of microorganisms are at risk from exposure to diflubenzuron, fungi might be considered the most likely to be susceptible because some fungi utilize chitin in their cell walls. As summarized in Table 4-2, however, the NOEC and LOEC values are several orders of magnitude higher than any plausible soil exposures.

4.3.2.5.2. 4-Chloroaniline – The only information encountered on the microbial toxicity of 4-chloroaniline is an ED_{10} of 1000 ppm for Fe(III) reductions by upper soil (Horizon A) microorganisms (Welp and Brummer 1999). As with diflubenzuron, this concentration is far above plausible levels of soil exposure.

4.3.3. Aquatic Organisms

4.3.3.1. Fish

4.3.3.1.1. Diflubenzuron – The toxicity data on diflubenzuron are sufficient to identify sensitive and tolerant species for both acute and chronic exposures (Table 4-4). For acute toxicity, the lowest and highest LC_{50} values will be used consistent with the data in the risk assessment presented by U.S. EPA/OPP (1997a). The LC_{50} value for sensitive fish species will be taken as 25 mg/L from the study by Johnson and Finley (1980) in yellow perch and the LC_{50} value for tolerant fish species will be taken as 500 mg/L from the study by Reiner and Parke (1975) in fathead minnow. Both of these are very protective values in that both concentrations are actually the highest concentration tested and less than 50% mortality was observed. As discussed further in Section 4.4, this protective approach has no impact on the risk assessment because the anticipated peak exposures to diflubenzuron are far below these concentrations. For longer term exposures, reproductive NOEC values will be used. The range of reported values is relatively narrow: 0.05 mg/L for mummichogs from the study by Livingston and Koenig (1977) to 0.1 mg/L for fathead minnows from the study by Cannon and Krize (1976).

4.3.3.1.2. 4-Chloroaniline – Very little information is available on the toxicity of 4-chloroaniline to fish. As reviewed by WHO (2003), an LC_{50} value of 2.4 mg/L is reported in bluegills and a reproductive NOEC of 0.2 mg/L in zebra fish is reported in Bresch et al. (1990). These values are used in the current risk assessment for characterizing risks to fish associated with exposures to 4-chloroaniline (Table 4-7).

4.3.3.2. Amphibians – The only information on the toxicity of diflubenzuron to amphibians comes from two field studies conducted by Pauley (1995a,b). As discussed in Section 4.1.3.2, these studies indicate a change in the diet of both terrestrial and aquatic salamanders following an application of diflubenzuron at 80g/ha. This change was secondary to changes in available food items. No data are available on the toxicity of 4-chloroaniline to amphibians. Because of the very low apparent risks to fish (Section 4.4), the limited data on effects of diflubenzuron to amphibians, and the lack of data on the effects of 4-chloroaniline to amphibians, a quantitative dose-response assessment for this group of organisms is not proposed.

4.3.3.3. Invertebrates

4.3.3.3.1. Diflubenzuron – The toxicity values used in this risk assessment for aquatic invertebrates are summarized in Table 4-6, with the top section of this table summarizing acute toxicity values that are used to characterize risks associated with peak exposures and the bottom section of the table summarizing toxicity values used to characterize risks associated with longer term exposures. In all cases, the toxicity values are based on no-observed-effect concentrations (NOECs). This approach is somewhat different from the approach taken by U.S. EPA (1997a), in which toxicity values are based on LC_{50} values but the studies used and basic conclusions of the current risk assessment are similar to those of U.S. EPA (1997a). Diflubenzuron is very highly toxic to some aquatic invertebrates.

As with the acute toxicity to terrestrial invertebrates, the dose-response assessment can be elaborated to include several groups of invertebrates rather than simply sensitive and tolerant species. Supporting information for the acute and chronic toxicity values are given in Table 4-8 and Table 4-9, respectively, and additional information from field studies is summarized in Table 4-10. More detailed summarizes of the acute and chronic toxicity studies are given in Appendix 7 and details of a large number of field studies are given in Appendix 3b.

As summarized in Table 4-6, there is a substantial variability in the response of different groups of aquatic invertebrates to diflubenzuron. Very small arthropods – i.e, cladocerans (*Daphnia* and *Ceriodaphnia*) as well as copepods – appear to be among the most sensitive aquatic species – with acute NOEC values in the range of 0.3 to about 1 ppb (µg/L) and chronic NOEC values in the range of 0.04 to 0.25 ppb. Based on acute NOEC values, larger arthropods, including crabs and larger insects, appear to be more tolerant, with acute NOEC values in the range of 2 to 2000 ppb. In some of these assays of larger invertebrates, the short duration of the assay may be a factor in the apparently greater tolerance of larger invertebrates compared to small invertebrates. For example, Lahr et al. (2001) note that the backswimmers tested in their bioassay evidenced a NOEC of 2000 ppb but that lower NOEC values could have been evident if the organisms had been in a molting stage. This supposition is supported by chronic toxicity data (Table 4-9) in which differences between small and larger arthropods are less remarkable, with stoneflies and mayflies (relatively large insects) having an NOEC value of 0.1 ppb, intermediate between *Daphnia* (0.04 ppb) and *Ceriodaphnia* (0.25 ppb). In the tests using stonefly and mayflies, response was characterized as an inhibition of emergence rather than pre-emergent mortality. Again, this probably relates to the inhibition of chitin synthesis by diflubenzuron. Molluscs (invertebrates including clams and snails) and worms (oligochaetes) appear to be much less sensitive to diflubenzuron.

Based on acute NOEC values, the range of sensitivities among aquatic invertebrates appears to span a factor of over 400,000 [125,000 ppb in molluscs ÷ 0.3 in *Daphnia* = 416,667] based on acute NOEC values and a factor of 8,000 [320 ppb in molluscs ÷ 0.04 in *Daphnia*] based on longer term NOEC values. These ratios are, at least to some extent, artifacts of experimental design. As summarized in Tables 4-8 and 4-9, acute and chronic NOEC and LOEC values are available for sensitive species such as daphnids. For molluscs, however, only NOEC values are available – i.e., no effects have been demonstrated in these species at the highest concentration tested.

Although there is a large number of field studies available on effects of diflubenzuron on aquatic invertebrates (Appendix 3b), these studies are not directly used in the dose-response assessments. Unlike the case with terrestrial invertebrates, application rates (e.g., g/ha) in aquatic field studies do not provide a uniform basis for comparing exposures among the different studies because the amount of diflubenzuron entering the water may and probably did vary remarkably among the different field studies based on site-specific and meteorological differences among the studies. The magnitude of possible differences is illustrated in Tables 3-2 and 3-3.

Nonetheless, some studies provide information on both application and concentrations in ambient water. An overview of these studies, summarized from Appendix 3b, is given in Table 4-10. As in the tables for standard toxicity studies, Tables 4-8 and 4-9, concentrations are given in braces [] between the species and the citation. Even these concentrations, however, are not readily comparable among studies, with some reported as peak concentrations and others as nominal or average concentrations over a given period. For example, Apperson et al. (1977) conducted a field study in which populations of cladocerans and copepods declined after an application of diflubenzuron to ponds and lakes at nominal concentrations of 2.5, 5, and 10 ppb. Actual monitored concentrations peaked at up to 32.2 ppb, however, and declined rapidly to less than 1 ppb. This type of pattern is typical in field studies in which concentrations will vary substantially both among different studies as well as over time within a single study. This probably accounts for the general pattern of field studies suggesting a higher tolerance in terms of reported concentrations than laboratory studies in which concentrations are better defined and less variable. The field studies summarized in Table 4-10, however, do support the general pattern of species sensitivity noted in the laboratory toxicity studies – i.e., small arthropods are more sensitive than larger arthropods and non-arthropod invertebrates.

Notwithstanding the limitations inherent in field studies in terms of actual exposures and temporal variations, the field studies are directly useful in risk characterization and are discussed further in Section 4.4. One very important feature of field studies is ability to assess population recovery, which is not typically assayed in laboratory studies. As summarized in Table 4-10, most field studies that detect adverse effects also find evidence of population recovery after application so long as the duration of the study is sufficiently long to permit the detection of recovery. This is also discussed further in the risk characterization (Section 4.4).

4.3.3.3.2. 4-Chloroaniline – The data on the toxicity of 4-chloroaniline to aquatic invertebrates is sparse, particularly when compared to the very rich data base on diflubenzuron. Notwithstanding this limitation, 4-chloroaniline appears to be much less toxic to aquatic invertebrates than diflubenzuron and the magnitude of the difference in potency can be quantified. In terms of acute toxicity to *Daphnia magna*, the 48-hour LC_{50} value for 4-chloroaniline has been reported as 0.31 mg/L (Kuhn et al 1989a), 400 times higher than the LC_{50} values of 0.0007 mg/L to 0.00075 mg/L for diflubenzuron (Corry et al. 1995; Kuijpers 1988; Majori et al. 1984). The corresponding NOEC for 4-chloroaniline is 0.013 mg/L (Kuhn et al 1989a), 40 times higher than the acute NOEC of 0.0003 mg/L for diflubenzuron (Corry et al. 1995).

Similarly, the chronic NOEC in *Daphnia magna* for 4-chloroaniline in a standard reproduction study is 0.01 mg/L (Kuhn et al 1989b). This is a factor of 250 times higher than the corresponding value of 0.00004 mg/L in *Daphnia magna* reported by Surprenant (1988).

As summarized in Table 4-7 (toxicity values for 4-chloroaniline), the acute NOEC of 0.013 mg/L (Kuhn et al 1989a) is used to characterize acute risks to aquatic invertebrates and the NOEC of 0.01 mg/L for reproductive effects (Kuhn et al 1989b) is used to characterize longer term risks to aquatic invertebrates.

4.3.3.4. Aquatic Plants

4.3.3.4.1. Diflubenzuron – Compared to aquatic invertebrates, relatively little information is available on the toxicity of diflubenzuron to aquatic plants (Section 4.1.3.4 and Appendix 8). The lowest reported effect is a decrease in periphyton at a concentration 7.0 µg/L in littoral enclosures (Moffett 1995). As noted in Section 4.1.3.4 and Appendix 8, Moffett (1995) attributed this change to a decrease in the population density of zooplankton grazers. This conclusion seems reasonable and is supported by standard plant toxicity studies reporting no effects at concentrations of up to 380 µg/L (Booth and Ferrell 1977; Thompson and Swigert 1993a,b,c). For assessing the risks of direct toxic effects on terrestrial plants, a NOEC of 45 µg/L will be used for possibly sensitive species (*Selenastrum capricornutum* in the study by Hansen and Garton 1982a) and a NOEC of 380 µg/L (*Navicula pelliculosa* in the study by Thompson and Swigert 1993c) will be used for apparently tolerant species. Since no LOEC values are available for any species of aquatic plants, these different NOEC values may simply reflect differences in the highest dose tested in the respective experiments rather than true differences in species sensitivity to diflubenzuron.

4.3.3.4.2. 4-Chloroaniline – The only information encountered on the toxicity of 4-chloroaniline is summarized in WHO (2003) from two publications in the German literature (Schmidt 1989; Schmidt and Schnabl 1988). Based on this information, 4-chloroaniline appears to be somewhat more toxic to aquatic plants than diflubenzuron. While WHO (2003) does not report NOEC values for 4-chloroaniline, an EC_{10} of 0.02 mg/L for cell multiplication in *Scenedesmus subspicatus*, a species of green algae, will be used as surrogate NOEC.

4.3.3.5. Microorganisms (excluding algae)

4.3.3.5.1. Diflubenzuron – Very little information is available on the toxicity of either diflubenzuron or 4-chloroaniline to aquatic microorganisms. As summarized in Section 4.1.3.5, marginal and transient effects on microbial decomposition and respiration have been noted at 50 µg/L and 50,000 µg/L (Kreutzweiser et al. 2001). Because of the insubstantial nature of the effects and the lack of a marked dose-response relationship, the concentration of 50 µg/L is used as a NOEC for aquatic microorganisms in Table 4-4.

4.3.3.5.2. 4-Chloroaniline – The only information on 4-chloroaniline is the results of a assay for bioluminescence with *Photobacterium phosphoreum* in which the 30-minute EC_{50} for the inhibition of bioluminescence was 5.1 mg/L (Ribo and Kaiser 1984). While the utility of this type of assay for risk characterization may be marginal, it is the only information available and is included in Table 4-7 and used for the risk characterization of 4-chloroaniline.

4.4. RISK CHARACTERIZATION

4.4.1. Overview

While the data base supporting the ecological risk assessment of diflubenzuron is large and complex, the risk characterization is relatively simple. Diflubenzuron is an effective insecticide and effects on some nontarget terrestrial insects are likely at application rates that are used to control the gypsy moth. Species at greatest risk include grasshoppers, various macrolepidoptera (including the gypsy moth), other herbivorous insects, and some beneficial predators of the gypsy moth. These species are at risk because of the mode of action of diflubenzuron (i.e., inhibition of chitin) and the behavior of the sensitive insects (the consumption of contaminated vegetation or predation on the gypsy moth). Some aquatic invertebrates may also be at risk but the risks appear to be less than risks to terrestrial insects. The risk characterization for aquatic invertebrates is highly dependant on site-specific conditions. In areas in which water contamination is likely to be minimal, no or only marginal effects are expected. During applications in which drift or direct deposition is not controlled well or in areas in which soil losses from runoff and sediment are likely, acute effects on some aquatic invertebrates are plausible and longer term effects on sensitive species could occur.

Direct effects of diflubenzuron on other groups of organisms – i.e., mammals, birds, amphibians, fish, terrestrial and aquatic plants, microorganisms, and non-arthropod invertebrates – do not appear to be plausible. Secondary effects in some nontarget species could occur. The most common secondary effects will be seen in and associated with animals that consume either the the gypsy moth or other invertebrates that may be adversely affected by diflubenzuron. The most common secondary effect will be a change in prey items that are consumed. Changes in feeding territory and prey items as well as reductions in body fat are likely to be transient.

There is no indication that 4-chloroaniline formed from the degradation of diflubenzuron will have an adverse effects on any species.

4.4.2. Terrestrial Organisms

4.4.2.1. Terrestrial Vertebrates – The risk characterizations for terrestrial vertebrates are essentially identical for both diflubenzuron and 4-chloroaniline. At the highest application rate of diflubenzuron that would be used in USDA programs, risks to mammals and birds are far below a level of concern. The quantitative risk characterization for terrestrial vertebrates (mammals and birds) is summarized in Worksheet G02a in the diflubenzuron worksheets (Supplement 1) and Worksheet G02 in the 4-chloroaniline worksheets (Supplement 2). The risk characterization is based on the estimates of exposure summarized in Section 4.2.3 and the toxicity values for diflubenzuron (Table 4-4) and 4-chloroaniline (Table 4-7) that were derived in Section 4.3.2.

The highest hazard quotient (HQ) for diflubenzuron is 0.2, the value associated with the upper range of exposure from the longer term consumption of contaminated vegetation in the treated area by a large mammal. As discussed in Section 4.2.2, this exposure scenario is based on the consumption of contaminated grass by a large mammal. For the gypsy moth program, this is an extremely conservative scenario in that most large wildlife mammals will not consume grass as an exclusive or even predominant proportion of their diet (exceptions being elk and some livestock animals). In addition, this scenario assumes that the grass is directly sprayed. In the application of diflubenzuron, canopy interception would reduce residues on grass in most circumstances. Other hazard quotients for diflubenzuron are below a level of concern by factors of 50 (the upper range HQ of 0.02 for the consumption of contaminated fish by a predatory bird) to 1 in one billion (the lower range HQ for the consumption of contaminated water by a small mammal).

The highest risk quotient for chloroaniline is 0.02, associated with the consumption of contaminated water by a small mammal. As discussed in Section 3.2.3.4, these peak exposures may occur months after the application of diflubenzuron and the concentrations of 4-chloroaniline in water are likely to vary substantially with different soils as well as rainfall rates. The peak concentrations of 4-chloroaniline are based on very conservative and perhaps extreme assumptions and the very low of hazard quotient of 0.02 – i.e., below the level of concern by a factor of 50 – indicates that there is no plausible basis for asserting that such exposures would be hazardous.

This risk characterization for terrestrial vertebrates is consistent with the risk characterization by U.S. EPA (1997a) as well as field studies which indicate a lack of adverse effects on terrestrial vertebrates after applications of diflubenzuron (Sections 4.1.2.1 and 4.1.2.2. and Appendix 3a). No toxic effects are likely to be seen in mammals or birds.

The most common secondary effects will be seen in and associated with vertebrates that consume either the target species (the gypsy moth) or other invertebrates that may be adversely affected by diflubenzuron (see Section 4.4.2.2.1). For such vertebrates, the most common secondary effect will be a change in prey items that are consumed.

4.4.2.2. Terrestrial Invertebrates

4.4.2.2.1. Diflubenzuron – While risks to terrestrial vertebrates are implausible, risks to some terrestrial invertebrates are virtually certain (Worksheet G02b, Supplement 1). At an application rate of 70 g/ha, adverse effects – i.e., mortality and decreases in populations – have been demonstrated in field studies for grasshoppers, various macrolepidoptera (including the gypsy moth), some mandibulate herbivores, and some beneficial predators to the gypsy moth. Effects on some beneficial predators may be secondary but at least in one species, *Apanteles melanoscelus*, a wasp that is a parasite on the gypsy moth, the effect appears to be due to direct toxicity (Madrid and Stewart1981). Effects in the same species are likely to be seen at lower application rates that may be used in USDA programs – i.e., 35 g/ha. For effects in these sensitive groups to be avoided, the application rate would need to be below about 2 g/ha [70 g/ha from Worksheet G02b divided by the HQ of 32 for the grasshopper]. This damage to non-target species appears to be unavoidable given the mode of action of diflubenzuron (i.e., inhibition of chitin) and the behavior of the sensitive insects (the consumption of contaminated vegetation or predation on the gypsy moth).

Most other insect groups are not likely to be affected at least directly. Some secondary effects associated with changes in available prey may be noted. As with most secondary effects, the changes in habitat or prey items are likely to be reversible. In other words, changes will be transient and populations will generally recover (e.g., Catangui et al. 1996).

4.4.2.2.2. 4-Chloroaniline – Very little information is available on the toxicity of 4-chloroaniline to invertebrates. One bioassay in earthworms reports an LC_{50} value of 540 mg/kg soil. The maximum concentration of 4-chloroaniline in soil is estimated at 0.0026 ppm (Table 4-3). The resulting HQ is 4.8×10^{-6}, below the level of concern by over 200,000. No data are available on the toxicity of 4-chloroaniline to other terrestrial vertebrates and risks cannot be quantified. Given the relatively low risks of 4-chloroaniline in aquatic invertebrates (4.4.3.2.2) as well as other organisms, there is no basis for asserting that substantial risks are plausible, particularly when compared to clear risks associated with diflubenzuron.

4.4.2.3. Terrestrial Plants and Microorganisms – No quantitative risk assessment to terrestrial plants is made for either diflubenzuron or 4-chloroaniline. As discussed in Section 4.1.2.4, there are no data on the phytotoxicity of either compound. This lack of data, however, adds no substantial uncertainty to this risk assessment. Diflubenzuron has been extensively tested in both the laboratory and field studies for efficacy in the protection of terrestrial plants from insect pests. If diflubenzuron were toxic to plants at applications at or substantially above those used to control the gypsy moth, it is likely that reports of such phytotoxicity would be noted. No such reports have been encountered (Appendix 3a and Appendix 8).

Limited information is available on the toxicity of diflubenzuron and 4-chloroaniline to soil microorganisms. As summarized in Worksheet G02b for diflubenzuron (Supplement 1), exposures of soil microorganisms to diflubenzuron are likely to be below a level of concern for sensitive species by a factor of over 600 at the upper range of plausible exposure – i.e., an HQ of 0.0016. For 4-chloroaniline, the toxicity value for microorganisms is 1000 ppm. As noted above, the highest estimated peak concentration of 4-chloroaniline in soil is 0.0026 ppm (Table 4-3). The resulting HQ is 2.6×10^{-6}, below the level of concern by over 350,000.

4.4.3. Aquatic Organisms

4.4.3.1. Aquatic Vertebrates – As with terrestrial vertebrates, the risk assessment for fish is unequivocal. There is no indication that diflubenzuron or 4-chloroaniline associated with the degradation of diflubenzuron will approach a level of concern.

The highest hazard quotient for diflubenzuron is 0.002 – i.e., longer term exposures to sensitive fish species (Worksheet G03b in Supplement 1). This is below the level of concern by a factor of 500. The toxicity of diflubenzuron has been assayed in relatively few fish species and it is likely that the most sensitive species of fish has not been identified. Nonetheless, there is no basis for asserting that species variability will encompass the factor of 500 associated with the highest HQ for diflubenzuron.

The risk characterization for 4-chloroaniline is virtually identical. The highest hazard quotient is 0.001. Below the level of concern by a factor of 1000 (Worksheet G03, Supplement 2).

4.4.3.2. Aquatic Invertebrates

4.4.3.2.1. Diflubenzuron – As noted by U.S. EPA (1997a), risks to aquatic invertebrates in some applications of diflubenzuron may be substantial – i.e., direct applications to standing bodies of water for mosquito control and forestry uses involving direct applications to bogs, swamps or other standing bodies of water (U.S. EPA 1997a, p. 64). These types of applications, however, are not used in and are thus not relevant to USDA programs for the control of the gypsy moth.

In USDA programs for control of the gypsy moth, risks to aquatic invertebrates appears to be substantially less than risks to terrestrial invertebrates. As noted in Section 2.3, USDA will use a 100 to 500 foot buffer between the application site of diflubenzuron and bodies of open water. While it is possible that small streams could be over-sprayed in aerial applications if the stream is not visible from the air, the covering foliar canopy would intercept some of the diflubenzuron which would in turn reduce the initial concentrations in stream water.

Based on the exposure assessments conducted in this risk assessment, which are consistent with several other exposure assessments as well as a number of relevant monitoring studies (Table 3-7), only the most sensitive species of aquatic invertebrates are likely to be adversely affected based on central estimates of plausible peak exposures. The central estimate of the hazard quotient for sensitive daphnids is only 1.3 (Worksheet G03a, Supplement 1). Typically, hazard quotients are rounded to a single significant digit. Thus, this hazard quotient reaches but does not exceed a level of concern. Based on central estimates of longer term exposures, all hazard quotients are less than 1 (Worksheets G03b, Supplement 1).

At the upper ranges of plausible peak exposures, the level of concern is reached for crabs (HQ=1), modestly exceeded for *Ceriodaphnia* and copepods (HQ=2), and exceeded by a factor of 5 for *Daphnia*. For *Daphnia*, LC_{50} values are only modestly above the NOEC (Table 4-8) and substantial mortality in these species would be plausible. At the upper range of longer term exposures, the hazard quotient exceeds a value of 1 only for *Daphnia* – i.e., HQ=3. This is in the range in which longer term effects on *Daphnia* productivity would be expected and such effects have been observed in field studies (Ali and Mulla 1978b).

Thus, based on the available toxicity data and dose response assessment, the risk characterization for aquatic invertebrates is highly dependant on site-specific conditions. In areas in which water contamination is likely to be minimal – i.e., areas with relatively low rainfall and areas in which drift can be controlled and runoff is limited – it is likely that no or only minimal effects would be observed (e.g., the field study by Ali et al. 1988). During applications in which drift or direct deposition is not controlled well or in areas in which soil losses from runoff and sediment are likely, acute effects on some aquatic invertebrates are plausible and longer term effects on sensitive species could occur.

That any of these effects would result in substantial secondary effects does not seem likely. A large number of field studies are available on diflubenzuron (Appendix 3b) that indicate direct effects on several species of invertebrates at concentrations in water that are above those that would be encountered in many applications for the control of the gypsy moth (see Section 4.1.3.3 for discussion). In addition, the only studies that suggest substantial secondary effects – such as decreased growth in fish – are litoral enclosure studies (Moffett and Tanner 1995; Tanner and Moffett 1995) in which fish were limited in their ability to seek prey. None of the field studies involving free-ranging fish have reported secondary effects other than a change in prey that are consumed.

4.4.3.2.2. 4-Chloroaniline **–** The risks to aquatic invertebrates associated with 4-chloroaniline are insubstantial relative to the risks associated with diflubenzuron. The highest hazard quotient is 0.2, associated with peak exposures to 4-chloroaniline in water.

4.4.3.3. Aquatic Plants and Microorganisms – Risks to aquatic plants and microorganisms appear to be low. There is essentially no identifiable risk associated with diflubenzuron. The highest hazard quotient is 0.04 and is associated with peak exposures to sensitive aquatic plants (Worksheet G03a, Supplement 1). Peak risks associated with 4-chloroaniline are somewhat higher, 0.2, the HQ associated with peak exposures to aquatic plants (Worksheet G03, Supplement 2).

A more plausible risk to aquatic plants may involve secondary effects – increased algal populations – associated with mortality in aquatic grazers such as Cladocerans. This effect has been noted in the mesocosm study by Boyle et al. (1996) . Apperson et al. (1977) noted a decrease in the concentration of a blue-green algae (*Anabaena* species) but no effect on diatoms or green algae. It is unclear if the effect was a primary, secondary, or incidental effect.

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Table 2-1. Selected physical and chemical properties of diflubenzuron [1]

Synonyms and trade names	DFB; Difluron; Dimilin; Duphacid; DU 112307; ENT 29054; Micromite; OMS 1804; PH 60-40; TH-6040
U.S. EPA Reg. No.	400-465 and 400-474 (C&P Press, 2003)
CAS number	35367-38-5 (USDA/ARS 1995)
Molecular weight	310.69 (USDA/ARS 1995; Meylan and Howard 1995)
Molecular formula	$C_{14}H_9ClF_2N_2O_2$ (USDA/ARS 1995; Budavari 1989)
SMILES Notation	O=C(NC(=O)c(c(F)ccc1)c1F)Nc(ccc(c2)Cl)c2
Appearance/state, ambient	Solid (USDA/ARS 1995)
Melting point	230 to 232 °C (USDA/ARS 1995)
Vapor pressure	0.00012 mPa (USDA/ARS 1995)
Water solubility (mg/L)	≈0.3 (Budavari 1989) 0.08 at 25°C (USDA/ARS 1995; Knisel et al. 1992) 0.0888 mg/L in deionized, 0.0926 mg/L in field water (Mabury and Crosby 1996)
log K_{ow}	3.89 (USDA/ARS 1995) [i.e., $K_{ow} = 10^{3.89} = 7762$] 3.59 (estimated) (Meylan and Howard 1995) 3.88 (experimental) (Meylan and Howard 1995) 3.83 ±0.02 (Marsella et al. 2000)
Koc	135.3 (organic soil) (Sundaram et al. 1997) 332.0 (silty clay loam) (Sundaram et al. 1997) 8700 (NOS) (USDA/ARS 1995) 10000 (Knisel and Davis 2000)
Kd	17.59 (organic soil) (Sundaram et al. 1997) 16.42 (silty clay loam) (Sundaram et al. 1997)
Foliar halftimes	9.3 days (Sundaram 1986, 1996) 8 days, 20-80% loss (Wimmer et al. 1993[2]) 29 days (hardwood, van den Berg 1986) 36 days (conifer, van den Berg 1986)
Foliar washoff	50% to 100% depending on formulation, intensity of rainfall, and time of rain after application (Sundaram and Sundaram 1994)
Litter halftimes	8.36 days (Sundaram 1986, 1996)
Soil halftimes	sterile: 346 days in sand and muck (NOS)(Chapman et al. 1985) natural: 18.7 days in sand and muck (NOS)(Chapman et al. 1985) 7.49 days (field study, Sundaram 1986, 1996)
Water photolysis halftime	17±4 hours at pH 7 in distilled water (Marsella et al. 2000) 8±2 hours at pH 9 in distilled water (Marsella et al. 2000) 12.3±0.7 hours at pH 9 in stream water (Marsella et al. 2000)
Aerobic microbial halftime (soil/water)	25.7 days for DFB; 39.7 days for 4-chlorophenylurea (Dzialo and Maynard 1999) 50 hours [2.1 days] (Walstra and Joustra 1990) 5.4 days in water, 8.6 days in sediment (Willard 2000a)
Anaerobic microbial halftime (soil/water)	34 days (Thus et al. 1991)
Water halftime (NOS)	0.97 (0.77-1.16) days without aeration (Anton et al. 1993)
Henry's law constant	0.00047 Pa m^3/mol at 25°C (USDA/ARS 1995) 0.234 ±0.002 Pa×m^3/mole at 20°C (Mabury and Crosby 1996)

[1] Specific environmental fate parameters used in modeling are discussed in Section 3.2.
[2] Reflects initial losses. Remaining DFB much more persistent.

Table 2-2: Commercial formulations of diflubenzuron [1]

Formulation (Supplier)	Type of formulation	%DFB (w/w) [2] (Concentration)	Application Rates [3] Single	Application Rates [3] Total for year	Uses
Adept (Uniroyal)	Water Soluble Bags	25%	N/A	N/A	Ornamentals
Dimilin 2L (Uniroyal)	Aqueous flowable	22% (2 lbs/gallon)	2-16 fl oz/acre	24 fl oz/acre	Trees and various crops
Dimilin 4L (Uniroyal)	**Liquid**	**40.4 % (4 lbs/gallon)**	**0.5-2 fl oz/acre**	**2 fl oz/acre**	**Forests, ground or aerial.**
Dimilin 25W [4] (Uniroyal)	**Wettable powder**	**25%**	**1-4 oz/acre**	**4 oz/acre**	
Dimilin SC (Uniroyal)	Liquid	40.4 % (4 lbs/gallon)	N/A	N/A	Mushrooms and ornaments
Micromite 25W [5] (Uniroyal)	**Wettable powder**	**25%**	**1-4 oz/acre**	**4 oz/acre**	**Forests, ground or aerial.**
Micromite 25WS (Uniroyal)	Water Soluble Bags	25%	1.25 lbs/acre	3.75 lbs/acre	Citrus crops, ground or aerial
Micromite 25WGS (Uniroyal)	Water Dispersible Granules	80%	6.25 oz/acre	18.75 oz/acre	Citrus crops, ground or aerial

[1] Source: Specimen labels from C&P Press, 2004. Only products in bold font are labeled for gypsy moth.
[2] The remainder of the product formulation is classified as *inerts*. See text for discussion.
[3] All application rates are expressed in amount (lb or oz) of formulation not amounts of active ingredient per acre. N/A indicated that the product is not labeled for broadcast applications. For products labeled for gypsy moth, the range of application rates are those that apply to the gypsy moth.
[4] A separate formulation is available for mushrooms and ornamentals.
[5] The registration for this formulation has been canceled (U.S. EPA/OPP 2002b)

TABLE 2-3: Use of diflubenzuron by USDA from 1995 to 2002 for Suppression, Eradication, and Slow the Spread [1]

Year	Suppression	Eradication	Slow the Spread	Total
1995	161,231			161,231
1996	111,362	6	1,248	112,616
1997	16,447			16,447
1998	757			757
1999	5,275		1,047	6,322
2000	18,090			18,090
2001	187,784		650	188,434
2002	131,601		3,938	135,539
2003	25,124			25,124
Total Acres	657,671	6	6,883	664,560
% of Total	98.96%	0.001%	1.04%	

[1] Source: ***GMDigest*,** Morgantown, WV (http://na.fs.fed.us/wv/gmdigest/)

Table 3-1: Chemical and site parameters used in GLEAMS modeling for diflubenzuron.

Chemical Specific Parameters

Parameter	Clay	Loam	Sand	Comment/ Reference
Halftimes (days)				
Aquatic Sediment	34	34	34	Thus et al. 1991
Foliar	9.3	9.3	9.3	Sundaram 1986, 1996
Soil	10	1.1	2.1	Note 1
Water		5.4		Note 2
Ko/c, mL/g		8700		Note 3
K_d, mL/g	261	130	26.1	Note 4
Water Solubility, mg/L		0.0926		Mabury and Crosby 1996, field sample
Foliar wash-off fraction		0.5		Note 5
Fraction applied to foliage		0.8		
Fraction applied to soil		0.2		

Note 1 Value for sand taken as reported half-time of 50 hours (2.0833 days) taken from Walstra and Joustra 1990. Value for loam taken as reported half-time in silt-loam from Thus and van der Laan-Straathof 1994. No studies on aerobic soil metabolism in clay were found. The value of 10 days is taken from Knisel and Davis (2000) as an upper range.

Note 2 Value for microbial halftime in water from Willard 2000a. Halftimes may be substantially less under conditions where photolysis is the principal route of degradation. See Table 2-1.

Note 3 A very wide range of Koc values (about 135 to 10,000) have been reported (see Table 2-1). The value of 8700 is recommended by USDA/ARS (1995) and is close to the value of 10,000 recommended by Knisel and Davis (2000).

Note 4 Based on the general relationship: $Kd = Koc \times OC$ using OC values of 0.003 for sand, 0.015 for loam, and 0.030 for clay (SERA 2003b).

Note 5 This is highly variable. Knisel and Davis (2000) recommend 0.05. The higher value of 0.5 is consistent with the field studies by Sundaram and Sundaram (1994) and Wimmer et al. (1993).

Site Parameters
(see SERA 2004, TD 2004-02.04a dated February 8, 2004 for details)

Pond	1 hectare pond, 2 meters deep, with a 0.01 sediment fraction. 10 hectare square field (1093' by 1093') with a root zone of 12 inches.
Stream	Base flow rate of 710,000 L/day with a flow velocity of 0.08 m/second or 6912 meters/day. 10 hectare square field (1093' by 1093') with a root zone of 12 inches.

Table 3-2: Summary of modeled concentrations of diflubenzuron in streams (all units are µg/L or ppb).

Annual Rainfall (inches)	Rainfall per Event (inches)[1]	Clay Average	Clay Maximum	Loam Average	Loam Maximum	Sand Average	Sand Maximum
		Concentration per lb/acre applied (from GLEAMS)					
5	0.14	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
10	0.28	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
15	0.42	0.04113	5.17705	0.00000	0.00000	0.00000	0.00000
20	0.56	0.11543	14.59505	0.00000	0.00000	0.00000	0.00000
25	0.69	0.20602	26.22114	0.00000	0.00000	0.00000	0.00000
50	1.39	0.60485	81.46441	0.00000	0.00000	0.00000	0.00002
100	2.78	1.02559	156.23308	0.03588	11.68278	0.00000	0.00028
150	4.17	1.04171	199.48431	0.09107	29.67516	0.00000	0.00105
200	5.56	0.97117	229.82322	0.15544	50.70660	0.00001	0.00258
250	6.94	0.88544	253.52663	0.22002	71.88424	0.00045	0.13780
	Application rate:	**0.0624**	lbs/acre				
		Concentration at above application rate					
5	0.14	0	0	0	0	0	0
10	0.28	0	0	0	0	0	0
15	0.42	0.003	0.32305	0	0	0	0
20	0.56	0.007	0.91073	0	0	0	0
25	0.69	0.0129	1.6362	0	0	0	0
50	1.39	0.0377	5.08338	0	0	0	0
100	2.78	0.064	9.74894	0.002	0.72901	0	0
150	4.17	0.065	12.4478	0.006	1.85173	0	0
200	5.56	0.0606	14.341	0.01	3.16409	0	0
250	6.94	0.0553	15.8201	0.0137	4.48558	0	0.009

[1] Rain is assumed to occur at the same rate every 10th day – i.e., 36 rainfall events per year.

Table 3-3: Summary of modeled concentrations of diflubenzuron in ponds (all units are µg/L or ppb)

Annual Rainfall (inches)	Rainfall per Event (inches)[1]	Clay		Loam		Sand	
		Average	Maximum	Average	Maximum	Average	Maximum
		Concentration per lb/acre applied (from GLEAMS)					
5	0.14	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
10	0.28	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
15	0.42	0.00704	0.07849	0.00000	0.00000	0.00000	0.00000
20	0.56	0.01700	0.26465	0.00000	0.00000	0.00000	0.00000
25	0.69	0.02989	0.56583	0.00000	0.00000	0.00000	0.00000
50	1.39	0.11171	3.32693	0.00000	0.00000	0.00000	0.00000
100	2.78	0.29257	12.37300	0.01577	1.63558	0.00000	0.00007
150	4.17	0.39616	23.59907	0.04933	5.81660	0.00000	0.00033
200	5.56	0.45379	35.86106	0.09695	12.41986	0.00001	0.00096
250	6.94	0.48619	48.35946	0.15210	20.70574	0.00035	0.05865
	Application rate:	**0.0624**	lbs/acre				
		Concentration at above application rate					
5	0.14	0	0	0	0	0	0
10	0.28	0	0	0	0	0	0
15	0.42	0.0004	0.0049	0	0	0	0
20	0.56	0.00106	0.016514	0	0	0	0
25	0.69	0.00187	0.035308	0	0	0	0
50	1.39	0.00697	0.2076004	0	0	0	0
100	2.78	0.018256	0.7720752	0.001	0.1020602	0	0
150	4.17	0.02472	1.472582	0.00308	0.3629558	0	0
200	5.56	0.028317	2.2377301	0.00605	0.7749993	0	0
250	6.94	0.030338	3.0176303	0.00949	1.2920382	0	0.00366

[1] Rain is assumed to occur at the same rate every 10^{th} day – i.e., 36 rainfall events per year.

Table 3-4: Chemical and site parameters used in GLEAMS modeling for 4-chloroaniline.

Chemical Specific Parameters

Parameter	Clay	Loam	Sand	Comment/ Reference
Halftimes (days)				
Aquatic Sediment		150		Note 2
Foliar		0.16		Note 2
Soil		37.5		Note1
Water		151		Note 2
Ko/c, mL/g		72		Note 1
K_d, mL/g	2.2	1.1	0.22	Note 3
Water Solubility, mg/L		3900		Note 1
Foliar wash-off fraction		0.5		
Coefficient of transformation		0.41		Note 4

Note 1 Estimated from EPI-Suite (Meylan and Howard 1998, 2000)

Note 2 WHO 2003. Foliar halftime is not given explicitly in WHO (2003) and is estimated here based on the atmospheric halftime of 3.9 hours.

Note 3 Based on Kd = Ko/c × OC, where OC is the proportion of organic carbon. The OC in sand, loam, and clay is taken as 0.003 for sand, 0.015 for loam, and 0.030 for clay (SERA 2004).

Note 4 This is the ratio of the molecular weight of chloroaniline (127.57) to that of diflubenzuron (310.69). See discussion by Knisel and Davis (2000, p. 110).

Table 3-5: Summary of modeled concentrations of 4-chloroaniline in streams (all units are µg/L or ppb)

Annual Rainfall (inches)	Rainfall per Event (inches)[1]	Clay Average	Clay Maximum	Loam Average	Loam Maximum	Sand Average	Sand Maximum
		Concentration per lb/acre applied (from GLEAMS)					
5	0.14	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
10	0.28	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
15	0.42	0.06559	4.19361	0.00048	0.01145	0.11234	2.57651
20	0.56	0.15452	10.45786	0.01616	0.32734	0.36403	10.48046
25	0.69	0.22436	15.84683	0.03969	0.85101	0.55917	19.16073
50	1.39	0.31156	27.90970	0.16080	4.59647	0.77622	44.23856
100	2.78	0.29226	30.80407	0.22906	9.17859	0.59128	52.72812
150	4.17	0.13293	24.52481	0.20128	9.67567	0.45074	51.02312
200	5.56	0.06009	14.09093	0.16267	8.73307	0.36145	49.79360
250	6.94	0.01924	5.74944	0.12680	7.21420	0.30139	47.06395
	Application rate:	**0.0624**	lbs/acre				
		Concentration at above application rate					
5	0.14	0	0	0	0	0	0
10	0.28	0	0	0	0	0	0
15	0.42	0.00409	0.2616813	0	0.0007	0.00701	0.1607742
20	0.56	0.00964	0.6525705	0.00101	0.020426	0.022715	0.6539807
25	0.69	0.014	0.9888422	0.00248	0.053103	0.034892	1.1956296
50	1.39	0.019441	1.7415653	0.010034	0.2868197	0.048436	2.7604861
100	2.78	0.018237	1.922174	0.014293	0.572744	0.036896	3.2902347
150	4.17	0.00829	1.5303481	0.01256	0.6037618	0.028126	3.1838427
200	5.56	0.00375	0.879274	0.010151	0.5449436	0.022554	3.1071206
250	6.94	0.0012	0.3587651	0.00791	0.4501661	0.018807	2.9367905

[1] Rain is assumed to occur at the same rate every 10th day – i.e., 36 rainfall events per year.

Table 3-6: Summary of modeled concentrations of 4-chloroaniline in ponds (all units are µg/L or ppb)

Annual Rainfall (inches)	Rainfall per Event (inches)[1]	Clay Average	Clay Maximum	Loam Average	Loam Maximum	Sand Average	Sand Maximum
		Concentration per lb/acre applied (from GLEAMS)					
5	0.14	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
10	0.28	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
15	0.42	0.31929	0.69851	0.00288	0.00477	0.65741	1.11311
20	0.56	0.56688	1.80242	0.07465	0.15746	1.72523	4.20894
25	0.69	0.74573	2.90175	0.16734	0.40004	2.48876	7.61750
50	1.39	1.04158	6.43073	0.63473	2.28508	3.46266	18.05225
100	2.78	1.01591	8.41740	0.97319	5.00787	2.89735	23.03849
150	4.17	0.60259	6.77759	0.90309	5.52346	2.34727	22.92303
200	5.56	0.29679	4.08394	0.75792	5.16526	1.96069	22.29465
250	6.94	0.10055	1.77278	0.60774	4.47424	1.68309	21.01092
	Application rate:	**0.0624**	lbs/acre				
		Concentration at above application rate					
5	0.14	0	0	0	0	0	0
10	0.28	0	0	0	0	0	0
15	0.42	0.019924	0.043587	0.0002	0.0003	0.041022	0.069458
20	0.56	0.035373	0.112471	0.00466	0.00983	0.1076544	0.2626379
25	0.69	0.046534	0.1810692	0.010442	0.024963	0.1552986	0.475332
50	1.39	0.064995	0.4012776	0.039607	0.142589	0.21607	1.1264604
100	2.78	0.063393	0.5252458	0.060727	0.3124911	0.1807946	1.4376018
150	4.17	0.037602	0.4229216	0.056353	0.3446639	0.1464696	1.4303971
200	5.56	0.01852	0.2548379	0.047294	0.3223122	0.1223471	1.3911862
250	6.94	0.00627	0.1106215	0.037923	0.2791926	0.1050248	1.3110814

[1] Rain is assumed to occur at the same rate every 10th day – i.e., 36 rainfall events per year.

Table 3-7: Estimated Environmental Concentrations (µg/L or ppb) of diflubenzuron in ponds and streams.

Scenario		Peak	Long-Term Average
MODELING FOR THIS RISK ASSESSMENT (0.0624 lb/acre or 70 g/ha)			
Stream			
	Direct Spray [1]	5.7	N/A
	100 Foot buffer [1]	0.11	N/A
	GLEAMS (Table 3-2)	2 (<0.01 to 16)	0.01 (0 to 0.06)
Pond			
	Direct Spray [2]	3.5	N/A
	100 Foot buffer [2]	0.07	N/A
	GLEAMS (Table 3-3)	0.2 (<0.005 to 3) at 0.06 lb/ac	0.007 (0 to 0.03) at 0.06 lb/ac
OTHER MODELING			
USDA (1995)		16.01 (stream, direct spray) 2.76 to 13.14 (stream, runoff) 1.22 (pond)	N/A
U.S. EPA/OPP 1997a. Pond: citrus crops		3.4 ppb at 6x 0.06 lb/ac 8.1 ppb at 0.67 lb/ac	0.74 ppb at 6x 0.06 lb/ac 0.87 ppb at 0.67 lb/ac
U.S. EPA/OPP 1997a. Pond: direct applications to water in forestry		11.7 ppb at 0.05 lb/ac 22.8 ppb at 0.07 lb/ac 46.2 ppb at 0.15 lb/ac 91.8 ppb at 0.32 lb/ac	N/A
Harned and Relyea 1997		Peak concentration of 1 ppb at an application rate of 350 g/ha. Longer term concentration of about 0.1 ppb. See text for discussion.	
Schocken et al. 2001		Peak concentrations of about 0.2 to 0.3 ppb in ponds and 0.9 ppb in steams at an application rate of 0.125 lb/acre. See text for discussion.	

[1] See Worksheet 10b
[2] See Worksheet 10a

Table 3-8: Concentrations of diflubenzuron in surface water used in this risk assessment (see Section 3.2.3.4.6 for discussion).

At application rate:	**0.0624**	**lb/acre**	
		Peak Concentration (ppb or µg/L)	Longer Term Concentration (ppb or µg/L)
	Central	0.4	0.02
	Lower	0.01	0.001
	Upper	16	0.1
Water contamination rate [1]		**mg/L per lb/acre applied.**	
		Peak Concentration (mg/L per lb/acre)	Longer Term Concentration (mg/L per lb/acre)
	Central	6.41e-03	3.21e-04
	Lower	1.60e-04	1.60e-05
	Upper	2.56e-01	1.60e-03

[1] Water contamination rates – concentrations in units of mg/L expected at an application rate of 1 lb/acre. These values are entered into Worksheet A04 for diflubenzuron. This rate is adjusted to the program application rate in all worksheets involving exposure to contaminated water.

Table 3-9: Concentrations of 4-chloroaniline in surface water used in this risk assessment (see Section 3.2.3.4.7 for discussion).

At application rate: 0.0624 lb/acre		
	Peak Concentration (ppb or µg/L)	Longer Term Concentration (ppb or µg/L)
Central	0.5	0.05
Lower	0.00003	0.0002
Upper	3	0.2
Water contamination rate [1] mg/L per lb/acre applied.		
	Peak Concentration (mg/L per lb/acre)	Longer Term Concentration (mg/L per lb/acre)
Central	8.01e-03	8.01e-04
Lower	4.81e-07	3.21e-06
Upper	4.81e-02	3.21e-03

[1] Water contamination rates – concentrations in units of mg/L expected at an application rate of 1 lb/acre. These values are entered into Worksheet A04 for 4-chloroaniline. This rate is adjusted to the program application rate in all worksheets involving exposure to contaminated water.

Table 4-1: Summary of field studies on the effects of diflubenzuron on terrestrial invertebrates [1]

Range of Application Rates (g/ha)	Species: No Adverse Effects	Species: Adverse Effects
<20	ants (Catangui et al. 1996) *Cotesia melanoscelus* (GM parasitic wasp) (Webb et al. 1989)	grasshoppers (Jech et al. 1993)
20 - <40	lacewing and beetles (Ables et al. 1977) carabids, crickets, lice (Butler et al. 1997) honey bee (Matthenius1975) honey bee [×8](Robinson 1978,1979)	gypsy moth and macrolepidoptera (Butler et al. 1997) grasshopper (Everts 1990) *Apanteles melanoscelus* # (GM parasitic wasp) (Madrid and Stewart1981)
40 - < 60	lacewing and beetles (Ables et al. 1977)	
60 - < 100	*Ooencyrtus kuvanae* (GM parasitic wasp) (Brown and Respicio 1981) lacewing and beetles (Deakle and Bradley1982) honey bee (Matthenius1975) sucking herbivorous insects, microlepidoptera, and predaceous arthropods(Martinat et al. 1988) spiders* and orthopteroid*(Martinat et al. 1993) mites and springtails (Perry et al. 1997) spiders** (Perry et al. 1997) non-lepidopteran insects (Sample et al. 1993a,b) mites* and collembolans* (Van Den Berg 1986)	grasshopper (Everts 1990) grasshoppers, moths, carabid beetles (Butler 1993) lepidoptera (Sample et al. 1993a,b) macrolepidoptera and other herbivorous insects (Martinat et al. 1988) Yellow jacket wasp (Barrows et al. 1994)
100 - < 150	ants (Weiland 2000) *Psylla* parasites and predators (Westigard 1979) lacewing and beetles (Ables et al. 1977) honey bee (Emmett and Archer 1980) honey bee [×8](Robinson 1978,1979)	soil mites (Blumberg 1986) Yellow jacket wasp (Weiland 2000)
150 - < 200	various arthropod predators (Keever et al. 1977)	lepidopteran egg mortality (low) (Kumar et al. 1994) mites (Marshall 1979)
200 - < 300	ants (Weiland 2000) carabid beetles (Heinrichs et al. 1979)	lacewing and beetles (Ables et al. 1977) mites (Marshall 1979) borer weevil (Schroeder 1996) predatory damsel bugs and sucking insects (Turnipseed et al. 1974) Yellow jacket wasp (Weiland 2000) *Psylla* parasites and predators (Westigard 1979) flying insects, esp. midges, gnats, and mosquitoes (Wilson and Wan 1977a)
≥ 300	honey bee (Buckner et al. 1975) honey bee (Emmett and Archer 1980) honey bee and other beneficial insects (Schroeder 1980)	lepidopteran egg mortality (high) (Kumar et al. 1994) *Psylla* parasites and predators (Westigard 1979)

[1] Studies summarized in Appendix 3a. See text for discussion. A single asterisk (*) indicates transient or equivocal effects. A double asterisk (**) indicates effects that were secondary to decrease in prey. The # symbol indicates an effect clearly due to toxicity. GM used as abbreviation for gypsy moth. Multiple applications are indicated in brackets with a × symbol followed by the number of applications.

Table 4-2: Summary of modeled concentrations of diflubenzuron in soil (all units are mg/kg or ppm)

Annual Rainfall (inches)	Rainfall per Event (inches)[1]	Clay		Loam		Sand	
		Average	Maximum	Average	Maximum	Average	Maximum
		Concentration per lb/acre applied (from GLEAMS)					
5	0.14	0.00841	0.14004	0.00092	0.11651	0.00169	0.12485
10	0.28	0.00926	0.14004	0.00106	0.11652	0.00194	0.12484
15	0.42	0.00924	0.13992	0.00106	0.11653	0.00193	0.12484
20	0.56	0.00918	0.13962	0.00106	0.11653	0.00193	0.12484
25	0.69	0.00910	0.13914	0.00106	0.11653	0.00193	0.12484
50	1.39	0.00834	0.13431	0.00106	0.11653	0.00192	0.12484
100	2.78	0.00650	0.11909	0.00104	0.11450	0.00190	0.12484
150	4.17	0.00412	0.09305	0.00099	0.10879	0.00188	0.12484
200	5.56	0.00234	0.06298	0.00091	0.09889	0.00186	0.12484
250	6.94	0.00104	0.05236	0.00080	0.08527	0.00184	0.12478
	Application rate:	**0.0624**	lbs/acre				
		Concentration at above application rate					
5	0.14	5.2e-04	0.00874	5.7e-05	0.00727	1.1e-04	0.00779
10	0.28	5.8e-04	0.00874	6.6e-05	0.00727	1.2e-04	0.00779
15	0.42	5.8e-04	0.00873	6.6e-05	0.00727	1.2e-04	0.00779
20	0.56	5.7e-04	0.00871	6.6e-05	0.00727	1.2e-04	0.00779
25	0.69	5.7e-04	0.00868	6.6e-05	0.00727	1.2e-04	0.00779
50	1.39	5.2e-04	0.00838	6.6e-05	0.00727	1.2e-04	0.00779
100	2.78	4.1e-04	0.00743	6.5e-05	0.00714	1.2e-04	0.00779
150	4.17	2.6e-04	0.00581	6.2e-05	0.00679	1.2e-04	0.00779
200	5.56	1.5e-04	0.00393	5.7e-05	0.00617	1.2e-04	0.00779
250	6.94	6.5e-05	0.00327	5.0e-05	0.00532	1.1e-04	0.00779

[1] Rain is assumed to occur at the same rate every 10th day – i.e., 36 rainfall events per year.

Table 4-3: Summary of modeled concentrations of 4-chloroaniline in soil (all units are mg/kg or ppm)

Annual Rainfall (inches)	Rainfall per Event (inches)[1]	Clay Average	Clay Maximum	Loam Average	Loam Maximum	Sand Average	Sand Maximum
		Concentration per lb/acre applied (from GLEAMS)					
5	0.14	0.00672	0.02893	0.00680	0.04917	0.00750	0.04216
10	0.28	0.00655	0.02685	0.00626	0.04550	0.00666	0.04159
15	0.42	0.00699	0.02697	0.00709	0.04556	0.00751	0.04167
20	0.56	0.00691	0.02665	0.00734	0.04562	0.00728	0.04168
25	0.69	0.00668	0.02618	0.00748	0.04566	0.00685	0.04157
50	1.39	0.00360	0.02252	0.00737	0.04582	0.00493	0.04032
100	2.78	0.00631	0.01739	0.00622	0.04519	0.00323	0.04015
150	4.17	0.00307	0.01146	0.00529	0.04326	0.00254	0.04001
200	5.56	0.00142	0.00759	0.00450	0.03994	0.00216	0.03997
250	6.94	0.00050	0.00357	0.00375	0.03540	0.00193	0.03999
	Application rate:	**0.0624**	lbs/acre				
		Concentration at above application rate					
5	0.14	4.2e-04	0.00181	4.2e-04	0.00307	4.7e-04	0.00263
10	0.28	4.1e-04	0.00168	3.9e-04	0.00284	4.2e-04	0.0026
15	0.42	4.4e-04	0.00168	4.4e-04	0.00284	4.7e-04	0.0026
20	0.56	4.3e-04	0.00166	4.6e-04	0.00285	4.5e-04	0.0026
25	0.69	4.2e-04	0.00163	4.7e-04	0.00285	4.3e-04	0.00259
50	1.39	2.2e-04	0.00141	4.6e-04	0.00286	3.1e-04	0.00252
100	2.78	3.9e-04	0.00109	3.9e-04	0.00282	2.0e-04	0.00251
150	4.17	1.9e-04	0.0007	3.3e-04	0.0027	1.6e-04	0.0025
200	5.56	8.9e-05	0.0005	2.8e-04	0.00249	1.3e-04	0.00249
250	6.94	3.1e-05	0.0002	2.3e-04	0.00221	1.2e-04	0.0025

[1] Rain is assumed to occur at the same rate every 10th day – i.e., 36 rainfall events per year.

Table 4-4: Summary of diflubenzuron toxicity values used in ecological risk assessment

Organism	Endpoint	Toxicity Value	Reference, Species
Mammals	Acute NOAEL	1118 mg/kg	Blaszcak 1997a, rats [Dimilin 2L]
	Chronic NOAEL	2 mg/kg/day	Greenough et al. 1985, dogs
Birds	Acute NOAEL	2500 mg/kg	Alsager and Cook 1975, blackbirds
	Chronic NOAEL	110 mg/kg	Beavers et al. 1990b, quail
Terrestrial arthropods		***See Table 4-5 for toxicity values***	
Soil invertebrates			
Earthworm	NOEC	780 mg/kg soil	Berends et al. 1992
Soil microorganisms			
Sensitive	50 ppm LOEC	50 ppm ÷ 10	Townshend et al. 1983
Tolerant	100 pp NOEC	100 ppm	Townshend et al. 1983
Fish Acute			
Sensitive	LC_{50}	25 mg/L	Johnson and Finley 1980, yellow perch
Tolerant	LC_{50}	500 mg/L	Reiner and Parke 1975, fathead minnow
Fish Chronic			
Sensitive	Reproductive NOEC	0.05 mg/L	Livingston and Koenig 1977, mummichog
Tolerant	Reproductive NOEC	0.1 mg/L	Cannon and Krize 1976, fathead minnow
Aquatic Invertebrates		***See Table 4-6 for toxicity values***	
Aquatic Plants			
Sensitive	NOEC for growth	0.045 mg/L	Hansen and Garton 1982a, *Selenastrum capricornutum*
Tolerant	NOEC for growth	0.38 mg/L	Thompson and Swigert 1993c, *Navicula pelliculosa*
Aquatic Microorganisms	NOEC for respiration	0.05 mg/L	Kreutzweiser et al. 2001 [4.3.3.4]

[1] NOECs are used directly when available. When only a LOEC is available, the LOEC is divided by 10 to approximate the NOEC. This is indicated by the "÷10" following the LOEC.

Table 4-5: Diflubenzuron toxicity values used in risk assessment for terrestrial arthropods (see Table 4-1 for additional details).

Organism	Endpoint	Toxicity Value[1]	Reference
Grasshoppers	Field LOAEL	22 g/ha ÷ 10	Jech et al. 1993
Apanteles melanoscelus[2]	Field LOAEL	30 g/ha ÷ 10	Madrid and Stewart1981
Macrolepidoptera	Field LOAEL	35 g/ha ÷ 10	Butler et al. 1997
Mandibulate herb. insects	Field LOAEL	70 g/ha ÷ 10	Martinat et al. 1988
Ooencyrtus kuvanae[2]	Field NOAEL	67 g/ha	Brown and Respicio 1981
Microlepidoptera	Field NOAEL	70 g/ha	Martinat et al. 1988
Predaceous arthropods	Field NOAEL	70 g/ha	Martinat et al. 1988
Sucking herbaceous insects	Field NOAEL/LOAEL	70/281 g/ha	Martinat et al. 1988/Turnipseed et al. 1974
Spiders	Field NOAEL	70 g/ha	Martinat et al. 1993
Mites and collembolans	Field NOAEL/LOAEL	70/140 g/ha	Perry et al. 1997/Blumberg 1986
ants	Field NOAEL	280	Weiland 2000
Lacewing	Field NOAEL/LOAEL	140/280 g/ha	Ables et al. 1977
Honey bee	Field NOAEL	400 g/ha	Emmett and Archer 1980

[1] Field NOAELs are used directly when available. When only a LOAEL is available, the LOAEL is divided by 10 to approximate the NOAEL. This is indicated by the "÷10" following the LOAEL.
[2] A parasitic wasp to the gypsy moth.

Table 4-6: Diflubenzuron toxicity values used in risk assessment for aquatic invertebrates.

Organism	Endpoint	Toxicity Value ppb or µg/L[1]	Reference
ACUTE (see Table 4-8 for additional details)			
Daphnia	NOEC	0.3	Corry et al. 1995
Ceriodaphnia	NOEC	0.75	Hall 1986
Copepods	NOEC	0.93	Savitz et al. 1994
crabs	NOEC	2	Cunningham and Meyers 1987
rotifers	NOEC	20	Corry et al. 1995
large insects	NOEC	2000	Lahr et al. 2001
molluscs	NOEC	125000	Wilcox and Coffey 1978
LONGER TERM (see Table 4-9 for additional details)			
Daphnia	NOEC	0.04	Surprenant 1988
stoneflies and mayflies	NOEC	0.1	Hansen and Garton 1982b
Ceriodaphnia	NOEC	0.25	Hall 1986
dragonflies	NOEC	0.7	O'Halloran and Liber 1995
ostracods	NOEC	2.5	Liber and O'Halloran 1995
coleoptera and oligochaetes	NOEC	50	Hansen and Garton 1982a
molluscs	NOEC	320	Surprenant 1989

[1] In worksheets, all concentrations in ppb are divided by 1000 to convert to concentrations in ppm or mg/L.

Table 4-7: Summary of 4-chloroaniline toxicity values used in ecological risk assessment

Organism	Duration/Endpoint	Toxicity Value	Reference, species
Mammals	Acute/Toxicity NOAEL	8 mg/kg/day	Used in HHRA
	Chronic/Toxicity NOAEL	1.25 mg/kg/day	Estimated from LOAEL of 12.5 mg/kg/day
Birds	Acute/Toxicity NOAEL	8 mg/kg/day	No data. Uses value for mammals
	Chronic/Toxicity NOAEL	1.25 mg/kg/day	No data. Uses value for mammals
Earthworms	NOEC	540 mg/kg soil	WHO 2003
Soil Microorganisms	NOEC	1000 ppm	Welp and Brummer 1999
Fish			
Acute	LC_{50}	2.4 mg/L	WHO 2003, Bluegill
Chronic	NOEC, reproduction	0.2 mg/L	Bresch et al. 1990, Zebra fish
Aquatic Invertebrates			
Acute	NOEC, mortality	0.013 mg/L	Kuhn et al 1989a
Chronic	NOEC, reproduction	0.01 mg/L	Kuhn et al 1989a
Aquatic plants	EC_{10}	0.02 mg/L	Schmidt and Schnabl 1988, green algae
Aquatic Microorganisms	NOEC (30 min)	5.1 mg/L	Ribo and Kaiser 1984, photobacteria

Table 4-8: Acute toxicity of diflubenzuron in aquatic invertebrates

Concentrations (µg/L or ppb)	No Effect Species/group [conc. ppb](Reference)	Adverse Effect Species/group [conc. ppb](Reference)
0.1 to <1	mysid shrimp[0.12] (Breteler 1987) *Daphnia* [0.3](Corry et al. 1995) *Daphnia* [0.45](Kuijpers 1988) *Ceriodaphnia* [0.75](Hall 1986) copepods [0.93](Savitz et al. 1994)	Mosquito [0.5] (Miura and Takahashi 1974) *Daphnia* [0.7](Corry et al. 1995) *Daphnia* [0.7](Kuijpers 1988) *Daphnia* [0.75, neonate](Majori et al. 1984) fairy shrimp [0.74] (Lahr et al. 2001)
1 to <10	fiddler crabs [2] (Cunningham and Meyers 1987) Horseshoe crabs[4] [5] (Weis and Ma 1987) amphipods [7] (Corry et al. 1995)	gammarids[1](Hansen and Garton 1982a) *Ceriodaphnia* [1.7](Hall 1986) copepods [1.7](Savitz et al. 1994) midges[1.8](Hansen and Garton 1982a) blue crab eggs [1.8] (Lee and Oshima 1998) grass shrimp [3.4](Tourat and Rao 1987) grass shrimp [2-3](Wilson and Costlow 1986) mysid shrimp[2.1]Nimmo et al. 1979
10 to <100	rotifers[20] (Corry et al. 1995) snails [45](Hansen and Garton 1982a)	Mayfly [10] (Miura and Takahashi 1974) Amphipods [13](Corry et al. 1995) *Daphnia* [23, adult](Majori et al. 1984) Dragonfly [50] (Miura and Takahashi 1974) Horseshoe crabs [50] (Weis and Ma 1987)
100 to <1000		beetles [100] (Miura and Takahashi 1974) fiddler crabs [200] (Cunningham and Meyers 1987) tricoptera [250] (Bradt and Williams 1990) grass shrimp[640] (Bionomics-EG&G 1975)
>1000	backswimmer[2] [2000] (Lahr et al. 2001) snail [125,000](Wilcox and Coffey 1978)	midge [560] (Julin and Sanders 1978)

[1] Macrocosm study
[2] No molting during short term exposures
[3] Litoral enclosures
[4] Marginal signs of toxicity

Table 4-9: Chronic toxicity of diflubenzuron in aquatic invertebrates

Concentrations (µg/L or ppb)	No Effect Species/group [conc. ppb](Reference)	Adverse Effect Species/group [conc. ppb](Reference)
>0.01 to 0.1	*Daphnia*[0.04]Surprenant 1988 stream inverts[1] [0.1](Hansen and Garton 1982a[1]) stoneflies and mayflies[0.1] (Hansen and Garton 1982b[1])	*Daphnia* [0.06] U.S. EPA 1997a [5] mysid shrimp[0.075]Nimmo et al. 1979 *Daphnia* [0.09]LeBlanc (1975) *Daphnia*[0.093]Surprenant 1988
>0.1 to 1	*Ceriodaphnia* [0.25](Hall 1986) mayflies, damselflies, and dragonflies[0.7] (O'Halloran and Liber 1995) mixed insects[3] [1](Liber 1995)	*Ceriodaphnia* [0.5](Hall 1986) clodacera and copopods[3][0.7] (Liber and O'Halloran 1995) copepods [0.7-0.9](Wright et al. 1996) grass shrimp (Bionomics-EG&G 1975) grass shrimp [0.7](Tourat and Rao 1987) stream inverts [1] (Hansen and Garton 1982a) stoneflies and mayflies[1] (Hansen and Garton 1982b[1])
>1 to 10	Ostracoda[3][2.5](Liber and O'Halloran 1995)	dipterans[10] (Hansen and Garton 1982a[1]) mixed insects[3] [1.9](Liber 1995) Ostracoda[3][7](Liber and O'Halloran 1995) mayflies, damselflies, and dragonflies[2.5] (O'Halloran and Liber 1995)
>10 to 100	coleoptera, oligochaetes, and gastropods[1][50] (Hansen and Garton 1982a) rotifers[3][30](Liber and O'Halloran 1995)	
>100 to 1000	clams [320](Surprenant 1989)	

[1] Macrocosm study
[2] No molting during short term exposures
[3] Litoral enclosures
[4] Marginal signs of toxicity
[5] Cited in U.S. EPA (1997a) as Beltsville Lab Test 2424. This study is not identified by MRID number or otherwise described.

Table 4-10: Summary of field studies on the effects of diflubenzuron on aquatic invertebrates [1]

Range of Application Rates (g/ha)	Species [conc ppb](Reference)		
	No Adverse Effects	Adverse Effects with Observed Recovery	Adverse Effects with No Observed Recovery
>0.1 to 1	pond invertebrates [0.2] Ali et al. 1988		
>1 to 10	shrimp, cyclops, and some cladocera (*Bosmina*), worms [3.7] (Ali and Mulla 1978a) worms [7.4] (Ali and Mulla 1978a)	zooplankton mortality and insect emergence [1.8](Wan and Wilson 1977) daphnids and copepods [3.7] (Ali and Mulla 1978a) copepods, shrimp [7.4] (Ali and Mulla 1978a) cladocera, copepods [2.5 to 10](Apperson et al. 1977) cladocerans, copepods and rotifers[10](Boyle et al. 1996)	amphipods [3.7] (Ali and Mulla 1978a) amphipods, daphnids [7.4] (Ali and Mulla 1978a)
>10 to 100	rotifers [13](Colwell and Schaefer 1980)	cladocera [10.4](Lahr et al. 2000) cladocera incl. *Bosmina*, copepods, [13](Colwell and Schaefer 1980)	shrimp [10.4](Lahr et al. 2000)

[1] The concentrations given in braces [] represent peak or typical concentrations shortly after exposure. In all cases, post-application concentrations will decline. See text for discussion.

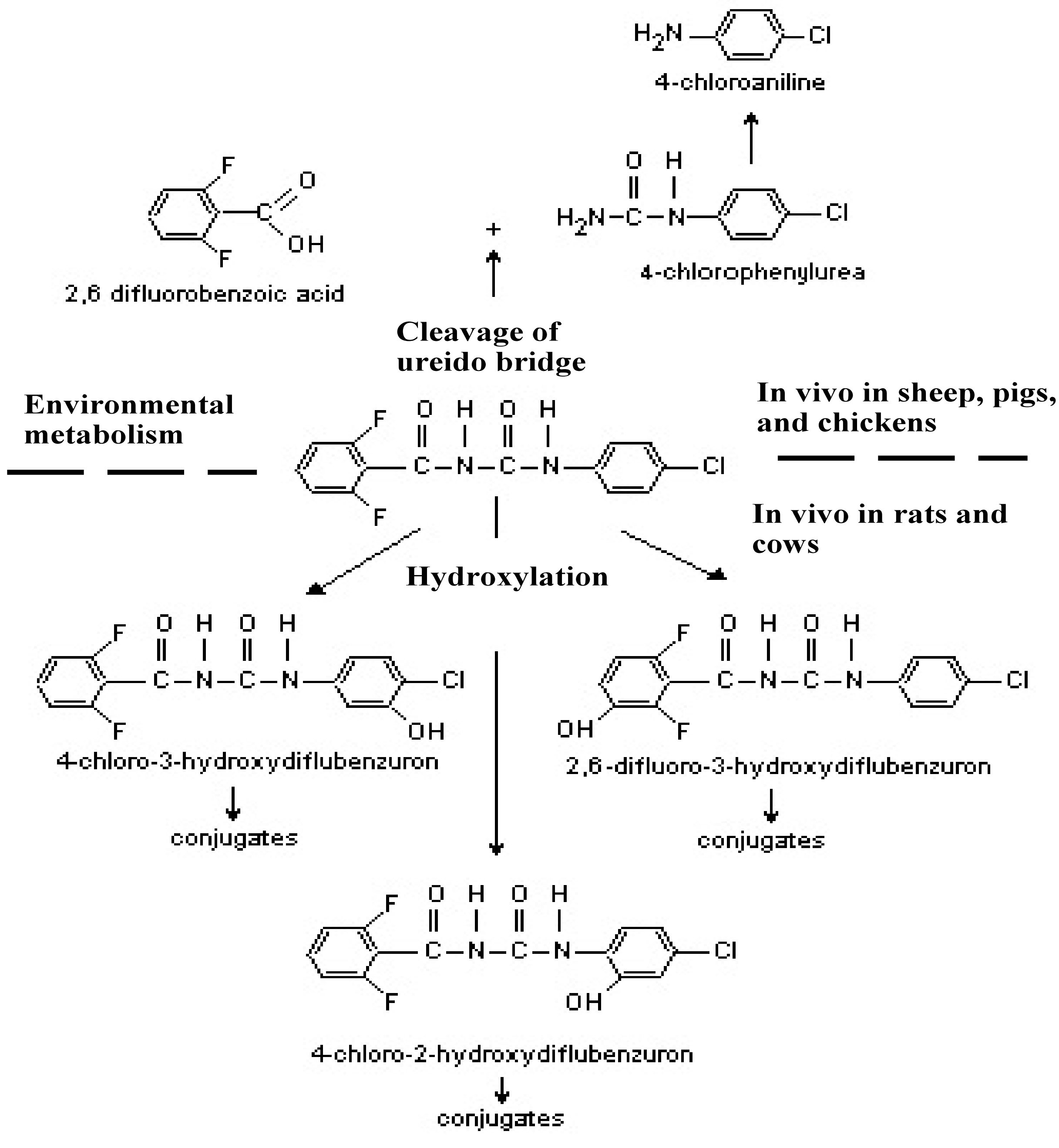

Figure 3-1: Overview of the *In vivo* and environmental metabolism of diflubenzuron (adapted from WHO 1996).

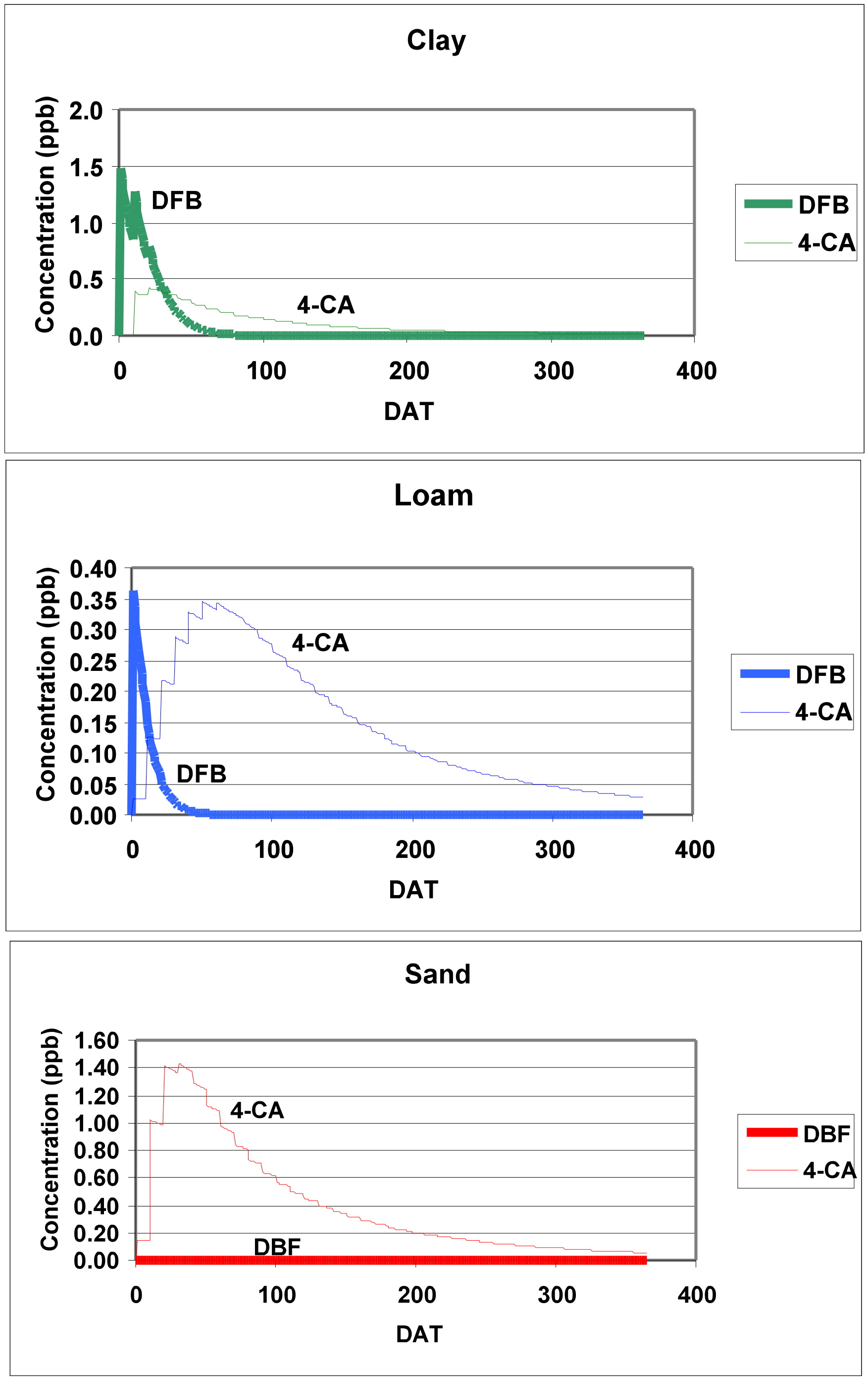

Figure 3-2: Modeled concentrations of diflubenzuron (thick lines) and 4-chloroaniline (thin lines) in ponds at an annual rainfall rate of 150 inches (see text for discussion).

APPENDICES

Appendix 1: Toxicity of diflubenzuron and 4-chloroaniline to experimental mammals

Animal	Dose/Exposure	Response	Reference
Oral			
		Diflubenzuron	
Acute Oral			
Mouse and rat	LD_{50}, technical grade	> 4640 mg/kg	WHO 1996
Mouse and rat	LD_{50},90% concentrate	> 5000 mg/kg	WHO 1996; U.S. EPA 1997a
Mouse and rat	LD_{50}, Du 112307 W.P. 25% (Dimilin WP 25%)	> 40,000 mg Dimilim/kg > 10,000 mg DFB/kg A marginal effects on methemoglobin levels.	Koopman 1977 MRID 00070025
Rat, Sprague-Dawley, 5 males(290-330 g) and 5 females (215-233 g), 9- to 12-weeks old	single gavage dose of 5000 mg/kg Dimilin 2L (22.36% pure)	No mortality. Except for moist rales in two treated rats on the day of dosing, no clinical signs of toxicity, all rats gained weight both 7 and 14 days after dosing, and no abnormalities observed during macroscopic postmortem evaluation. NOEC = 5000 mg/kg as Dimilin 2L 1118 mg/kg as DFB	Blaszcak 1997a MRID 44574504
Subchronic Oral			
Cat (NOS)	0, 30, 100, 300, or 1000 mg/kg/day diflubenzuron for 3 weeks	NOEC (Hb) >1250 mg/kg/day NOEC (%PCV) not estimated NOEC (RBC) not estimated NOEC (reticulocyte count) not estimated NOEC (MetHb) = 30 mg/kg/day NOEC (SulpHb) = 3 mg/kg/day (calculated with regression analysis) NOEC (spleen weight) >1000 mg/kg/day	Keet et al. 1982

Appendix 1: Toxicity of diflubenzuron and 4-chloroaniline to experimental mammals

Animal	Dose/Exposure	Response	Reference
Dogs, beagle, pure-bred, 15 males and 15 females	dietary levels of 10, 20, 40 or 60 ppm (**actual dosages levels of 0.42, 0.84, 1.64, or 6.24 mg/kg/day**) Du 112307 for 13 weeks	No mortality; no clinical signs of toxicity, no adverse effects on food or water consumption, no ocular effects, no treatment-related macroscopic post mortem findings, no adverse effects on organ weights, and no morphological abnormalities considered to be treatment related. At 2 weeks, all laboratory tests were within normal limits; at 4 and 6 weeks, SAP and SGPT were increased among some dogs at 40 or 160 ppm; after 6 weeks, the presence of **methaemoglobin** and other abnormal haemoglobin pigments was apparent in dogs at 160 ppm; after 12 weeks, one dog at 160 ppm had an elevated SGPT level and one dog at 160 ppm and one dog had a greater **methaemoglobin** value than all the other dogs. NOEC = 20 ppm	Chesterman et al. 1974 MRID 00038706
Dog (NOS)	0, 2, 10, 50, or 250 mg/kg/day diflubenzuron for 13 weeks	NOEC (Hb) = 10 mg/kg/day NOEC (%PCV) not estimated NOEC (RBC) >250 mg/kg/day NOEC (reticulocytes) = 50 mg/kg/day NOEC (MetHb) = 50 mg/kg/day NOEC (SulpHb) = 10 mg/kg/day NOEC (spleen weight) not estimated	Keet et al. 1982

Appendix 1: Toxicity of diflubenzuron and 4-chloroaniline to experimental mammals

Animal	Dose/Exposure	Response	Reference
Mice, 40/sex/dose group	in diet concentrations of 0, 80, 400, 2000, 10,000, or 50,000 ppm 97.2% pure, technical grade, air-milled diflubenzuron for 14 weeks with 7-week interim sacrifice. The **calculated mean intake** of diflubenzuron was 9.7, 50.7, 240, 1174, or 6114 mg/kg/day (males) and 11.1, 54.9, 288, 1393, or 7506 mg/kg/day (females) [*cf* page 27]	No treatment-related mortality throughout the study; no significant, treatment-related changes in food consumption or body weight; numerous hematological effects, including statistically significant increases (see pg 29) in Met Hb% and Sulph Hb% in males and females at 400-50,000 ppm; statistically significant increase in spleen weight in males and females at 400-50,000 ppm; statistically significant increase in liver weight of males and females at 2000-50,000 ppm;	Colley et al. 1981 MRID 00114330
Rats, Swiss-albino, males, weighing 90 g, 5/dose group	gavage doses of 96.7 mg/kg of Dimilin in corn oil solution each day for 48 days (i.e., total of 4640 mg/kg of Dimilin)	Mean hemoglobin concentration (g/100 mL blood) was significantly lower than that of controls; mean hematocrit percent of the Dimilin was significantly higher than that of controls.	Berberian and Enan 1989
Rats, Sprague-Dawley, 40/sex/ dose group	in diet concentrations of 160, 400, 2000, 10,000, or 50,000 ppm technical grade diflubenzuron for 90 days	No mortality; no clinical signs of toxicity, no adverse effects on body weight or food consumption. Treatment-related adverse effects included a significant increase in **methemoglobin** at weeks 7 and 13 in males at 400, 2000, 10,000, and 50,000 ppm and in females at all dose levels, as well as significant increases in sulfhemoglobin at week 7 in 50,000 ppm males and 10,000 and 50,000 ppm females, and at week 13 in males at 10,000 and 50,000 ppm and in females at 2000, 10,000, and 50,000 ppm. Other pathological, treatment-related changes included decreases in hematocrit and hemoglobin values and the erythrocyte count and an increase in the number of reticulocytes, increases in absolute liver weight and absolute and relative spleen weights, and enlargement of the spleen. NOEC (for males only) = 160 ppm	Burdock et al. 1980 MRID 00064550

Appendix 1: Toxicity of diflubenzuron and 4-chloroaniline to experimental mammals

Animal	Dose/Exposure	Response	Reference
Sheep (NOS)	0, 25, 125, or 500 mg/kg/day diflubenzuron for 13 weeks.	NOEC (Hb) >500 mg/kg/day NOEC (%PCV) >500 mg/kg/day NOEC (RBC) >500 mg/kg/day NOEC (reticulocyte count) not estimated NOEC (MetHb) = 25 mg/kg/day NOEC (SulpHb) = 3 mg/kg/day (calculated with regression analysis) NOEC (spleen weight) >500 mg/kg/day	Keet et al. 1982
Sheep	0, 500, 2500 and 10,000 mg/kg in feed for 13 weeks.	No treatment-related effects were observed on food consumption, body weight gain, hematological parameters or urinalysis. Increase in MetHb and SulfHb and a reduction in the weight of the thyroid.	Ross et al. 1977

Appendix 1: Toxicity of diflubenzuron and 4-chloroaniline to experimental mammals

Animal	Dose/Exposure	Response	Reference
Chronic Oral			
Dogs, beagle, 5/sex/dose group	daily oral administration of 0, 2, 10, 50, or 250 mg/kg/bw technical grade, air-milled diflubenzuron via gelatin capsules, 7 days/week for 52 consecutive weeks.	There were no clinical signs of toxicity, no treatment-related effects on body weight, food consumption, or water consumption; no ocular effects; there were treatment-related *marginal but statistically significant* increases in met Hb% and sulph Hb% (at ≥10 mg/kg/day bw) and in Heinz body counts (at 50 and 250 mg/kg/day bw); there was a marginal but consistent compound-related decrease in MCHC (at ≥10 mg/kg/day bw); histopathological changes included increased spleen weight (statistically significant in males at ≥50 mg/kg/day bw), increased liver weight (significant at ≥50 mg/kg/day bw in males and females) and hemosiderin deposition in the liver. The investigators conclude: *the no effect level demonstrated...was 2 mg/kg/day. However, this level is based on minor hematological changes of no toxicological significance seen at 10 mg/kg/day. Hence it is more realistic to consider the no effect level based on organ weights and histopathology as being at least 10 mg/kg/day.* Mortality: 2 females dogs died during the study. One dog at 250 mg/kg/bw) was sacrifice *in extremis* at week 33 due to liver failure and the other dog (at 50 mg/kg/day bw) died during week 40 due to bronchopneumonia. These effects were not attributable to treatment.	Greenough et al. 1985 MRID 00146174 **[This study is the basis for the chronic RfD]**

Appendix 1: Toxicity of diflubenzuron and 4-chloroaniline to experimental mammals

Animal	Dose/Exposure	Response	Reference
Mice, CFLP, approximately 8 weeks old, 36/sex/dose group	In diet concentrations of 16, 80, 400, 2000, or 10,000 ppm (**intake values = 1.24, 6.40, 32. 16, 163.29, or 835.55 mg/kg/day for males and 1.44, 7.26, 35.38, 186.59, or 958.51 mg/kg/day for females**) technical grade DFB (97.6% pure) for 91 weeks.	Treatment-related clinical sign of toxicity was a blue/gray discoloration of the extremities and dark eyes in all mice at 10,000 ppm, a majority of mice at 2000 or 400 ppm, and in a number of mice at 80 ppm. The NOEC for this effect =16 ppm. No obvious treatment-related effect on mortality was observe; no obvious treatment-related effect on food consumption, body weight, food efficiency, or water intake was observed; treatment-related changes were principally associated with oxidation of the haemoglobin or with hepatocyte changes. DFB is not carcinogenic to DFLP mice.	Keet et al. 1984b
Mice, 88/sex/dose group	in diet concentrations of 0, 16, 80, 400, 2000, or 10, 000 ppm 97.6% pure difllubenzuron for 91 weeks. The **calculated mean intake** of diflubenzuron was 1.24, 6.40, 32.16, 163.29, or 835.55 mg/kg/day (males) and 1.44, 7.26, 35.38, 186.59, or 958.51 mg/kg/day (females) [*cf* page 47]	No treatment-related mortality throughout the study, no evidence of tumorigenic effect; treatment-related effects were primarily associated with oxidation of haemoglobin (**treatment-related increases in Met Hb% were recorded from week 26 onwards and in Sulph Hb% from week 52 onwards; these changes principally affected mice at 80-10,000 ppm and were dose-related in degree**) or with hepatocyte changes (**an increased incidenc of hepatocyte enlargement was observed in males and females at 400-10,000 ppm**).	Colley et al. 1984 MRID 00142490
Rats, Sprague-Dawley, 50/sex/dose group	in diet concentrations of 0, 156, 625, 2500, or 10,000 ppm technical grade diflubenzuron (97.6% a.i.) for 104 weeks.	No treatment related effects with regard to mortality or clinical observations; no evidence of carcinogenicity after 2 years of dietary exposure to diflubenzuron; statistically significant dose-related increases in met Hb% and sulph Hb% in males and females; numerous hematological effects; histomorphological changes observed in sections of the spleen, liver, and bone marrow; in general adverse effects were most pronounced at the 2500 and 10,000 dose levels.	Burdock 1984 MRID 00145467

Appendix 1: Toxicity of diflubenzuron and 4-chloroaniline to experimental mammals

Animal	Dose/Exposure	Response	Reference
Rats, Sprague-Dawley, approximately 7 weeks old, 50/sex/dose group	In diet concentrations of 156, 625, 2500, or 10,000 ppm **(intake values =6.99, 28, 36, 114.35 or 463.80 mg/kg/day for males and 9.23, 37.98, 153.96, or 633.41 mg/kg/day for females)** technical grade DFB (97.6% pure) for 104 weeks.	No treatment related clinical signs observed; no obvious treatment-related effect on mortality; no obvious treatment-related effect on food consumption or body weight, except in high dose females where terminal body weight was significantly less than controls; no evidence of tumorigenic effects, treatment-related changes were principally associated with oxidation of haemoglibin or with hepatocyte changes. DFB is not carcinogenic to Sprague-Dawley CR-CD rats.	Keet et al. 1984a

Appendix 1: Toxicity of diflubenzuron and 4-chloroaniline to experimental mammals

Animal	Dose/Exposure	Response	Reference
Reproduction Studies			
Rats, Crl:CD(SD)BR	0 or 1000 mg/kg bw per day on days 6–15 of gestation	Screening assay for teratogenicity. No signs of developmental toxicity, birth defects or maternal toxicity.	Kavanagh 1988a
Rabbits, New Zealand White	0 or 1000 mg/kg bw per day on days 7–19 of gestation	Screening assay for teratogenicity. No signs of developmental toxicity, birth defects or maternal toxicity.	Kavanagh 1988b
Rats, Charles River 32/sex/dose group	in diet nominal concentrations of 0, 500, 5000, or 50,000 ppm technical diflubenzuron through two consecutive generations. F_0 generation mean intake values (weeks 1-10 *pre-mate*) were 36.2, 360, or 3755 mg/kg/day for males and 42.0, 427, or 4254 mg/kg/day for females. F_1 generation mean intake values (weeks 5-16 *pre-mate*) were 39.2, 394, or 4089 mg/kg/day for males and 44.9, 473, or 4611 mg/kg/day for females	No treatment-related morality; toxicity manifested as hematological effects characterized primarily by anemia and increases in MetHb% associated with increased spleen weight and pathological lesions of hemosiderosis of the spleen and brown pigmented Kupffer cells in the liver were observed all dose levels. Increases in MetHb ranged from about 115% in the low dose group to over 300% in the high dose group (see Section 3.3 for more complete discussion and details). Other treatment related effects on the parental rats included lower body weight gains of the F_0 generation at 50,000 ppm, with higher food intake values in males; increased water consumption among males and females at 5000 or 50,000 ppm and among males at 500 ppm. No treatment-related effects on reproductive performance at any dose level. In the F_1 generation, liter and mean pup weights of the offspring from parents in the 50,000 dose group were lower than controls. The effect was not observed in the F_2 offspring. NOEL = 50,000 ppm for reproductive function NOEL = 5000 ppm for pre-weaning development of the offspring. NOEL = >500 ppm for MetHb	Brooker 1995 MRID 43578301 NOTE: U.S. EPA (1996) appears to classify the low dose group as the LEL for MetHb but specifies the dose as 25 mg/kg/day. This error appears to be based on the use of default values for converting food concentrations to mg/kg/day doses.

Appendix 1: Toxicity of diflubenzuron and 4-chloroaniline to experimental mammals

Animal	Dose/Exposure	Response	Reference
DERMAL			
Rabbits, New Zealand white, 5 males and 5 females	Dermal application of 5000 mg/kg Dimilin 2L (22.36% pure) to closely clipped intact trunks (approximately 10% of the body surface area). Treated area covered with gauze and occlusive wrap for 24 hours.	No mortality; no pharmacological or toxicological signs of toxicity; no severe dermal effects; no abnormalities observed during postmortem macroscopic evaluation. NOEC = 5000 mg/kg	Blaszcak 1997b MRID 44574505
Rabbits, New Zealand white, 4 males and 2 females, young adults, 2.2-2.6 g	Dermal application of 0.5 mL Dimilin 2L (22.36% pure) to intact skin of backs (hair closely clipped). Test site was semi-occluded with gauze for 4 hours	4/6 rabbits had slight, barely perceptible, erythema; 1/6 had slight erythema; 1/6 had no signs of dermal irritation. Dimilin 2L considered *slightly irritating* (FIFRA Primary Irritation Index = 0.5)	Blaszcak 1997d MRID 44574508
Guinea pigs, Dunken Hartley, 10/sex	Induction dose of approximately 0.3 mL Dimilin 2L (22.36% pure) for 6 hours; challenge dose after 14 days with 100% test material	No dermal sensitization responses during induction or challenge phase.	Blaszcak 1997e MRID 44574509
Rats. Charles River, 10/sex/dose group, weight = 284-314 g (males) and 201-233 g (females)	Dermal application of 20, 500, or 1000 mg/kg/day Dimilin (technical diflubenzuron) to shaved intact skin for 21 days.	No treatment-related effects on survival, clinical signs of toxicity, dermal observations, body weights, food consumption or macroscopic and microscopic pathology. Females in the 500 and 1000 mg/kg/day group had mild but statistically significant decreases in mean erythrocyte counts, hemoglobin, and hematocrit values; males in the 1000 mg/kg/day group had mild but statistically significant decreases in mean hemoglboin and hematocrit values. At 500 and 1000 mg/kg/day, males and females had an increased incidence of polychromasia, hypochromasia, and anisocytosis. At 1000 mg/kg/day, males and females had mild but statistically significant increases in Met Hb values and males also had mildly increased Sulph Hb values. NOEL = 20 mg/kg/day.	Goldenthal 1996 MRID 43954100-01

Appendix 1: Toxicity of diflubenzuron and 4-chloroaniline to experimental mammals

Animal	Dose/Exposure	Response	Reference
Rats, Sprague-Dawley, males, 12/dose group	single dermal applications of ^{14}C-diflubenzuron suspended in 0.25% (w/v) gum tragacan WLC-grade water at 0.005 or 0.05 mg/cm^2 to shaved skin for periods of 1, 4, and 10 hours.	> 89% of the applied dose was removed by washing; 6% of the applied dose was found in the skin and increased exposure time did not increase the percent of dose found in the skin, although the amount of test material found in the skin was nearly proportional to dose; blood, carcass, and excreta accounted for negligible amounts of the applied dose; systemic absorption, excluding the skin was <1% of the total applied dose. These data indicate that the material that was absorbed was absorbed quickly. and the percent of applied dose that was absorbed appeared to be constant regardless of dose.	Andre 1996 MRID 44053101
EYES			
Rabbits, New Zealand white, 6	0.1 mL Dimilin 2L instilled in lower conjunctival sac of the right eye of each rabbit. Observations for ocular irritation made at 1, 24, 48, and 72 hours.	Positive scores (slight to moderate conjunctival irritation) in 3/6 rabbits within 24 hours of exposure with full recovery within 48 hours. No signs of iridial or corneal changes. The remaining 3 rabbits did not have positive scores for ocular irritation at any time during the study. Study demonstrates that Dimilin 2L is an “eye irritant” based on the results of positive scores in 3/6 animals with all changes being reversible.	Blaszcak 1997c MRID 44574507
INHALATION			
Rats, Sprague-Dawley, approximately 6-weeks old, 10/sex/dose group	Nose-only exposure to 0, 10, 30, or 100 mg/m^3 Dimilin technical 6 hours/day, 5 days/week for 4 consecutive weeks.	Dimilin technical produced minimal toxicity, including a slight (5-7%) decrease in erythrocytes, slight statistically significant decreases in hemoglobin and hematocrit in males and females at 100 mg/m^3 and an increase in bilirubin in males at 100 mg/m^3. No treatment-related effect observed on methemoglobin. NOEC = 30 mg/m^3	Eyal 1999 MRID 44950601

Appendix 1: Toxicity of diflubenzuron and 4-chloroaniline to experimental mammals

Animal	Dose/Exposure	Response	Reference
Rats, Sprague-Dawley, 9 weeks old, 5 males (323-335 g) and 5 females (234-249 g)	4-hour nose only exposure to 2.0 mg/L Dimilin 2 L (22.36% pure) with 14-day post exposure observation period	No mortality; signs of toxicity during exposure included red nasal discharge and labored breathing; chromodacryorrhea, red nasal discharge, and excessive salivation, labored breathing, and moist rales were observed in some rats up to 1 day after exposure with complete recovery thereafter; slight weight loss was observed in some females during the first week after exposure followed by complete recovery during the second week; no abnormal macroscopic effects were observed during postmortem evaluation. LC_{50} >2.0 mg/L	Hoffman 1997 MRID 44574506
Rats, Sprague-Dawley, 20 males and 20 females, 5/sex/dose group	Whole body exposure to nominal concentrations of 0.5, 5.0, or 50 mg/L air 5 days/week for 3 weeks. Corresponds to 500, 5000, and 50,000 mg/m^3 – i.e., 1000 L = 1 m^3.	No signs of irritation at 0.5 mg/L; frequent blinking and occasional bouts of persistent sneezing and slightly labored breathing during exposures to 5.0 mg/L, followed by rapid recovery between exposures; at 50 mg/L, the signs observed in the mid-dose group were more pronounced and more persistent but repeated exposure did not result in cumulative adverse effects and recovery was rapid after each exposure period. No changes in body weight, compared with controls and no effects on water or food consumption were observed. Post-exposure **methaemoglobin** levels were increased 0.2-0.5 g% over controls (0.1 g%). The increase was statistically significant in the mid and high-dose males and in all treated females.	Berczy et al. 1975 MRID 00044325

Appendix 1: Toxicity of diflubenzuron and 4-chloroaniline to experimental mammals

Animal	Dose/Exposure	Response	Reference
Rats, Sprague-Dawley, males and females, 6-weeks-old, 10/sex/dose group	Nose-only exposure to 0, 10, 30, or 100 mg/m^3 (measured as 12, 34, or 109 mg/m^3 diflubenzuron technical (95.6% purity) 6 hours/day, 5 days/week for 4 weeks.	Minimal toxicity: slight decrease (5-7%) in erythrocytes, slight statistically significant decreases in hemoglobin and hematocrit in males and females at 100 mg/m^3; increase in bilirubin males at 100 mg/m^3. A reduction in 'grid count' was evident in a neuro-functional assessment at the highest concentration. No effect observed on methemoglobin. NOEC = 30 mg/m^3	Newton 1999 MRID 44950601
		4-chloroaniline	
Rats, Wistar, SPF albino, males and females, 10/sex/dose group	daily oral doses of 0, 8.0, 20.0, or 50.0 mg/kg **4-chloroaniline (4-CA)** for 3 months	All rats at 50 mg/kg had increased numbers of Heinz bodies (>20/100 RBC) and a reticulocyte response (>2%); however there was no evidence of a decrease in hemoglobin, packed cell volume, or RBC count. Histological changes were observed only in the high dose group and included increased extramedullary haematopoiesis in spleen and liver and occasionally in the lung; increased hemosiderin (from hemoglobin breakdown) in the liver and spleen and occasionally in the kidneys (epithelium of proximal convoluted tubules). NOEC = 8.0 mg/kg	Scott and Eccleston 1967

Appendix 1: Toxicity of diflubenzuron and 4-chloroaniline to experimental mammals

Animal	Dose/Exposure	Response	Reference
Dog, Beagle, males and females, 4/sex/dose group	daily oral doses of 0, 5, 10, or 15 mg/kg **4-chloroaniline (4-CA)** for 3 months	One dog in the 15 mg/kg dose group died as a result of excessive haemolysis (after receiving 25 mg/kg 4-CA). 5/7 remaining dogs receiving 15 mg/kg 4-CA showed an early and marked decrease in RBC count (>1.5 M) and packed cell volume (>15%) with a concomitant decrease in hemoglobin levels. The same trend was observed in half the dogs at 10 mg/kg and one of the dogs at 5 mg/kg. Lowest levels of RBC and hemoglobin were reached at approx 3-4 weeks, after which time, there was a slow but steady improvement in all values, despite the persistence of increased numbers of Heinz bodies. A reticulocyte response and an in crease in Heinz bodies were observed in all dogs at 15 mg/kg, most dogs at 10 mg/kg, and three dogs at 5 mg/kg, while the control group remained normal. All treated dogs showed histological changes, including evidence of hematopoietic response in extramedullary activity in spleen and liver at all doses (The marrows showed hyperplasia of the erythroid phase) and marked evidence of RBC destruction in the spleen, and liver.	Scott and Eccleston 1967
Rats, Fischer 344, males, 10/dose group	In diet concentrations of 1240 ppm **4-chloroaniline** or 1240 or 4320 ppm **p-chlorophenylurea** for 7 days	1240 ppm **4-chloroaniline** caused statistically significant increases in methemoglobin values at all intervals of analysis No treatment related effects on methmoglobin values in rats treated with 1240 or 4320 ppm **p-chlorophenylurea**. The only macroscopic change observed was enlargement of the spleen in rats from the 1240 ppm **4-chloroaniline** group. No mortality.	Goldenthal 1999b MRID 44871303

Appendix 1: Toxicity of diflubenzuron and 4-chloroaniline to experimental mammals

Animal	Dose/Exposure	Response	Reference
Rats, Fischer 344, approx 6-weeks old, males and females, 25/sex/dose group	In diet concentrations of 250 or 500 ppm **4-chloroaniline** for 78 weeks with a 24-week observation period.	Mean body weight depression associated with treatment was observed in high dose females, compared with controls. No significant treatment-related mortality among females; however, there was a significant (p=0.0294) correlation between dose and mortality in males rats. In the high dose male rates, the incidence of unusual splenic neoplasms (i.e., fibroma, fibrosarcoma, sarcoma, hemangiosarcoma, and osteosarcoma) was increased (0/20 controls; 0/49 low dose, 10/49 high dose). This finding was considered strongly suggestive of carcinogenicity because of the rarity of the rumors in the spleens of controls rats. Formation of non-neoplastic lesions of the splenic capsule in rats in all dose groups.	NCI 1979
Mice B63CF1, approx 6-weeks-old, males and females, 25/sex/dose group	In diet concentrations of 2500 or 5000 ppm **4-chloroaniline** for 78 weeks with a 24-week observation period	Mean body weight depression associated with treatment was observed in all mice, compared with controls. No significant treatment-related mortality in mice of either sex.	NCI 1979

Appendix 2: Laboratory and simulation studies on environmental fate of diflubenzuron and its metabolites.

Data Summary	Reference
Aquatic Sediments	
anaerobic aquatic metabolism of 1.3 mg/kg ^{14}-C diflubenzuron in silt loam/water system. DT_{50} = 34 days for total hydrosoil/water system and 18 days for water-phase only. 2,6-difluorobenzoic acid, and 4-chlorophenylurea were main metabolites that accumulated in the anaerobic water phase; hardly any bound residue detected.	Thus et al. 1991 MRID 41837601
two model ditch (water/sediment) systems (sandy loam or silt loam covered with surface water) with addition of 0.94 ppm. diflubenzuron with continuous flow through upper layer of surface water. Incubation at 20±1° w/12 hour photo period. Results indicate rapid disappearance of compound from model ditch systems due to rapid metabolism and adsorption to sediment. Water phase DT_{50} = 1.1 day (silt loam) and 1.9 days (sandy loam). Complete sediment/water systems DT_{50} = 10 days (silt loam/surface) and 25 days (sandy loam/surface). Only metabolites were DFBA and CPU	Thus and van der Laan-Straathof 1994 MRID 44399307
0.013 ppm DFB in a microbially viable soil/water test system DFB was readily degradable under aerobic aquatic conditions half-life (first-order kinetics) = 25.7 days (r^2=0.709) DT_{50} = 5.3 days major metabolite formed, 4-chlorophenylurea half-life (first-order kinetic) = 39.7 days (r^2=0.671)	Dzialo and Maynard 1999 MRID 44895001
degradation rate of 50 µg/L diflubenzuron in seawater in the presence of salmon feces and sediment is temperature dependent: at 15°, DT_{50} = 3 ½ weeks (anaerobic) or 4 ½ weeks (aerobic); however at 5°C, there was no significant difference between the anaerobic (DT_{50} = 99 days) or the aerobic (DT_{50} = 100 days) test conditions. The metabolites included 4-chlorophenylurea, 2,6-difluorobenzoic acid, 2,6-difluorobenzamide, and CO_2	van der Laan 1995 *In*: Technology Sciences Group 1998 MRID 44399307

Appendix 2: Laboratory and simulation studies on environmental fate of diflubenzuron and its metabolites.

Data Summary	Reference
laboratory microcosm study using 10 µg/L DFB in seawater with or without sediment. half-life of DFB in seawater **without** sediment = 18.7 days half-life of DFB in seawater **with** sediment = 5.2 days presence of organic sediment in DFB-treated microcosm significantly reduced the efficacy of DFB in seawater as measured by toxicity of aged DFB (initial nominal concentration of 10 µg/L) to 5-day old grass shrimp embryos. By day 30, embryos reared in seawater from DFB-sediment microcosm produced larvae with no signficant morphological abnormality and larval viability was comparable to controls; embryos reared in DFB-treated seawater **without sediment** produced larvae with severe abnormalities and very low viability even after the seawater aged for 65 days.	Wilson et al. 1995
persistence of diflubenzuron (Dimilin) in sod-lined water pools after repeated applications: Bioassay data indicate toxicity greatest during the first 24 hours; DFB fell below detection limits (1µg/L) within 24 hours, whereas chlorophenylurea concentration increased for several days after treatment.	Madder and Lockhart 1980
Bioconcentration	
Channel catfish, *Ictolurus punctatus*: No bioconcentration. In 0.01 ppm tanks, concentration in muscle was below 0.002 ppm and concentration in viscera peaked at about 0.003 ppm (Figure 2). Similar pattern in 0.5 ppm tanks (Figure 3). **Algae:** BCFs of 2412 at hour 1 to 109 at day 4. Probably reflects degradation – i.e., algae degraded 80% of the DFB in a 1-hour incubation period.	Booth and Ferrell 1977
Laboratory algae culture system of *Scenedesmus subspicatus* exposed at an initial concentration of 200 µg/L DFB for 7 days no growth inhibition; half-life = 3 days DFB radioactivity in algae increased steadily and leveled off at approx. 60% after 5 days BCF values decreased from 4310 to 889 during the exposure period elimination was rapid during the first hours.	Yu-Yn et al. 1993
Hydrolysis	
rapid decrease in of residue levels. Half-life w/aeration = 0.41899 days (tap water and natural sunlight) Half-life wo/aeration = 0.96685 days (tap water and natural sunlight)	Anton et al. 1993

Appendix 2: Laboratory and simulation studies on environmental fate of diflubenzuron and its metabolites.

Data Summary	Reference
Two applications of Dimilin 25W (25% a.i. by weight) to surface of littoral enclosures using portable hand sprayer at rates of 4-210 g/ha. Maximum residues in water column measured withing first 24 hours after application, Half-lives ranged from 3.28 to 8.23 days with a mean of 4.28 days. By 14-35 days (or a mean of 18.5 days), 95% of the diflubenzuron dissipated. Principal loss from water column early in the study probably due to adsorptive processes because temperature and pH were not favorable for rapid aqueous hydrolysis.	Knuth 1995 MRID 44386201 (This is chapter 2 of Moffet 1995)
11 µg/L ^{14}C-diflubenzuron in a CO_2-evolution test (concentration below aqueous solubility). DT_{50} = approximately 2.5 days; hydrolysis products are DFBA, CPU, and CO_2	van der Laan and Thus 1993 *In*: Technology Sciences Group 1998 MRID 44399307
High temperature (121˚C) increased the degradation of diflubenzuron in aqueous media at levels greatly above its solubility in water and resulted in its rapid degradation to as many as seven identified products: 4-CPU, 2,6-DFBA, 2,6-difluorobenzamide, 4-chloroaniline, *N,N'*-bis (4-chlorophenyl) urea, 1-(4-chlorophenyl)- 5-fluoro-2,4 (1H,3H)-quinazolinedione and 2-[(4-chlorophenyl) amino]- 6-fluorobenzoic acid. 4-Chloroaniline, *N,N'*-bis (4-chlorophenyl) urea and 2[(4-chlorophenyl) amino]-6-fluorobenzoic acid were not detected at lower temperatures (0.1 mg [^{14}C]-diflubenzuron/L water or buffer at 36˚C). 4-Chloroaniline was a major degradation product of diflubenzuron in heat-treated samples, but it was not seen at lower temperatures	Ivie et al. 1980
Photolysis	
Photodegradation half-lives of diflubenzuron in deionized water (pH 7) = 17 hours; in deionized water (pH 9) = 8 hours; and in river water (pH 9) = 12.3 hours. In a solar simulator using river water buffered to pH 9.0, the half-life for diflubenzuron =12 hours; dark controls showed no loss of parent compound over similar time periods. Log Kow = 3.8 (determined using reverse phase HPLC)	Marsella et al. 2000

Appendix 2: Laboratory and simulation studies on environmental fate of diflubenzuron and its metabolites.

Data Summary	Reference
Residues on Plants	
persistence of diflubenzuron (commercial grade 25% WP) on Appalachian forest leaves. Leaves sprayed in spring and left to weather during growing season. white oak leaves collected in July and August and placed in headwater stream to monitor residual diflubenzuron showed rapid decrease in residue (36% in July and 23% in August) within the first 48 hours of stream incubation, reaching less than 10% of the original concentration within 3 weeks. Yellow poplar, read maple, and white oak leaves collected in December and place in headwater stream showed a much slower rate of loss. After 54 days in the stream, yellow poplar and red maple leaves retained 45 and 40%, respectively of the original diflubenzuron concentration and white oak showed no significant loss. Stream water temperatures averaged 17°C lower in December than in August (temperature readings were not made in July).	Harrahy et al. 1993
Soil Degradation/Transport	
fate of 4-chloroaniline in nonautoclaved and autoclaved soil. in soil treated with 4-chloroanline and incubated for 6 weeks, no CO_2 evolution in occurred in autoclaved soil; in nonautoclaved samples, CO_2 was determined as 7.5% of the originally applied radioactivity.	Bollag et al. 1978
Cell suspension of 0.04 g *Pseudomonas putida* in 2 mL of 0.05 *M* phosphate buffer (pH 7.0) incubated with 10 µg ^{14}C-PH-6040 (DFB) (both A and B labels) for 6 hours produced no evidence of degradation upon extraction. Both labeled preparation were recovered intact as 99.9+% of total ^{14}C	Metcalf et al. 1975
10 ppm ^{14}C-PH-6040 (DFB) added to fresh, air-dried Drummer soil (17.4% moisture) and incubated at 80°F for 1, 2, or 4 weeks. Compound appeared to be very stable, with degradation products comprising only 0.7% of total extracted radioactivity after 4 weeks.	Metcalf et al. 1975
aerobic soil metabolism of 0.69 mg/kg ^{14}-C diflubenzuron in sandy loam DT_{50} = 50 hours; DT_{90} = 181 hours CO_2, 2,6-difluorobenzoic acid, and 4-chlorophenylurea were main metabolites; 2,6-difluorobenzamide and 4-chloroaniline were minor metabolites.	Walstra and Joustra 1990 MRID 41722801

Appendix 2: Laboratory and simulation studies on environmental fate of diflubenzuron and its metabolites.

Data Summary	Reference
10 ppm technical DFB applied on quartz sand to natural sandy loam and much soils at 12 weeks: 2-12% remaining (compared with 80-87% remaining in sterilized soil), indicating that soil microorganisms play a major role in the degradation of DFB. Kinetic analysis based on 1st order dependence indicates that the rate constants for disappearance reactions decreased with time.	Chapman et al. 1985
breakdown of DFB by soil isolates: *Rhodotorula* sp. half-life of detectable DFB = 18 days (carbon source: acetone) *Fusarium* sp. half-life of detectable DFB = 7 days (carbon source: DFB/acetone) *Penicillium* sp.half-life of detectable DFB = 14 days (carbon source: acetone) *Cephalosporium* sp.half-life of detectable DFB = 13 days (carbon source: acetone) Control half-life of detectable DFB = 27 days.	Seuffer et al. 1979
^{14}C-DFB readily degraded in various agricultural soils and in hydrosoil: 50% of applied dose (1 mg/kg) metabolized in ≤2 days. Chief products of hydrolysis were 4-chlorophenylurea and 2,6-difluorobenzoic acid.	Nimmo et al. 1984
initial dose of 1 mg/kg **4-chlorophenylurea** in decreased to 50% in about 5 weeks in aerobic sandy clay and in about 16 weeks in anaerobic hydrosoil Investigators assume that two sorts of bound residues are formed from **4-chlorophenylurea**: one is fairly stable and might consist of bound 4-chloroaniline or its transformation products and the other is presumed to be a degradable derivatie of **4-chlorophenylurea**.	Nimmo et al. 1986
2-6-difluorobenzoic acid is rapidly and completely degraded in soil: time to 50% disappearance in 9 days in humus sand and after 12 days in sandy clay. DFBA completely disappeared in the humus sand after 32 days.	Nimmo et al. 1990
DFB (technical), Dimilin WP-25, and Dimilin SC-48 were applied separately at 70, 210, or 630 g ai./ha (corresponding to 17.23, 51.69, or 155.07 µg a.i.) To top layer of columns (30x5.6 cm id) packed either with sandy or clay loam forest soils. Mobility of DFB was low and did not increase with dosage. At deposit rate equivalent to 70 g a.i./ha, nearly all the residues were found with 2.5 cm of the top of the column. At 630 g a.i./ha, only about 9% of the technical DFB, 7% of Dimilin SC-48, and 4% of Dimilin WP-25 moved below the 2.5 cm level in sandy loam. No residues were found below the 10 cm level or in the leachates in either soil type at all dosage levels. In addition to soil type, mobility of DFB was also influenced by the additives present in the formulations with technical DFB > Dimilin SC-48 > Dimilin WP-25.	Sundaram and Nott 1989

Appendix 2: Laboratory and simulation studies on environmental fate of diflubenzuron and its metabolites.

Data Summary	Reference
Organic soil and silty clay loam soil collected from a boreal forest in northern Ontario, Canada maximum amount adsorbed: 88 µg/g (organic soil); 73 µg/g (silty clay loam) time required for maximum adsorption: 18 h (organic soil); 24 h (silty clay loam) Organic soil characterized as about equal parts sand, silt, and clay and 21% OM and 13% OC. Silty clay loam characterized as 22% sand, 49% silt, and 29% clay, and 8.2% OM and 5.1% OC. K_D = 17.59 (organic soil) K_D = 16.42 (silty clay loam) K_{oc} = 135.3 (organic soil) K_{oc} = 332.0 (silty clay loam) calculated K_{oc} = 144.4 (organic soil) calculated K_{oc} = 345.3 (silty clay loam)	Sundaram et al. 1997

Appendix 3a: Summary of terrestrial field or field simulation studies on diflubenzuron and its formulations.

Application	Observations	Reference
33, 66, and 140 g a.i./ha (0.5, 1, and 2 oz a.i./ac)	No evidence of negative effects on predators/parasites – lacewing (*Chrysopa carnea*), ladybird beetle (*Hippodamia convergens*), Wasp parasite *Trichograma pretiosum* of bollworm (*Heliothis*). Immigration from untreated fields could mask negative effects on beetles seen in lab (see Appendix 5).	Ables et al. 1977
280 g a.i./ha (4 oz a.i./ac)	Caged lacewing suffered increased mortal. eating treated eggs. No effect on parasitic wasp through 2-3 generations; wasp developed in treated eggs and in eggs produced by treated adults, and direct exposure to adults was not toxic.	Ables et al. 1977
187 ppm spray to apple orchards (NOS)	No adverse effects in Phytoseiid and stigmaeid mites No population increases following treatment in European red and rust mites	Anderson and Elliott1982
Application (spray) of Dimilin WP, 0.6 kg in 600 L/ha to a 2.4 ha apple orchard (integrated pest management program). 250 g Dimilin/ha, 62.5 g a.i./he	DFB persisted on foliage until leaf-fall and was detected on the peel of harvested fruit. Mean residue on harvested Worcester fruit = 0.05 mg/kg fresh weight and on harvested Cox fruit, mean residue = 0.02 mg/kg fresh weight.	Austin and Carter 1986
4-year field study (1992-1995) in apple orchards in a codling moth control program based on 4 seasonal sprays/year. Diflubenzuron at 3-12 g/100 L. Application rate in g/ha not specified.	Spider fauna (26 genera and 30 identifiable spider species) in apple orchards of Western Oregon. DFB was harmless to spider species tested (p>0.05)	Bajwa and AliNiazee 2001
Dimilin 4 liquid applied at 70 g a.i./ha to watersheds in a central Appalachian broadleaf forest	Yellowjackets, (10 species of wasps, Family Vespidae): Diflubenzuron decreased worker number during application year but not in post application year. There was no effect of trap site on worker sample size.	Barrows et al. 1994
140 g a.i./ha (2 oz a.i./ac). 4.05 ha in 41 ha woods.	Some species of soil mites were adversely affected. Half the number in treated v. untreated samples.	Blumberg 1986
67 g a.i./ha (0.96 oz a.i./ac)	Wasp parasite on Gypsy moth eggs (*Ooencyrtus kuvanae*) on gypsy moth. Egg masses in treated plots were parasitized as heavily as egg masses in control plots. Lab data showed no effect on development and emergence from treated eggs or from eggs laid by treated adults.	Brown and Respicio 1981

Appendix 3a: Summary of terrestrial field or field simulation studies on diflubenzuron and its formulations.

Application	Observations	Reference
350 g a.i./ha (5 oz a.i./ac)	5 hives (Honey bee, *Apis mellifera*.) in treated and untreated sites. No effects on egg hatch, brood production, numbers of adults, and honey production.	Buckner et al. 1975
70 g a.i./ha (1 oz a.i./ac)	Under tree bands, Carabidae (beetles), Gryllacrididae (grasshoppers), and two families of moths were significantly reduced in total taxa richness and abundance on treated sites.	Butler 1993

Additional Notes on Butler 1993: Foliage sampling found reduced abundance and richness in the following groups: Lepidoptera, Symphyta (sawflies, horntails), some herbivorous Coleoptera (beetles), Psocoptera (book lice, wood lice), predatory Thysanoptera (thrips), some Homoptera (leaf hoppers, aphids, cicadas), Diptera (flies), Orthoptera (grasshoppers), and Arachnida (spiders). Some affected by direct toxicity and others (predators) indirectly through prey reduction.

Application	Observations	Reference
Aerial application of Dimilin 4L (35.1 g a.i./ha) to two watersheds in a Central Appalachian forest; two untreated watersheds served as controls.	Gypsy moth larvae decreased in number on the treated watersheds, especially during the treatment and post-treatment year. Macro lepidoptera larvae also decreased in number during the treatment year.	Butler et al. 1997 Butler 1995

Additional Notes on Butler et al. 1997: In treated watersheds, there was an overall reduction in arthropod family diversity and abundance on foliage and a significant reduction in the number of macro Lepidoptera and beetles. 27 months after treatment, total arthropod abundance and macro lepidoptera abundance on foliage remained significantly reduced. Decreases in the numbers of Carabidae (ground beetles), Gryllacrididae (crickets), Psocoptera (booklice/barklice), Phlaeothripidae (alligatorweed thrips), and some sapfeeders were observed but reductions were not significant.

Application	Observations	Reference
Aerial application of 0.0084, 0.0168, or 0.0336 kg a.i./ha Dimlin 2F [8.4, 16.8, 33.6 g/ha] or 0.0168 kg a.i./ha Dimilin 25W [16.8 g/ha] to mixed-grass rangelands near Amidon, ND (experimental plots were 0.4x0.4 km).	Abundance of ants was not significantly reduced by treatment at any levels. Ant diversity declined temporarily (13-19 days) after treatment with Dimilin 25W, but recovered immediately the following week and no further declines were observed. Twenty species of ants were encountered in the experimental site.	Catangui et al. 1996
Aerial application of diflubenzuron (25% WP) to treatment plots at a rate of 70.75 g/ha on May 8, 1985 and May 9, 1986 as part of Gypsy moth suppression program in WV. Plots were located in an 8000 ha oak-hickory forest. Untreated plots served as controls.	**Abundance**: No significant differences were observed ($p<0.10$) in abundance of 21 species of birds examined between treated and control plots. **Diets**: All species in untreated plots ate more Lepidoptera larvae than species on treated plot; difference was significant ($p<0.10$) in 5 of 7 species. **Foraging**: Vireo foraging areas were 3.1 and 2 times larger on treated areas, compared with untreated areas.	Cooper et al. 1990

Appendix 3a: Summary of terrestrial field or field simulation studies on diflubenzuron and its formulations.

Application	Observations	Reference
70 g a.i./ha (1 oz a.i./ac) to cotton, applied in paraffinic crop oil (Dimoil) and water. Sampling took place 1 week after each treatment. Fields 15 ha each.	Assay of populations of predators of bollworms (*Heliothis*): lacewings (*Chrysopa* spp.), ladybird beetle (*Hippodamia convergens*), *Coleomegilla maculata* big-eyed bug (*Geocoris punctipes*), *Nabis* spp., *Orius insidiosus*. Numbers of predators unaffected by 4 treatments 1 week apart. The study did not look at parasite numbers. The authors note that crop oil could have affected some species.	Deakle and Bradley1982
0.3 to 3.3 kg Dimilin 25W/ha [75 g a.i. to 825 g a.i./ha]	No effect on breeding success or growth of nestlings for tree sparrows (*Passer montanus*) or two species of tits (*Parus major* and *Parus caeruleus*). Endpoints examined included number of occupied nest boxes, mean number of offspring, nesting period, mortality of nestlings, and breeding success.	De Reed 1982
110 to 400 g a.i./ha	Honey bee, *Apis mellifera*. No effect from spray on trees on adults or larvae.	Emmett and Archer 1980
38 and 83 g a.i./ha applied in diesel oil (0.54 and 1.19 oz a.i./ac)	Nearly 90% reduction in grasshoppers (nymphs and adults) 7 d. after treatment at higher rate. Low rate had minimal effects on larval grasshoppers. At least one taxon of beetle showed reductions of 50% at highest dose. Possible reduction in trap catches of members of 1 of 3 families (the Gnaphosidae) of ground spiders, at highest dose, 4 weeks after treatment. Reduced populations of Ichneumonids and Braconids in sprayed plots for at least 3 weeks. Possibly due to effects on host species rather than direct toxicity. Tiphiids unaffected by treatments. Predatory wasp reduced in treated plot, possibly a response to prey reduction (grasshoppers).	Everts 1990
Brazil: 250 g a.i./ha (3.6 oz a.i./ac). Applied 3x by mistblower.	No effect on adult levels of predator *Calosoma*, nor on nabids or geocorids.	Heinrichs et al. 1979
70 g a.i./ha (1 oz a.i./ac) in 4.7 l/ha crop oil (Savol) + H2O, applied 6x at 5 d. intervals	Treatments reduced parasitism by *Trichogramma pretiosum* to *Heliothis* spp. by 44% after spray.	House et al. 1980
Apple orchard in Union, CT. 57 g a.i./10 gal water with spreader sticker. Applied with backpack sprayer.	Parasitic wasp *Apanteles melanoscelus* Parasitism rate on treated vs. control trees roughly equal before spray, but lower on treated trees 7 d. after spray (1.81% v. 0.67%). Some adult wasps developed successfully, perhaps those in later stages of development.	Granett and Dunbar 1975

Appendix 3a: Summary of terrestrial field or field simulation studies on diflubenzuron and its formulations.

Application	Observations	Reference
Apple orchard in Brooklyn, CT. 3.5 g a.i./10 gal. water with spreader sticker. Applied w/ backpack sprayer.	Parasitic wasp *Apanteles melanoscelus* 1st application of spray decreased parasitism rate. 2nd and 3rd applications did not.	Granett and others1976
About 11 and 22 g a.i./ha (0.75% and 1.0% a.i./kg. At 1.1 and 2.2 kg/ha.) Treated bran bait.	30+ spp. of grasshoppers, counted on treated and control fields. Total populations were reduced 28 days after treatment by 60 and 70% at highest rates of application (0.75 and 1.0% a.i./kg; 2.2 kg/ha). Populations reduced <20% at half that rate. Greater effects early instars.	Jech et al. 1993
Cotton fields treated with nine applications of 2 oz a.i./acre (140 g/ha) diflubenzuron (NOS) from June17-Aug12	Monitoring of arthropod predator populations: *Geocoris punctipes*, *Nabis* spp., *Hippodamia convergens*, *Coleomegilla maculata*, *Orius insidiosus*, *Chrysopa* spp. Diflubenzuron treatment did not skew the relative abundance of the predators sampled. For 6 days after collection, egg hatch in the laboratory held *H. convergens* was significantly lower in females collected from treated cotton fields, compared with those form untreated cotton fields.	Keever et al. 1977
Backpack application of 8 oz Dimilin 25W or 0.5 pints Dimilin 2L (0.125 lbs a.i./acre in each case) to maturing cotton foliage in Fresno, CA or East Bernard TX	Over 5 weeks, dislodgeable foliar residue ranged from 0.40 $\mu g/cm^2$ down to 0.01 $\mu g/cm^2$ (limit of quantitation). Regression analysis predicted mean dislodge able residues on cotton leaves of 0.189 $\mu g/cm^2$ at 4 hours and 0.180 $\mu g/cm^2$ at 24 hours at both locations.	Korpalski 1996a MRID 44081401
Three applications of Micromite 25W via calibrated airblast sprayer to orange trees at a rate of 1.25 lbs (0.3125 lbs a.i./acre) in LaBelle, FL. [0.35 g/ha × 3]	Over 5 weeks, dislodgeable foliar residue ranged from approximately 0.8 to 1.0 $\mu g/cm^2$ shortly after the last application and down to 0.22 to 0.48 $\mu g/cm^2$ at 35 days post application. Regression analysis predicted mean dislodgeable residues on orange tree leaves of approximately 0.59-0.82 $\mu g/cm^2$ at 4 hours and approximately 0l58-0.81 $\mu g/cm^2$ at 24 hours at both locations.	Korpalski 1996b MRID 440814012
Diflubenzuron at 150, 450, or 750 g a.i/ha.	Gram pod borer, *Helicoverpa armigera* (Lepidotera: Noctuidae) [crop pest] field collected eggs on gram plants in sprayed and unsprayed plots. % egg mortality: Controls = 13.0% ; 150 g/ha. =39.0%; 450 g/ha. = 61.0%; 750 g/ha. = 100.0 %	Kumar et al. 1994

Appendix 3a: Summary of terrestrial field or field simulation studies on diflubenzuron and its formulations.

Application	Observations	Reference
Site 1: 140 g a.i./ha (2 oz a.i./ac) Site 2: 280 g a.i./ha (4 oz a.i./ac) both in Kamloops, British Columbia	Mites counted in the top 6 cm of soil. About half of the taxa showed significant decreases in abundance from diflubenzuron applications. Overall population unaffected by spraying; increases in some species compensated for decreases in others. Mites in upper 3 cm of soil more severely affected than mites below. Some predators decreased and some increased (trophic level not predictive of susceptibility). 4 species apparently eliminated from site 2, after a year; other species persisted at low levels a year after spray.	Marshall1979
34 and 68 g a.i./ha (0.5 and 0.97 oz a.i./ac)	Honey bee, *Apis mellifera*. Hives placed in gypsy moth treatment blocks. No effects from applications on numbers of adults, larvae, or honey production.	Matthenius1975
Aerial application of Dimilin 25-W at a rate of 70.75 g/ha (2 oz/acre) to 770x770 m (60 ha) plots on May 8, 1985. Plots were separated by at least 150 m to minimize the effects of spray drift. The study area (Morgan Co, WV) was characterized by mature oak-pine and oak-hickory forests. Gypsy moths were mostly 1st and 2nd instars and foliage was not fully expanded at the time of treatment.	Foliage residues: 1 day after treatment = 0.45±0.25 ppm 3 days after treatment =0.31±0.16 ppm 10 days after treatment =0.10±0.06 ppm 21 days after treatment =0.18±0.16 ppm	Martinat et al. 1987
Aerial application of Dimilin 25-W at a rate of 70.75 g/ha (2 oz/acre) to 770x770 m (60 ha) plots on May 8, 1985 and May 9, 1986 Plots were separated by at least 150 m to minimize the effects of spray drift. The study area (Morgan Co, WV) was characterized by mature oak-pine and oak-hickory forests.	Significant, treatment-related reductions were observed primarily in canopy macrolepidoptera and non-lepidopteran mandibulate herbivores. Sucking herbivorous insects, microlepidoptera, and predaceous arthropods were not affected.	Martinat et al. 1988
70 g a.i./ha (1 oz a.i./ac)applied to oak-pine and oak-hickory hardwood.	120 species of spiders (Araneae) and orthopteroid (Orthoptera and Dictyoptera). Significant effects from treatments noted on spider on 1 of 10 sampling dates, and on orthopteroid abundance on 2 of 10 sampling dates. Trend in expected direction on other dates. No change in diversity of these groups. Effect on spiders could be from loss of prey or direct toxicity. Orthropoids picking up from litter that they ingest.	Martinat et al. 1993

Appendix 3a: Summary of terrestrial field or field simulation studies on diflubenzuron and its formulations.

Application	Observations	Reference
Application of 280 g/ha a.i. Dimilin WP-25 via backpack sprayer to rice field 5 days after emergence of rice leaves out of the water.	Half-life (calculated from first order kinetics) = 27 hours; residues were below detection limit after 96 hours.	Mabury and Crosby 1996
Additional notes on Maybury and Crosby 1996: Sensitized photolysis was the primary route of degradation, although partitioning to sediment and volatilization may have played minor roles in the fate of the compound. Rapid photolysis of DFB to CPU and DFBA. This mixture was as toxic to daphnids as DFB. Photolysis in distilled water is slow. Halftime of alkaline (pH 8.8) photodegradation was 157 hours (2.4 days) and filtered field water (pH 7.4) was 32 hours (1.3 days). Slower rates of photodegradation for CPU and DFBA. Field dissipation halftime for DBF of 27.3 hours (1.1 days) with typical initial increase in concentrations of CPU.		
30 g a.i./ha, in 4.78 l water (0.43 oz a.i./ac)	Wasp parasite on gypsy moth larvae (*Apanteles melanoscelus*)Parasitic fly in family Tachinidae. Wasp mortality 80% in 2 weeks from field spray. Development halted in most cases, failed to spin cocoons upon emergence, etc. 100% mortality in tachinid parasite. Gypsy moths in 2nd, 3rd, and 4th instar.	Madrid and Stewart1981
Aerial (fixed-wing aircraft) application of Dimilin WP-25 at a rate of 75 g a.i. in 50 L water/ha in A total of 1160 ha of insect-infested forest in Finland in August 1984 in an effort to control the pine looper, *Bupalus piniarius.*A solution of hydroxyethyl cellulose and 15 g sodium bicarbonate in 50 L water/ha was added to formulation to minimize drift, especially near the borders of the treated area.	Residues in run-off water decreased from 5 µg/L one day after spraying to 0.1 µg/L after 2 months. The concentration in water in open pits was 0.1 µg/L 1 and 7 days after application and 0.2 µg/L 1 month after application. After 2 months no residues were detected. All water samples taken from outside the treated area contained < 0.1 µg/L (the limit of sensitivity). No DFB was detected in the treated area the year following application or outside the treated area. Neither 4-chloroaniline nor 4-chlorophenylurea was detected in the water at any time. Residue data for the litter layer, humus layer, pine needles, wild mushrooms, boletus samples, and bilberries are provided.	Mutanen et al. 1988
DFB (25% WP) via handgun to four-tree Valencia orange blocks at a rate of 10 oz a.i./acre. Trees were sprayed to runoff to control citrus rust mite.	Half-lives of DFB surface residues (Exp 1 cool-dry period: March to April): leaves =*essentially none* fruit =118±100 days; soil (middle) = 19±11 days; soil (dripline) = 21±10 days; Half-lives of DFB surface residues (Exp 1 hot-wet period: March to April): leaves + 27±8 days; fruit 18±2days; soil (middle) = levels too low to be detected; soil (dripline) = levels too low to be detected	Nigg et al. 1986

Appendix 3a: Summary of terrestrial field or field simulation studies on diflubenzuron and its formulations.

Application	Observations	Reference
Aerial application of 70 g a.i./ha Dimilin to experimental watershed (two treated; two controls) in the Fernow Experimental Forest, WV. Soil and leaf litter arthropods were monitored before and after application for a total of 36 months.	Throughout the study, mites (49%) and springrtails (28%) dominated the soil core sample. A total of 19 taxonomic groups were suitable for statistical analysis. No significant treatment effects were observed, based on total organism counts or counts by trophic categories ($p<0.05$).	Perry et al. 1997 Perry 1995b
Additional Notes on Perry et al. 1997: No significant treatment-related effects for populations of major taxonomic groups, except for Araneae (spiders) were observed. Analysis of leaf-litter bags also indicated no significantly differences in total numbers of invertebrates or in trophic categories between treated and untreated watersheds during the 12-month post treatment study. There appeared to be an indirect effect on spiders as a taxon, which may have resulted from changes in prey populations.		
Aerial application of Dimilin 25W at a rate of 33.23 g a.i./ha in 9.4 L/ha to a 20-ha forest block in central PA. Leaf samples were collected from the upper and lower canopies of 27 oaks and understory within the block on the day of application, May 29, 1991. Canopy leaves were also collected on May 31, June 10, July 29, and September 26, 1991.	On the day of application, DFB residues on the upper canopy, lower canopy, and understory averaged 81.18, 39.65, and 8.35 ng/cm^2. DFB residues on canopy leaf residues were: 14.83 ng/cm^2 (day 2 post spray) 16.75 ng/cm^2 (day12 post spray) 12.84 ng/cm^2 (day 61 post spray) 11.20 ng/cm^2 (day 120 post spray) DFB residues on litter-leaf sample collected after leaf senescence 169 and 323 days after treatment contained measurable amounts of DFB in 51 and 59% of the samples, respectively.	Prendergast et al. 1995
Three cover sprays of diflubenzuron (NOS) at 3.7 or 7.4 g a.i./100 L in a pear orchard in northern CA. [Data to calculate application rate in g/ha not given]	DFB treatment had no direct effect on pear psylla (pest species), did not induce phytophagous mites, and was weak, compared with the synthetic pyrethroid, fenvalerate against the codling moth.	Riedl and Hoying 1980
0.5 and 2 oz a.i./ac, w/ crop oil, sprayed 8 times on cotton. [35 to 140 g/ha × 8]	Direct spray of bee hives. No effects noted on adult mortality, rate of larval growth, brood production, or honey or wax production. No residues in wax or honey. Not caged study, so bees could have foraged outside of spray area.	Robinson 1978,1979
Aerial application of oil formulation of DFB (Dimilin 45 ODC) on August 31st in a conifer forest in the north of Spain at a dose of 56.3 g a.i./ha a(125 cm^3 Dimilin in 5 L diesel oil) (volume rate of application = 5 L/ha). The day of application was clear with no rainfall in the previous 48 hours.	DFB persisted for 10-12 weeks on the foliage of the conifer forest; 55-80% of the insecticide was removed from the foliage within 22-30 days after treatment; aerial application resulted in residue levels of 867.5-1824.4 ng/g, depending on the forest characteristics. 2,6-difluorobenzmide was the only metabolite detected and persisted only until the first rainfall.	Rodriguez et al. 2001

Appendix 3a: Summary of terrestrial field or field simulation studies on diflubenzuron and its formulations.

Application	Observations	Reference
Aerial application of Dimilin 25-W at a rate of 70.75 g/ha (2 oz/acre) to 770x770 m (59.2 ha) plots on May 9, 1986 Plots were separated by at least 150 m to minimize the effects of spray drift. The study area (Morgan Co, WV) was characterized by mature oak-pine and oak-hickory forests.	Diets of five species of forest birds were significantly different between treated and untreated plots. Treatment generally decreased the biomass of Lepidoptera larvae and increased the biomass of other orders (Homoptera, Diptera, Coleoptera, etc.).Two species of birds in treated sites had decreased total gut biomass. The investigators conclude that DFB has an indirect adverse effect on forest birds by reducing the availability of Lepidoptera larvae.	Sample et al. 1993a
Aerial application of Dimilin 25-W at a rate of 70.75 g/ha as part of a gypsy moth suppression program in WV.	Treatment adversely affected Lepidoptera resulting in decreased abundance and species richness; no effects were observed among Coleoptera, Diptera, or Hymenoptera. Trap catches of 3 families of Hymenoptera were unaffected, including two parasitic families, Ichneumonidae and Braconidae.	Sample et al. 1993b
Application of Dimilin *on a regular basis* (i.e., 8 applications between May 16th and December 14th 1977) to a small citrus grove in which there were two bee hives.	The hives remained in the same location throughout the study and were covered with plastic as a means of protection. There were no adverse effects on brood development of honey bees.	Schroeder 1978a MRID 00099731

Appendix 3a: Summary of terrestrial field or field simulation studies on diflubenzuron and its formulations.

Application	Observations	Reference
Aerial application of 350 g a.i./ha diflubenzuron to a commercial citrus grove to control *Diaprepes abbreviatus*	Residues ***in ppm*** on fruit harvested 27 days after the 6th application were: 0.34 on unwashed fruit; 0.11 on washed fruit; 0.26 on dried pulp; 0.31 on peel fruit; 0.12 on chopped peel; and 20.55 in oil.	Schroeder 1980
Additional Notes on Schroeder 1980: No detectable residue (<0.05) of DFB was found in the finisher pulp, fruit juice, pressed liquor, molasses, prewash or afterwash water, and emulsion water fractions. No detectable residue (<0.05) of 4-chlorophenylurea or 4-chloroaniline was found in the citrus fractions or in the prewash or afterwash water. The total sealed brood in honey bee (*Apis mellifera*) was not significantly different from control at 7 months and there was no detectable residue (<0.05 ppm) of DFB,CPU, or 4-chloroaniline was found in the honey obtained after 8 aerial sprays. Populations of non-target citrus pests and beneficial species were not affected by the spray program.		
Sour orange (*Citrus aurantium*) trees sprayed to runoff with Micromite 25W at 149 or 298 g a.i./1000 liters Efficacy study.	Diflubenzuron, formulated as Micromite 25W, significantly affected the reproductive potential of the sugarcane rootstock borer weevil, *Diaprepes abbreviatus* (pest of sugarcane and citrus).	Schroeder 1996
Aerial application of Dimilin formulated as 25% wettable powder at the rate of 140g/ha to 770 m square plots with a buffer strip of at least 150 m between adjacent plots in May 1985 and 1986.	Estimates of density of white-footed mouse, *Peromyscus leucopus*) did not differ significantly (p>0.05) between treated and untreated areas. Juvenile/adult female ratios on untreated areas were significantly higher (p<0.05), compared with those on treated sites. Mice on treated sites consumed less Lepidotera prey, compare with controls (p<0.05); however, the total amount of food consumed per mouse did not differ significantly between treated and untreated areas (p>0.05). There were no treatment-related adverse effects on body measurements, weight, or fat content.	Seidel and Whitmore 1995
Aerial application of Dimilin (NOS) at a rate of 140 kg/ha. The application rate is presumably a.i. but this is not specified in the publication.	No effect on bird populations that could be attributed to diflubenzuron. Various changes in the populations of different bird species are discussed but detailed data are not reported in the publication.	Stribling and Smith 1987
Simulated aerial application of diflubenzuron in acetone or in fuel oil each at 90 g a.i. in 18 L/ha to spruce foliage (*Picea glauca*).	The residue levels 1 hour after application varied, respectively, from 23.8 to 30.6 µg/g in foliage and from 3.08 to 4.60 µg/g in litter. Forty-five days after spraying the residue levels in foliage were 0.80 and 3.9 µg/g, respectively, for acetone and fuel-oil formulations.	Sundaram 1986 MRID 00161955 Sundaram 1986

Appendix 3a: Summary of terrestrial field or field simulation studies on diflubenzuron and its formulations.

Application	Observations	Reference
Simulated aerial spray application of technical grade DFB in acetone formulation with tracer dye or in fuel oil with tracer dye at a rate of 90 g a.i. in 18 L/ha to white spruce foliage of uneven height. The forest floor was flat and covered with grass and moss patches.	The half-lives for DFB in foliage, litter, and soil for the acetone-based formulation were 9.30, 8.36, and 7.49, respectively. 45 days after application, the residue levels in foliage were 0.80 µg/g (fresh weight) for the acetone-based formulation. There were no detectable residues in litter or soil on the 45th day post application of the acetone-based formulations.	Sundaram 1996
Soybeans in S.C. treated with 281 or 562 g a.i./ha (4 or 8 oz a.i./ac)	Significantly fewer nabids and geocorids on treated v. control sites.	Turnipseed et al. 1974
Aerial application of 8 oz Dimilin WP-25/acre (equivalent to 0.0625 lb/acre) to 10-acre mixed hardwood-conifer forested plot near Boone N. Carolina, which consisted of a stream, two stream pools, and a stream-fed pond outside the treated area. Sandy loam soil. Cumulative rainfall of 43.1 cm (16.9 inches) over a 1 year period. Daily rainfall and temperature data are given.	Initial concentration on leaves in canopy of 13 ppm on hardwood and 5.9 ppm on conifer. Initial concentrations on understory vegetation of about 0.13 ppm that increased initially as with litter. Diflubenzuron was rather persistent on leaf litter. Initial residues of 0.07 ppm. This increased over a 60 day period, probably due to drying of litter, washoff of DFB, and leaf fall from canopy.	Van Den Berg 1986 MRID 00163853

Additional Notes on Van Den Berg 1986: A single application resulted in initial water concentrations in treatment area of 0.127-0.203 ppb. Declined to 0.029-0.045 ppb after one day. No detectable contamination in an adjacent pond after heavy rains. Initial soil concentrations of 0.02 ppm and 0.03 ppm after a 6.5 cm rain (probably washoff). No DFB in 3"-6" soil samples. The study authors conclude that the effects on the mites and collembolans present at the time of application were insubstantial. In general, fewer of each group on treated than untreated sites. The data are somewhat difficult to interpret because of erratic capture patterns over time the populations of collembolans were different at the control and treated sites prior to treatment. [NOTE: Data on other species presented in Tables 10 and 11 but the numbers of insects are too small for analysis. Species list in Table 11 cut off on fiche]

Internal Note: See Van Den Berg 1986.xls may want to make figures if time.

28 g a.i./ha (0.4 oz a.i./ac)	Wasp parasite on Gypsy moth larvae (*Cotesia melanoscelus*) Pathogen: gypsy moth nuclear polyhedrosis virus (NPV). Numbers of the wasp no different on Control v. treated plots. Incidence of NPV significantly lower in treated plots. Late instar spraying may preserve larvae long enough for parasitoid to complete development. Earlier spraying kills host too quickly, hence parasitoid as well. NPV lower in treated plots because fewer Gypsy moths to transmit virus.	Webb et al. 1989

Appendix 3a: Summary of terrestrial field or field simulation studies on diflubenzuron and its formulations.

Application	Observations	Reference
application of 2 or 4 oz a.i./acre [140 to 280 g/ha] to plots with large, active nests of yellowjackets	Yellowjackets (*Vespula* or *Dolichovespula*). Treatment decreased populations and the effect was readily observed during the following year. No effects observed on Mound-building ants (*Formica)*	Weiland 2000 MRID 45245403
560, 280, and 140 g a.i./ha (8, 4, and 2 oz a.i./ac). 2 and 3 treatments. Handgun and air-carrier sprayer.	Nearly twice as many *Psylla* predators and parasites per season in the lowest application rate. Higher rates resulted in higher populations of the pear psylla.	Westigard 1979
Aerial application of 0.03lbs a.i./acre Dimilin 25WP to Appalachian forest ecosystem during 1991 season (20 trees representing 7 species) in WV Univ. Experimental Forest.	Residue on leaves: significant loss of DFB from foliage ranging from 20 to 80% within the first 8 days after application; remaining DFB generally persisted for the rest of the growing season until leaf fall, at which time 13/20 treated trees retained more than 20% of the original pesticide applied.	Wimmer et al. 1993
Dimilin (TH-6040) formulated as dispersable powder (a.i. 25% by weight) applied aerially at the rate of 0.28 kg a.i./ha (0.25 lbs a.i./acre) to a Douglas-fir forest ecosystem in British Columbia	Treatment decreased the total number of flying insects and the effect was sustained throughout the study period, with the greatest impact observed on midges and gall gnats. Mosquitoes were completely wiped out as a result of treatment.	Wilson and Wan 1977a MRID 00095419 Wilson and Wan 1977b MRID 00129973 [Appear to be duplicate submissions.]

Appendix 3b: Summary of aquatic field or field simulation studies on diflubenzuron and its formulations.

Application	Observations	Reference
Two applications (NOS) of granular diflubenzuron at 0.11 kg a.i./ha (about 3.7 µg/L) or 0.22 kg a.i./ha (about 7.4 µg/L) to residential-recreational lakes in San Bernadino County (June 1967 - January 1977)	**At 0.11 kg a.i./ha application**: *Daphnia pulex* and *Daphnia galeata*: 62-75% decrease in population during 7 days after treatment; populations recovered in the second week after treatment.	Ali and Mulla 1978a

Additional Notes on Ali and Mulla 1978a: 0.11 kg/ha continued. *Diaptomus* spp. (copepods): 30% decrease in population observed 2 days after treatment. *Hyalella azteca* (amphipods): 97% decrease in population observed 3 weeks after treatment; populations remained below pretreatment levels throughout 8-9 week evaluation. Treatment had no detectable effects on *Cyprihnotus* sp.(seed shrimp), *Cyclops*, or *Bosmina longirostris* (Cladocera).

At 0.22 kg a.i./ha application: *Daphnia pulex* and *Daphnia galeata*: completely eliminated for 3 weeks after treatment. *Diaptomus* spp (copepods): populations decreased to 0 within 7 days after treatment, but recovered completely *soon thereafter*. *Hyalella azteca* (amphipods): 30-100% decrease in population during 2 ½ months after treatment. *Cyprihnotus* sp.(seed shrimp): population *stressed for only 2 weeks*. *Oligochaete* (mostly *Naididae* found in marine, brackish, and freshwater habitats): no significant effects observed at either treatment level.

Two spray application of diflubenzuron (25% WP) to entire surface of residential-recreational lake in Riverside County at a rate of 156 g a.i./ha-surface (about 0.012 ppm) in April and August 1977.	**First application (April)** *Daphnia leavis* and *Ceriodaphnia* sp: population eliminated within 1 week with **no recovery** 6 months after treatment.	Ali and Mulla 1978b

Additional Notes on Ali and Mulla 1978b: *Bosmina longirostris* (cladocerans): population eliminated within 1 week with recovery after 11 weeks. *Cyclops* sp. (crustaceans): population eliminated within 1 week with recovery within 6-7 weeks. *Diaptomus* spp. (copepods): population eliminated within 1 weeks with recovery after 4 months. *Hyalella azteca* (amphipods): population eliminated within 4 weeks with **no recovery** 6 months after treatment. *Caenis* sp. [Hemeroptera (mayflies, immature)]: elimination within 3 weeks with recovery within 6-7 weeks. *Physa* sp. (sinistral snails, referred to as pond snails or pouch snails): no adverse effects. *Cypridopsis* sp.(bivalve): no adverse effects. **Second application (August)** *Bosmina longirostris* (cladocerans): population eliminated after 1 week; reappearance in small numbers 8-9 weeks after treatment. *Cyclops* sp. (crustaceans): population eliminated within 1-2 weeks with recovery after 4 weeks. *Diaptomus* spp. (copepods): population absent prior to treatment; reappearance in small numbers 1-2 months later. *Caenis* sp. [Hemeroptera (mayflies, immature)]: elimination within 2-3 weeks with recovery within 4-5 weeks.
Study does not provide monitoring data. See Ali et al. 1988 below.

Appendix 3b: Summary of aquatic field or field simulation studies on diflubenzuron and its formulations.

Application	Observations	Reference
Application via airblast sprayer of Dimilin 25 WP at a rate of 0.56 kg a.i./ha to 0.8 ha of citrus immediately surrounding a pond located in Winter Garden, FL. The pond was exposed to air-drift diflubenzuron from surrounding citrus area commercially treated for the control of citrus rust mite. The control pond was located 0.4 km NE of the exposed pond.	No apparent adverse effects on zooplankton and benthic invertebrates in treated pond. Minor reductions of copepods and cladocerans during post-treatment period most likely due to short life cycle, seasonal population changes, and possible sampling deficiencies. Largest detected diflubenzuron residue = 197 ppt, 2 days after application with levels returning to trace amounts (<27 ppt) by day 14 after application. Specifics on the pond: circular,2 ha at the surface; 3/4 of its border was lined by citrus trees.	Ali et al. 1988
One surface application (via rowboat hand sprayer)of Dimilin (25% WP in 20.5 L water) to each of three ponds (0.6-0.2 hectares) at rates of 2.5, 5, or 10 ppb a.i. in California to control gnats (*Chaoborus astictopus*)and one application to a large lake at a rate of 5 ppb a.i. Surface area of ponds ranged from 0.06-0.2 ha; ponds were rectangular in shape with steep sides and flat bottoms.	Treatment was effective against gnats, decreasing larval abundance by 99%. Crustacean zooplankton populations declined precipitously at all application rates, but the effects were not permanent. Cladocerans were more susceptible than copepods and required longer recovery period. *Anabaena* sp (blue-green algae) decreased by approximately 70% within 2 weeks after treatment and remained at low levels throughout the study period; treatment seemed to have no effect on diatoms or green algae. The bioaccumulation of diflubenzuron in bluegill sunfish diminished rapidly as the residues in water decreased. No effect on growth of bluegills.	Apperson et al. 1977 MRID 00099897 Apperson et al. 1978

Additional Notes on Apperson et al. 1977, 1978: The investigators indicate that no severe or permanent nontarget effects were observed in this study. ***Residues***: In pond water, residues in the 10 and 5 ppb ponds 1 hour after treatment ranged from non-detectable to 23.6 and 32.2 ppb and averaged 9.8 and 4.6 ppb, respectively and residues levels in the 2.5 ppb pond at 4 hours after treatment ranged from N.D. to 8.3 ppm with an average of 1.9 ppb. Maximum values in bottom water samples in the 5 and 2.5 ppb ponds occurred at 4 hours and 14 days and averaged 5.3 and .5 ppb, respectively. The DFB residues declined steadily soon after treatment and at the end of the study, levels averaged 0.2, 0.3, and 0.5 ppb for the 10, 5, and 2.5 ppb ponds, respectively. No residues were found in the sediment samples.

Applications to test ponds at 1X and 4X of the typical application rate.	No effects on invertebrates or fish. [This study is poorly documented and should be given minimal weight.]	Birdsong 1965
Four applications of Dimilin W25 to ponds located in Salt Lake County Utah between 7/14/15 and 10/7/75	Algae (*Plectonema*) degraded 80% of the TH-6040 in a 1-hour incubation period. Degradation products were primarily p-chlorophenyl urea and p-chloroaniline.	Booth and Ferrell 1977 MRID 00099884

Additional Notes on Booth and Ferrell 1977: Bacteria (*Pseudomonas* sp.) accumulated “rather large amounts” of TH-6040 from the incubation media when used as the sole carbon source. No degradation products were observed in the media. Channel catfish id not bioaccumulate DFB residues from treated soil in a simulated lake ecosystem constructed in the laboratory.

Appendix 3b: Summary of aquatic field or field simulation studies on diflubenzuron and its formulations.

Application	Observations	Reference
Repeated, pulsed exposures of diflubenzuron on twelve outdoor aquatic mesocosms (0.1 ha each). Random assignment of mesocosms (four/treatment) to either monthly (five total 10 µg/L applications) or biweekly (nine total 10 µg/L applications). Direct and indirect impacts on mesocosms were measured over 16 weeks after treatment.	Within 4 weeks after monthly and biweekly treatment, direct effects on Cladocerans, Copepods and Rotifers included 5-fold decrease in total numbers, 2-fold decrease in species richness, and 2-fold increase in zooplankton. Direct reductions in the numbers of invertebrate grazers caused indirect increases in algal biomass. Decreased invertebrate numbers resulted in decreases in invertebrate food resources that resulted in a 50% reduction in both biomass and individual weights of juvenile bluegills. There were no statistically significant impacts observed on adult bluegills or largemouth bass for the duration of the study.	Boyle et al. 1996

Additional Notes on Boyle et al. 1996: DFB concentrations averaged 9.9 µg/L 24 hours after chemical application. The half-life of disappearance of DFB from water, calculated across all ponds and dates using a negative exponential decay model was 2.33 days (range = 1.76-2.96 days). There were no significant differences in DFB dissipation rate between treatment type (monthly or weekly; $p \geq 0.5815$) or season (early or late in the study; $p \geq 0.4728$.

Application	Observations	Reference
aerial application of 35 g/ha in Canada	No toxic effect on bullheads or sunfish.	Buckner et al. 1975
Two ground spray applications (at 2-week intervals) to each of two CA sites (one in Tiburon, Marin County and one in Roseville, Placer County). The first Tiburon application = 13 g/ha (0.19 oz/acre) and the second Tiburon application = 35g/ha (0.5 oz/acre);both Roseville applications = 26.25 g/ha (0.38 oz/acre) of Dimilin 25W (diflubenzuron 25% a.i.). Foliage was sprayed to the point of drip. Each site was approximately 0.8 ha. The applications were made in March-April 1990.	***Foliage***: DFB concentrations from 0 (not detected) to 18.31 µg/g immediately after the second application; and from 0(not detected) for background to 0.252 µg/cm^2 leaf area immediately after the second application. 28 days after the second application, the DFB concentration decreased sharply suggesting possible degradation during that period, but no samples were collected during the 28 days to document a degradation trend. ***Air***: During 3 of the 4 applications, DFB concentrations in air ranged from 0.0106 to 0.0187 µg/m^3. DFB was not detected in any background air samples or in any 1 day post application air samples (i.e., DFB was detected in air only during application periods). ***Water***: Samples collected from streams and water bodies in and near the treated areas on the day prior to application, immediately after each application, and 7 days after each application showed no detectable levels of DFB (minimum detection limit = 0.5 ppb).	Carr et al. 1991

Appendix 3b: Summary of aquatic field or field simulation studies on diflubenzuron and its formulations.

Application	Observations	Reference
Application (NOS) of diflubenzuron to five experimental, rectangular ponds in Lakeport, CA, yielding a mean concentration of 13 µg/L DFB. Each pond had a surface area of about 0.01 ha (1 ha =10,000 m^3) and a depth of 1.2 m.	**Residues in water** decreased below detectable limits (0.2 µg/L) by 14 days after treatment; at one hour after treatment, the mean concentration of DFB in water was 13.2 µg/L.	Colwell and Schaefer 1980

Additional Notes on Colwell and Schaefer 1980: Cladocerans: most abundant species included *Ceriodaphnia*, *Diaphanosoma*, *Chydorus*, *Bosmina*, and *Daphnia*, all of which showed population reductions in all treated ponds within a few days of DFB application. **Copepods**: abundance of naupli decreased in all ponds after treatment and returned to pretreatment levels from 7 days to >4 weeks after treatment. *Diaptomus* (filter feeders) and *Cyclops* were similar in their susceptibilities to DFB, although in most of the treated ponds, *Diaptomus* populations recovered more rapidly than *Cyclops* populations. **Rotifers**: *Brachionus*, *Keratella*, and *Hexartha* populations increased in treated and control ponds during the first 8 days after treatment. *Asplanchna*, which are mostly predatory increased from 0.18 to 0.43 organisms/L after treatment. **Fish**: Young-of-the year black crappie, *Pomoxis nigromaculatus*, and brown bullhead, *Ictalurus nebulosus*, accumulated DFB and then eliminated all residues by day 7 after treatment. No fish mortalities occurred after treatment. For 1 month after treatment, the stomach content analyses of exposed fish indicated major alterations in diet. Neither growth rates or general condition of the fish 3 months after treatment differed from those of controls.

Six aerial applications of 28 g/ha of diflubenzuron over 18 months (June 1974 through Sept 1975) to a Louisiana intermediate marsh	Treatment resulted in statistically significant differences in population density of non-target aquatic organisms (target organism - mosquito), compared with controls, but none of the affected organisms were completely eliminated from the ecosystem. The investigators speculate that the untreated marsh areas would provide populations of aquatic organisms that could repopulate the treated areas.	Farlow 1976 MRID 00099678 [Also published as Farlow et al. 1978]
Six applications of diflubenzuron (28 g a.i./ha) in a Louisiana coastal marsh over an 18-month period.	Statistically significant differences in the population density of aquatic organisms; however, none of the organisms affected were completely eliminated from the ecosystem.	Farlow et al. 1978

Additional Notes on Farlow et al. 1978: Significant populations decreases observed in five taxa: nymphs of *Trichocorixa louisianae* (water boatman) and *Buenoa* spp.(backswimmers), Coenagrionidae naiad spp.(damselflies), *Berosus infuscatus* adults (water beetles), and *Hyalella azteca* (amphipods). Significant increases were observed in populations of 15 taxa exposed to diflubenzuron, i.e., *Physa* sp. (snails), *Ceanis* sp. and *Callibaetis* sp. naiads (mayflies), *Noteridae* larvae (water beetles), *Hydrovatus cuspidatus*, adults (water beetles), *Hydrovatus* sp. larvae (water beetles), *Dytiscidae* larvae (great diving beetle), *Mesovelia mulsanti* adults (water treaders), *Trichocorixa louisiana* adults (water boatman), larvae of Chironomidae (non-biting or true midges), Ephydridae (shore flies), Dolichopodidae (long-legged flies) and Tabanidae (horseflies), as well as mosquito fish (*Gambusia affinis*) and American flag fish (*Jordanella floridae*). The 27 remaining aquatic organisms (members of the Hemiptera, Coleoptera, Mysidacea, Decapoda, Diptera and Odonata) showed no statistically significant differences, compared with untreated populations.

Appendix 3b: Summary of aquatic field or field simulation studies on diflubenzuron and its formulations.

Application	Observations	Reference
Aerial application of Dimilin 4 L at a rate of 35.1 g a.i./ha to two stream catchments in the Fernow Experimental Forest, WV in May 1992.	Treatment decreased the adult emergence of stoneflies, *Peltroperla arcuata*, during the first 4 months after treatment, compared with untreated catchments. Adults populations of other species did not decrease in the treatment catchments during the period of study.	Griffith et al. 1996
Additional Notes on Griffith et al. 1996: The investigators speculate that additional detritivourous species might have shown an adverse effect if the monitoring were extended through the period after treated leaves entered the streams. Stoneflies *are considered to be obligate large-particulate organic matter feeders and like ingested diflubenzuron from leaves that fell earlier in the year, thus ingesting diflubenzuron*. Diflubenzuron was not detected in water samples taken from the streams following treatment, perhaps due rainfall just prior to treatment.		
Aerial application of Dimilin 4 L at a rate of 35.1 g a.i./ha to two stream catchments in the Fernow Experimental Forest, WV in May 1992. During 1993, no additional diflubenzuron was applied to any of the watersheds.	The investigators tested the hypothesis that diflubenzuron affected adult flight following emergence during the year following abscission and possible ingestion of the treated leaves. The flight of the stonefly, *Leuctra ferruginea*, was reduced in the treatment watersheds, compared with the reference watersheds during the year following abscission of the treated leaves. Adult flight of other species did not decrease in the treatment watersheds during 1993.	Griffith et al. 2000
Aerial application of Dimlin 4L at a rate of 70 g a.i./ha to two of four watersheds in the Fernow Experimental Forest, WV.	Stream macroinvertebrate taxa that had reduced mean densities in treated watersheds ($\propto$ = 0.05) included the stoneflies, *Leuctra* sp. and *Isoperla* sp., mayflies, *Paraleptophlebiaspia* sp., and cran flies, *Hexatoma* sp. Shredders, the dominant functional feeding group also had reduced mean densities in treated watersheds. Densities of Oligochaeta (aquatic worms) and Turbellaria (flat worms) increased in treated watersheds.	Hurd et al. 1996
Spray application (via portable garden sprayer) of Dimilin (25% wettable powder) at recommended rate of 0.03 lbs a.i./acre or 4X application rate to each of two 10-acre earthen ponds (avg depth of 3 ft). 4X applications were made biweekly beginning in early Feb.	No appreciable mortality of fish or clams in any of the ponds. Treatment significantly decreased *Daphnia spp*. populations and virtually eliminated dipterans. Olgochaete populations, which increased in the control pond during the study, decreased in response to treatment.	Jackson 1976 MRID 00099891

Appendix 3b: Summary of aquatic field or field simulation studies on diflubenzuron and its formulations.

Application	Observations	Reference
Aerial application of 0.06 lbs a.i./acre (67.26 g/ha) Dimilin to 75-acre watershed containing small, first order stream.	Dimilin reached the stream channel during aerial application and as a result of wash-off from the foliage during several subsequent rainfall events. DFB levels (measured) exceed the acute (1.0-1.8 ppb) and chronic (60 ppt) toxicity doses for tolerant taxa, like Ephemeroptera (mayflies) and Plecoptera (stone flies). The residence time for Dimilin in these high-gradient streams was very short, and as a result of the short residence time or low concentrations, toxic effects were not evident.	Jones and Kochenderfer 1987
Spray application of 60 g a.i./ha diflubenzuron to five Sahelian temporary ponds (surface areas 0.36-0.65 ha) conducted in mid-September (half-way through rainy season) in vast savannah-type cultivated region in Senegal's ground-nut producing area. Table 1 provides a summary of wind speed, surface area treated, quantity of formulation applied in mL and calculated application rates at each of the 5 treated ponds.	Average initial concentrations in water = 10.4 µg/L, with an estimated half-life of <24 hours. DFB only affected crustaceans (i.e., cladocerans and fairy shrimp) in the treated ponds. DFB virtually eradicated the abundant fairy shrimps, *Streptocephalus* spp., and the populations did not recover despite the rapid disappearance of DFB. In general, cladocerans populations were initially wiped out (densities dropped to 0) after DFB treatment but returned to normal values in 3-4 weeks (*M micrura*), 4-6 weeks (*D senegal*), or 6-7 weeks *C quadrangula*).	Lahr et al. 2000
Application (via backpack sprayer) of Dimilin WP-25 at 280 g/ha a.i. 5 days after emergence of rice leaves out of the water to sic 20 m^2 flooded plots in June 1991 and 1992.	Field dissipation rates were similar for the six replicate plates with a half-life (1st order) of 27 hours; residues dropped to below detection limit after 96 hours. Residues in sediment were 0.16 µg/g (after 24 hours), 0.10 µg/g (after 48 hours) and 0.08 µg/g (after 72 hours); residues were below detection limit after 4 days.	Mabury and Crosby 1996
Spray application (via hand sprayer)of Dimilin 25% WP (TH6040) to semi-natural pools at the Univ. Delaware Experimental Farm to study the cumulative toxicity to killifish (3 applications over 29 days) and crustaceans (one 13-day test and one 15-day test). Applications were made at the rate of 0.01, 0.04, 0.10, and 0.20 lbs a.i./acre – i.e., up to 224 g/ha.	There was no significant mortality in killifish after three successive applications of Dimilin at 0.01-0.20 lbs a.i./acre. Behavioral responses were similar to those of controls. In the first test involving crustaceans, grass shrimp mortality was 83.3% ($p<0.01$) after the first application of 0.20 lbs a.i./acre. After two applications the average mortality ($p<0.01$) was 86.6% at 0.4 lbs a.i./acre and 100% at 0.10 and 0.20 lbs a.i./acre.	McAlonan 1975 MRID 00099895

Appendix 3b: Summary of aquatic field or field simulation studies on diflubenzuron and its formulations.

Application	Observations	Reference
Additional Notes on McAlonan 1975: In the second test involving crustaceans, grass shrimp average mortality ($p<0.01$) was 91.6% at 0.4 lbs a.i./acre, 96.6% at 0.10 lbs a.i./acre, and 98.3% at 0.20 lbs a.i./acre. In the first test involving crustaceans, fiddler crab average mortality was 60.0% and 46.6% ($p<0.01$) after one application of 0.10 or 0.20 lbs a.i./acre, respectively. After two applications of 0.04 and 0.10 lbs a.i./acre the average mortality ($p<0.01$) was 53.3% and 66.6%, respectively. In the second test involving crustaceans, fiddler crab average mortality ($p<0.05$) was 46.6% at 0.4 lbs a.i./acre,60.0% at 0.10 lbs a.i./acre, and 66.6% at 0.20 lbs a.i./acre.		
Aerial application of 0.56 kg a.i./ha (8 oz a.i./acre) Dimilin 25 WP to a citrus grove in Florida with an experimental pond	DFB was not observed in water samples at quantitative methods 1 hour post application; maximum levels occurred at 1 and 2 days post application, primarily along the line of drift. Pad data indicate that the pesticide drift deposited along a small portion of the shoreline at a rate 7% of the theoretical application rate (38÷104÷5.6) and the drift continuing out into the pond was as much as 0.8% the application rate (4.4÷104÷5.6).	Nigg and Stamper 1987 MRID 40197002
Dimilin 4L at a rate of 80g/ha (0.03 lb/acre) in two forest watersheds	Decreased populations of stoneflies in treated areas. In untreated areas, the populations of stoneflies increased. After treatment, populations of roundworms, flatworms, and segmented worms were higher in treated areas.	Perry 1995a
Aerial application of 0.0624, 0.125, or 0.25 lbs/acre Dimilin to plots in Oxbow, Maine that included four streams. [up to 280 g/ha]	Effects of a single application (to control spruce budworm) on stream invertebrate fauna (*Trichloptera*, *Plecoptera*, *Ephemeroptera*, *Diptera*, *Odonata*, and *Coleptera*). No pattern of decrease in any individual genus; no treatment-related increase in drift among samples; no treatment related changes in the number of dead drift when collections were made 1-2 days after treatment.	Rabeni and Gibbs 1975 MRID 00159905
Application (NOS) of 1.25 ppm Dimilin 25WPfor 1 hour on July 13, 1984 to four points of the Kokawa River in the Izu Peninsula to control blackflies. The gradient of the river was approx. 2% and sampling stations are located between 50 and 250 m above sea level.	Most invertebrates were eliminated within 2 weeks, while Hydropsycidae (caddisfly) died out gradually. Adults of Elmidae (Riffle beetles), previously absent, appeared 1 week after treatment in large numbers at the uppermost of the treated region. No fish mortality was observed.	Satake and Yasuno 1987

Appendix 3b: Summary of aquatic field or field simulation studies on diflubenzuron and its formulations.

Application	Observations	Reference
Aerial application of Dimilin WP-25 at a rate of 70 g a.i. in 10, 5, and 2.5/H to three spray blocks in a mixed boreal forest near Kaladar Ontario Canada. Water, sediment and aquatic plants were analyzed for DFB residues. Ponds appear to have been directly sprayed.	The duration of detectable DFB residues in water, sediment, and aquatic plants differed for each substrate but in all cases was less than 2 weeks. There was significant mortality in two groups of caged pond invertebrates (amphipods and corixidae [water boatman]) 1-6 days after treatment. Three taxa of littoral insects (mayflies, dragonflies, and damselflies) were significantly reduced in abundance in treated ponds 21-34 days post treatment but recovered to pre-treatment levels by the end of the season. Cladoceran and copepod populations were reduced 3 days after treatment and remained suppressed for 2-3 months.	Sundaram et al. 1991
5 monthly surface applications of 0.05 lbs a.i./acre Dimilin (25% WP) [56 g/ha] to artificial pond containing mosquito fish (*Gambusia affinis*)	No adverse effects on population growth of fish.	Takahashio and Miura 1975 MRID 00016545
2x application of Dimlin W-25 at a rate of 0.03 lbs a.i./acre at 14-day interval to an outdoor 750 gallon aquarium containing pond water and sediment, bluegill sunfish, clams, and crayfish; fate of diflubenzuron in all elements of the simulated ecosystem was monitored for 42 days from initial treatment.	Rapid dissipation of DFB (half-life < 12 hours); rapid accumulation of compound by fish and clams with rapid elimination (plateau of approx. 55 ppb by day 27 which was maintained for the duration of the experiment); fish samples contained several degradation products (CPU and DFB represent the only organo-extractable residues; clam samples contained only DFB; crayfish did not accumulate any of the compound during the week after the initial treatment.	Thompson-Hayward Chemical Co 1979 *In*: Technology Sciences Group Inc. 1998 MRID 44460702
Aerial application of Dimilin at a rate of 4.5 kg/ha (4 lbs granules/acre) to a tidal flood plain of the Fraser River in British Columbia in June 1976 . The organisms in the tidal flats of the Fraser River at the time of the study included crustaceans (zooplankton), insects, water mites and bugs, snails, and clams.	**Residue**: Dimilin, which was detected in the water up to 71 days after treatment, peaked at 1.8 ppb 8 days after application and decreased slowly to a minimum level of 0.24 ppb at 2 months after application. In mud, Dimilin peaked at 5.66 ppb 4 hours after application and decreased to a minimum level of 1.3 ppb by 2 months after treatment. **Biological effects**: Treatment arrested mosquito development but also decreased the population of zooplankton and suppressed the emergence of non-target insects of the same order as the mosquitoes.	Wan and Wilson 1977 MRID 00095416
Dimilin forestry spray at 67 g DFB/ha	No effect on aged brown trout in stream from day -7 to day +6. Observations along length of stream revealed no indication of fish mortality. Based on population estimates 6 weeks following application, no delayed effects on fish populations.	White 1975

Appendix 3b: Summary of aquatic field or field simulation studies on diflubenzuron and its formulations.

Application	Observations	Reference
Broadcast foliar spray at rate of 0.25 lbs a.i./acre of Dimilin 2L to rice paddy test plots in Arkansas and California 40 days after rice planting.	DFB and its metabolites (DFBA and CPU) dissipated rapidly in the aquatic environment and there was no downward movement of DFB or its degradation products in aquatic soil/sediment.	Willard 1999 MRID 45009601
Broadcast spray application of Dimilin 25W to entire surface area of pond (containing fish) at a rate of 0.36 lbs a.i./acre.	calculated half-life for DFB in water = 5.4 days calculated half-life for DFB in soil/sediment = 8.6 days.	Willard 2000a MRID 45191001
Benthic communities in outdoor experimental streams , concentrations of 1 or 10 mg/L diflubenzuron for 30 minutes	No drift of macrobenthos was induced at the time of application. However, diflubenzuron affected the emergence of all species examined. High larval mortality for a species of chironomid was observed directly in the stream treated with diflubenzuron, where numbers of mayfly nymphs and caddisfly larvae were also decreased	Yasuno and Satake 1990

Appendix 4: Toxicity of diflubenzuron and diflubenzuron formulations to birds

Species	Nature of Exposure	Exposure Time	Effects	Reference
Single Dose				
Mallard ducks, males and females, 10 birds/dose group	single gavage doses ranging from 1000 to 5000 mg/kg bw TH-6040 (99.4% pure)	single dose	No mortality, no signs of abnormal behavior or toxicity, and no gross pathological changes to organs. NOEC = 5000 mg/kg bw	Roberts and Parke 1976 MRID 00073936
Bobwhite quail	5000 mg/kg single gavage dose	single dose	LD_{50} >5000 mg/kg bw	U.S. EPA/OPP 1997a

Note on above study: U.S. EPA/OPP 1997a attributes this study to Roberts and Parke 1976. Roberts and Parke 1976, however, only assayed mallard ducks. A review of the CBI files did not identify an acute oral study in bobwhite quail. The above entry is included in the peer review draft *but should be deleted* in the final report unless the value can be verified.

Species	Nature of Exposure	Exposure Time	Effects	Reference
Red-winged black birds, *Agelaius phoeniceus*, 5 or 6/dose group	single gavage dose of 1000, 2500, 3000, 4000, or 5000 mg/kg bw technical grade (99%) TH 6040; observation period of 14 days	single dose	Mortality: 1/6 at 1000 mg/kg (considered unrelated to treatment); 0/5 at 2500 mg/kg 1/6 at 3000 mg/kg following signs of piloerection, asthenia, and ataxia; 4/6 at 4000 mg/kg 5/6 at 5000 mg/kg NOEC = 2500 mg/kg bw	Alsager and Cook 1975 MRID 00038614

Acute Dietary

Species	Nature of Exposure	Exposure Time	Effects	Reference
Mallard ducks	in diet concentrations ≤4640 ppm technical grade TH-6040 (purity assumed to be 100%) dissolved in corn oil	8 days	NOEC =4640 ppm; no mortality and no observable signs of toxicity.	Fink and Petrocelli 1973 MRID 00038613

Species	Nature of Exposure	Exposure Time	Effects	Reference
Reproduction Studies				
Mallard ducks, *Anas platyrhynchos*, young adults, 16/sex/dose group	dietary nominal concentrations of 0, 250, 500, or 1000 ppm. Based on mean body weights (about 1.25 kg) and mean food consumption (about 160 g/day), the dietary concentrations correspond to about 0, 32, 64, and 128 mg/kg bw/day.	20 weeks	No treatment-related mortality; no overt signs of toxicity; no treatment-related effects on body weight or feed consumption; no treatment-related effects of reproduction; and no treatment-related effects on body weights of hatchlings or 14-day old survivors.. At 1000 ppm, there was slight, but statistically significant decrease in mean egg shell thickness. NOEC = 500 ppm	Beavers et al. 1990a MRID 41668001
Bobwhite quail, *Colinus virginianus*, young adults, 16/sex/dose group	dietary nominal concentrations of 0, 250, 500, or 1000 ppm. Based on mean body weights (about 200 g) and mean food consumption (about 22 g/day), the dietary concentrations correspond to about 0, 27.5, 55, and 110 mg/kg bw/day.	21 weeks (1-generation)	No treatment-related mortality, overt signs of toxicity, or effects on body weight or food consumption during experimental period. At 1000 ppm, there was a marginal decrease in the number of eggs laid. NOEC (based on possible effect on egg production at 1000 ppm) =500 ppm.	Beavers et al. 1990b MRID 41668002 Beavers et al. 1990c

Appendix 4: Toxicity of diflubenzuron and diflubenzuron formulations to birds

Species	Nature of Exposure	Exposure Time	Effects	Reference
Bobwhite quail, *Colinus virginianus*, adults	dietary nominal concentrations of 2.5, 25, or 250 ppm *air-milled* (99.9% pure) diflubenzuron	12 weeks	No adverse effects on the reproductive parameters measured, including eggs laid, cracked eggs, eggs set, fertile eggs, hatched eggs, egg shell thickness, feed consumption, adult deaths, or chick survival. NOEC = 250 ppm based on review by U.S. EPA/OPP 1997a. The study authors attribute some observed differences between treated groups and controls to random variation and the large sample size (i.e, 500 eggs).	Booth et al. 1977 MRID 00099719
Chickens, White leghorn laying hens, 27-weeks old 10/dose group	dietary nominal concentrations of 0, 10, 50, 100, or 500 ppm diflubenzuron	8 weeks	No adverse effects on food consumption, body weight, egg production, egg weight, egg shell thickness, fertility, hatchability, or progeny development. Diflubenzuron accumulated in eggs and body tissues; 5 weeks after treatment, diflubenzuron was not delectable in the egg, liver, fat, or muscle tissues of hens fed any of the dose levels of the compound.	Cecil et al. 1981 MRID 00156781 Cecil et al. 1981 [published in the open literature]
Growing male broiler and layer chickens	Diflubenzuron at dietary concentrations of up to 250 mg/kg feed	from 1 day of age to 98 days	No consistent differences over time on body weight, food consumption, or testes, liver, comb and feet weights.	Kubena 1981
Layer-breed chickens, males and females	diflubenzuron was fed at levels of 0, 2.5, 25 and 250 mg/kg feed	from 1 day of age through a laying cycle	No effects on egg production, egg weight, eggshell weight, fertility, hatchability or progeny.	Kubena 1982

NOS = Not otherwise specified.

Appendix 5: Toxicity of diflubenzuron to terrestrial invertebrates

Species	Exposure	Effects	Reference
House fly(*Musca domestica*) and parasitoid *Muscidifurax raptor*	Dimilin, topical exposure	No effect to eggs or pupae at 10,000 ppm. > 90% mortality to intermediate to late stage larvae at 1.25 to 10 ppm. No effects to parasitoid.	Ables et al. 1975
Gypsy moth predators: lacewing (*Chrysopa carnea*), ladybird beetle (*Hippodamia convergens*), Wasp parasite *Trichograma pretiosum* of bollworm (*Heliothis*)	10 mg on 9-cm filter paper (contact); and 5 ppm sugar-water fed to host.	Lab rearing of hosts on diflubenzuron diets and raising parasites on those eggs. And raised lacewings from topically treated eggs and adults. Negative effects on lacewing and ladybird beetle in lab; egg hatch of beetle returned to normal after 30-40 d.	Ables et al. 1977
Honey bees, *Apis mellifera L.*	Dietary exposure at concentrations of 0.59, 5.9, and 59 mg/kg diet for 10 days. Vehicle: Sugar syrup.	Reduced brood production at the highest concentration. No effect at two lower concentrations.	Barker and Taber 1977
Honey bees, *Apis mellifera L.*	Diflubenzuron (25% WP) formulation (100 ppm a.i.) supplied in water and 60 ppm supplied in sucrose syrup to colonies of honey bees in outdoor cages.	Brood production almost eliminated; treated bees consumed significantly less water and pollen cake and produced significantly less comb, brood, and new workers. Number of eggs increased in treated colonies. No significant differences in survival of treated bees, compared with controls and both treated and untreated colonies built queen cells when the original queen was removed.	Barker and Waller 1978
Rice swarming caterpillar adult *Spodoptera mauritania*	Dimilin 25-WP, dietary exposure	60-64% sterility at 10 ppm, 100% sterility at 100-1,000 ppm	Beevi and Dale1984
Gypsy moth *Lymantria dispar*	topical exposure	LD_{50} = 3.58 mg/kg (alder) LD_{50} = 8.96 mg/kg (douglas fir)	Berry et al. 1993
Gypsy moth *Lymantria dispar*	acute oral exposure	LC_{50} = 0.06 ppm diet (alder) LC_{50} = 0.45 ppm diet (douglas fir)	Berry et al. 1993
earthworm (Eisenia fetida)	soil exposure	NOEC = 1 g Dimilin WP-25 per kg dry soil	Berends and Thus 1992
earthworm (Eisenia fetida)	soil exposure	NOEC = 780 mg diflubenzuron per kg dry soil	Berends et al. 1992

Appendix 5: Toxicity of diflubenzuron to terrestrial invertebrates

Species	Exposure	Effects	Reference
Nontarget insects (lacewing *Chrysopa oculata*, braconid wasp *Macrocentrus ancylivorous*, assassin bug *Acholla multispinosa*)	Dimilin 25-WP - topical exposure up to 300 ppm and contact with treated leaves consumption of treated host larvae	Considerable mortality and inhibition of molting to lacewing, but no effects to wasp or bug. reduced emergence of wasp, but no effect on lacewing.	Broadbent and Pree1984a
cockchafer *Melolontha melolontha*, leaf beetle *Gastroidea viridula*	beech or sorrel leaves treated with 0.1% Dimilin 25-WP	repellant effects and 100% ovicidal effect to chafer. Effective against larvae and eggs of beetle.	Büchi and Jossi1979
Honey bee	Dimilin - topical exposure	LD_{50} = 52.9 mg/kg (3rd instar) LD_{50} = 45.51 mg/kg (4th instar) LD_{50} = 22.33 mg/kg (pupa)	Chandel and Gupta1992
Bee *Apis cerana indica*	Dimilin - topical exposure	LD_{50} = 56.15 mg/kg (3rd instar) LD_{50} = 49.13 mg/kg (4th instar) LD_{50} = 22.69 mg/kg (pupa)	Chandel and Gupta1992
Spined soldier bug, *Podisus maculiventris*, (predator)	Topical, residual, and oral exposure to diflubenzuron 48% suspension concentrate.	Diflubenzuron harmless to predatory bug by direct and residual contact, but highly toxic when ingested via drinking water. Five days after adult emergence, LC_{50} (for ingestion to 5th instar nymphs) = 7.20 µg/mL. Exposure of 5th instars to sublethal concentrations (around LC_{10}) had no adverse effects on reproduction of emerging adults.	De Clercq et al. 1995b
Flower bug, *Orius laevigatus*, predatory bug used as a biological control for thrips. N= 20	5th instar nymphs were exposed to formulated diflubenzuron WP 25 via ingestion of contaminated (saturated) cotton wool plug and residual contact for 3 days.	LC_{50} (residual contact) = 391.1 mg a.i./L (95% CI = 140.5-825.6 mg a.i./L) LC_{50} (ingestion) = 229.9 mg a.i./L (95% CI = 108.0-397.3 mg a.i./L)	Delbeke et al. 1997
Migratory grasshopper *Melanoplus sanguinipes*	Dimilin 25-WP, dietary exposure	LC_{50} = 0.08 ppm (lettuce diet) LC_{50} = 0.1 ppm (wheat seedling diet)	Elliott and Iyer1982
Honey bee	Dimilin - topical or dietary exposure	LD_{50} > 30 µg/bee (topical) LD_{50} > 200 µg Dimilin WP-25 per bee (dietary). No adverse effects at 5.9 ppm.	Gijswijt1978

Appendix 5: Toxicity of diflubenzuron to terrestrial invertebrates

Species	Exposure	Effects	Reference
Rove beetle (*Aleochara bilineata)* and Cabbage maggot (target)	Consumption of cabbage maggot treated with Dimilin 25-WP	No adverse effects on rove beetle. Suppression of egg hatching and larva development of the cabbage maggot *Delia radicum*	Gordon and Cornect1986
Desert locust (*Schistocerca gregaria*)	Dietary exposure	LD_{50} = 886.7 μg AI (2nd instar) LD_{50} = 207.4 μg AI (4th instar) LD_{50} = 325.2 μg AI (5th instar)	Jepson and Yemane1991
Mealworms, *Tenebrio molitor*, adults	10 mg/g technical Diflubenzuron incorporated into the diet (wheat flour) for period of ecysis to 9 days	Treatment quantitatively and qualitatively altered the lipid metabolism during sexual maturation. Fatty acid composition of the ovaries was not affected.	Khebbeb et al. 1997
Gram pod borer, *Helicoverpa armigera* (Lepidotera: Noctuidae) [crop pest] eggs 0-24 and 24-48 hours.	eggs dipped for two minutes in different concentrations (NOS) of a suspension of diflubenzuron in distilled water.	IC_{50} (0-24 hours) = 0.0055 ppm (fiducial limits= 0.007-0.004 ppm) IC_{50} (24-48 hours) = 0.0061 ppm (fiducial limits= 0.01-0.0034 ppm)	Kumar et al. 1994
Honey bee	acute topical exposure	LD_{50} > 100 μg/bee (adult) LD_{50} >0.0125 μg/bee (larva)	Kuijpers1989
Honey bee	acute oral exposure	LD_{50} > 100 μg/bee (adult) LD_{50} > 0.030 μg/bee (larva)	Kuijpers1989
Oxya japonica (Orthoptera)	Dimilin 25-WP, topical exposure	LD_{50} = 0.06 μg per insect or 0.31 mg/kg	Lim and Lee1982
Australian ladybird beetle, *Cryptolaemus montrouzierei* , adults (excellent predator of mealybug species)	200 ppm diflubenzuron on treated surface	No adverse effects on longevity or feeding; however treatment had effects on adult females, yielding only 278 progeny, compared with 419 yielded by controls.	Mani et al. 1997
Gypsy moth	Dimilin 25-WP, dietary exposure at 0.1 mg/kg	100% lethal to larvae	Martinat et al. 1988

Appendix 5: Toxicity of diflubenzuron to terrestrial invertebrates

Species	Exposure	Effects	Reference
Grasshopper, *Poekilocerus pictus*, 2-day-old, virgin females	20 µg/insect Diflubenzuron dissolved in acetone applied on the ventral side of the abdomen.	In few treated females, the abdomen could not come out of the sand after egg laying and mortality occurred in the same position. When the abdomen was stretched back, the normal position was not attained again, which may be attributed to the chitin synthesis inhibiting activity of diflubenzuron. Ovaries of treated females were adversely affected by treatment, which probably accounts for the decrease in reproduction.	Mathur 1998
Mexican bean beetle	Dimilin 25-WP, dietary exposure	LC_{50} = 3.4 ppm (3rd instar)	McWhorter and Shepard 1977
Lacewing, *Chysoperla carnea*, adults <24 hours old	topical application	At a diflubenzuron at dose of 7,000 ng/insect, no mortality among adults; 100% inhibition of egg hatching due to death embryo. At the lowest dose, 75 ng/insect), 32% reduction in egg hatch.	Medina et al. 2002
Lacewing, *Chysoperla carnea*, adults <24 hours old	topical application	LD_{50} = 2.26 ng/insect LD_{10} = 0.74 ng/insect LD_{90} = 6.87 ng/insect No effect on reproduction at a dose of 0.5 ng/insect.	Medina et al. 2003
Honey bees, caged colonies	10 mg/kg diflubenzuron for 10 weeks	No adverse effects on pollen consumption or brood production; however treatment resulted in a 50% decrease in the amount of syrup stored.	Nation et al. 1986
Cotton leafworm *Spodoptera littoralis*	Dietary exposure	LC_{50} = 1 mg/kg	Neumann and Guyer1987
Predacious phytoseiid mite, *Amblyseius womersleyi*, adult females	Diflubenzuron (Dimilin) (25% pure) at field rate of 100 ppm on bean leaf disks dipped in test substance	No mortality 3 days after treatment.	Park et al. 1996
Oncopeltus fasciatus, Large milkweed bug	Topical exposure to 1 µg/insect	Inhibition of reproduction	Redfern et al. 1980

Appendix 5: Toxicity of diflubenzuron to terrestrial invertebrates

Species	Exposure	Effects	Reference
Brown lacewing, *Micromus tasmaniae* (beneficial predator)	contact exposure: 0.07 $\mu g/cm^2$ a.i. as Dimilin 25 WP sprayed on petri dishes	Treatment caused a strong trend toward decrease in fertility where 13% of all pairs did not lay any eggs; total numbers of eggs produced per females were reduced by approx. 50%; treated females deposited significantly fewer eggs per day than the control females ($p<0.01$).	Rumpf et al. 1998
Brown lacewing, *Micromus tasmaniae* (beneficial predator)	contact exposure: Dimilin 25 WP sprayed on petri dishes 32 hours after the 2nd larval molt	120 hour LC_{50} = 0.069% a.i. (95% CI: = 0.049-0.107% a.i.) 360 hour LC_{50} = 0.009% a.i. (95% CI: = 0.003-0.012% a.i.)	Rumpf et al. 1997
European earwig *Forficularia auricularia*	12.5 g a.i./ha	growth and mobility adversely affected	Sauphanor et al. 1993
Pieris brassicae (Large White Butterfly)	Topical exposure	LD_{50} = 2.5 µg/insect or 1.07 mg/kg	Sinha et al. 1990
Mealworms, *Tenebrio molitor*, adults	5 or 10 mg/g Diflubenzuron (NOS) incorporated into diet for 3 or 6 days post emergence.	Diflubenzuron had no significant effect on fat body protein.	Soltani-Mazouni and Soltani 1995a
Mealworms, *Tenebrio molitor*, adults	5 or 10 mg/g Diflubenzuron (NOS) incorporated into diet . Duration of exposure not clear.	treatment caused a decrease in both the cell density of germarium and the thickness of chorion.	Soltani and Soltani-Mazouni 1997
Mealybug ladybird beetle, *Crptolaemus montrouzieri*, predator of mealybugs	freshly emerged final instar nymphs were fed with mealy bugs treated with 0.153 ppm Diflubenzuron and sacrificed after 24, 48, 72, or 96 hours.	There was a significant reduction in protein content after 2 hours; however, with prolonged exposure, the insect was found to adapt itself to the toxic stress and the adverse effect was much less pronounced after 96 hours.	Sundari et al. 1998
Honey bee	oral and contact LD_{50} values	>30 µg/bee	Stevenson 1978

Appendix 5: Toxicity of diflubenzuron to terrestrial invertebrates

Species	Exposure	Effects	Reference
Honey bee, *Apis mellifera*	0.1, 1, & 10 ppm in Sugar-cake for 12 wks. 0.01, 0.1, & 1.0 ppm in sucrose syrup next year for 10 weeks.	At 10 ppm diflubenzuron in sugar-cake, significantly fewer sealed brood were produced, and colony size was reduced significantly compared to control and lower dosed colonies. No effects on brood production, colony size or adult bee mortality were seen the following year, when lower doses in a fluid solution was used. Degradation in sucrose solution might have reduced the potential for adverse effects.	Stoner and Wilson 1982
Fruit-sucking moth, *Othreis materna*, 5th instar larvae	topical application of 0 or 0.025 µL Dimilin (25 WP) in 5 µL acetone to ventral region of the abdomen. Larvae were sacrificed 24, 48, or 72 hours after exposure.	Inhibition of molting in larvae seems to occur due to neuroendocrine failure. See Section 4.1.2.3. for discussion.	Tembhare and Shinde 1998
Honey bee colonies	Diflubenzuron diluted with sucrose to a rate equivalent to maximum application rate on flowering crops.	Treatment with diflubenzuron resulted in short-term decrease in the numbers of adult bees and brood, compared with controls. No significant effect on development of brood during the following spring; however, there appeared to be a slower expansion, compared with controls. No adverse effects on queen viability.	Thompson and Wilkins 2003
Nematodes	10 day dietary exposure to Dimilin at 10 ppm	Adults unaffected but reproduction hindered and egg hatch prevented. Population reductions of 5% for *Pelodera* sp., 47% for *Panagrellus redivivus*, and 94% for *Acrobeloides* sp.	Veech 1978
German cockroach *Blatella germanica*	Dimilin 25W® - contact with spray of treated cage plywood panels	population reduction of 67.3% at 30 mg/m^2, 93% at 60 mg/m^2, and 98.2% at 120 mg/m^2. egg hatch unaffected, but high first instar mortality.	Wadleigh et al.1991
Codling moth (*Cydia pomonella*), neonates of field-collected and laboratory strains	Dimilin WP	5-day LC_{50} = 13.9 mg/L (95% CI = 10.7-18.2 mg/L)	Weiland 2000 MRID 45245403

Appendix 5: Toxicity of diflubenzuron to terrestrial invertebrates

Species	Exposure	Effects	Reference
Honey bee	Dimilin 25-WP, dietary	LC_{50} = 3.7 ppm	Wittmann1982
Honey bee	Diflubenzuron dietary	No toxicity at concentrations up to 1000 mg/kg in the diet.	Yu et al. 1984
Stinkbug, *Podisus nigrispinus*, eggs and nymphs	Diflubenzuron sprayed on eggs and nymphs.	No effect on egg viability.	Zacarias et al. 1998
Host: Mexican bean beetle (*Epilachna varivestis*). Parasite: wasp (*Pediobius foveolatus*).	100, 1,000, and 10,000 ppm	Topical application to adults did not affect survival or reproduction, nor that of their progeny. Emergence of parasite from larvae treated after parasitism and before was 0 or nearly 0.	Zungoli et al. 1983

Appendix 6: Toxicity of diflubenzuron to fish

Species	Nature of Exposure	Exposure Time	Effects[a]	Reference
			Diflubenzuron	
Acute				
Bluegill sunfish, *Lepomis macrochirus*	static renewal bioassay	96 hours	LC_{50} = 135 mg/L	Marshall and Hieb 1973 MRID 00056150
Fathead minnow	static	96 hours	LC_{50} > 500 mg/L	Reiner and Parke 1975 MRID 00060376
Mummichog, *Fundulus heteroclitus*	static renewal bioassay	96 hours	NOEC = 29.86 mg/L LC_{50} = 32.99 (CL = 29.01-37.52 mg/L)	Lee and Scott 1989
Rainbow trout, *Salmo gairdneri*	static renewal bioassay	96 hours	LC_{50} = 140 mg/L	Marshall and Hieb 1973 MRID 00056150
Rainbow trout, Channel Catfish, and Bluegills	static	96 hours	LC_{50} > 100 mg/L	Johnson and Finley 1980
Brook trout	static	96 hours	LC_{50} > 50 mg/L	Johnson and Finley 1980
Yellow perch	static	96 hours	LC_{50} = 25 mg/L	Johnson and Finley 1980
Rainbow trout	static	96 hours	LC_{50} = 240 mg/L as Dimilin 25-WP	Julin and Sanders 1978
Channel catfish	static	96 hours	LC_{50} = 370 mg/L as Dimilin 25-WP	Julin and Sanders 1978
Fathead minnow	static	96 hours	LC_{50} = 430 mg/L as Dimilin 25-WP	Julin and Sanders 1978
Bluegill sunfish	static	96 hours	LC_{50} = 660 mg/L as Dimilin 25-WP	Julin and Sanders 1978
Yellow perch	static	96 hours	LC_{50} > 50 mg/L	Mayer and Ellersieck, 1986
Brook trout	static	96 hours	LC_{50} > 50 mg/L	Mayer and Ellersieck, 1986
Cutthroat trout	static	96 hours	LC_{50} > 60 mg/L	Mayer and Ellersieck, 1986
Atlantic salmon	static	96 hours	LC_{50} > 50 mg/L	Mayer and Ellersieck, 1986

Appendix 6: Toxicity of diflubenzuron to fish

Species	Nature of Exposure	Exposure Time	Effects[a]	Reference
Longer Term				
Fathead minnows	continuous exposure to concentrations of 0, 0.00625, 0.0125, 0.025, 0.05, or 0.10 ppm 99.4% pure TH-6040 (air milled)	10 months	No effects on survival, growth, behavior or reproduction, compared with controls; no observable effects on hatchability of eggs spawned by fish. Fry, hatched from eggs spawned by treated fish showed no appreciable differences, compared with controls after 60 days of exposure to TH-6040, under same conditions as parental fish.	Cannon and Krize 1976 MRID 00099755
Salmonids (steelhead trout) and non-salmonids (fathead minnows and guppies) fish species	Diflubenzuron under flow-through conditions at concentrations up to 45 µg/L.	96 hours or 30 days (survival and growth in early life stages	No effects at any concentration. NOEC >45 µg/L (highest concentration tested)	Hansen and Garton 1982a
Mummichug, *Fundulus heteroclitus* (marine species)	Life cycle involving continuous (flow through) exposure to TH-6040 dissolved in acetone to deliver concentrations of 0.003, 0.006, 0.0125, 0.025, or 0.05 ppm	life cycle (2-generations)	No significant dose-response relationships.	Livingston and Koenig 1977 MRID 014402120 Livingston and Koenig 1977 MRID 00099722
Mesocosm				
Bluegill sunfish, *Lepomis macrochirus*, "young-of-the year"	Dimilin at nominal treatment levels of 0.7, 2.5, 7.0, or 30 µg/L to littoral enclosures	70 days	NOEC = 0.7 µg/L LOEC = 2.5 µg/L Secondary effects on endpoints based on growth (individual fish size). See additional notes below.	Moffett and Tanner 1995 ***In***: Moffett 1995 MRID 44386201

Species	Nature of Exposure	Exposure Time	Effects[a]	Reference

Additional Notes on Moffett and Tanner 1995: In indigenous fish species, mean fish size, population numbers, and biomass were not affected by exposure to diflubenzuron (≤30 µg/L). Indigenous species included brook stickleback, northern redbelly dace, and central mudminnows. Young-of-the-year bluegill growth rates were directly correlated to the density of several invertebrates (cladoceran and copepods) in the enclosures and inversely correlated to the measured concentration of diflubenzuron. The results indicate that the indirect effects of diflubenzuron on bluegill sunfish were caused by a reduction in food resources due to the direct toxicity of the pesticide on the chitinous invertebrates preferred by the bluegill.

Bluegill sunfish, *Lepomis macrochirus*	Dimilin 25 W in littoral enclosures at nominal concentrations of 2.5 or 30 µg/L	reproductive cycle	Treatment adversely affected reproductive success by decreasing growth of young of the year bluegills at 2.5 and 3.0 µg/L by eliminating or reducing preferred bluegill food choices (cladocerans and copepods).	Tanner and Moffett 1995 ***In***: Moffett 1995 MRID 44386201

Additional Notes on Tanner and Moffett 1995: No behavioral effects related to reproduction of adult bluegills were observed in the enclosures. There was no clearly determined effect on spawning; however it appeared by spawning was influenced more by water temperature than by diflubenzuron. No direct effects on larvae prior to swim-up; however secondary effects on growth were evident following swim-up, apparently due to the precipitous decrease of zooplankton and the decline of chironomids and other macroinvertebrates.

Bioconcentration

Bluegill sunfish, *Lepomis macrochirus*	dynamic 42-day study to evaluate bioconcentration of C ^{14}-diflubenzuron	28 days under flow-through conditions, with 14 day depuration period	In fillet, the BCF was 120 after 1 day and 170 after 28 days with a peak of 200 after 7 days. In whole fish, the BCF was 260 after 1 day and 350 after 28 days with a peak of 360 after 7 days.	Burgess 1989 MRID 42258401
White crappies	10 ppb DFB	24 hours	BCF = 82.2	Schaefer et al. 1979
Bluegill sunfish	10 ppb DFB	24 hours	Residues of approximately 848 ppb; 218 ppb in skin and 232 ppb in inner tissues (NOS); residues decreased rapidly when fish were transferred to the rinse tank for ≥48 hours.	Schaefer et al. 1979

Appendix 6: Toxicity of diflubenzuron to fish

Species	Nature of Exposure	Exposure Time	Effects[a]	Reference
			p-Chloroaniline	
Acute				
Bluegill *Lepomis macrochirus*	Static	96 hour	LC_{50} value = 2.4 mg/L	WHO 2003
Longer Term				
Medaka, *Oryzias latipes*	Larval growth; flow-through	28 days	MATC <2.25 mg/L	WHO 2003
Zebra fish *Brachydanio rerio*	growth and reproduction at 0.04, 0.2, and 1 mg/liter	5 weeks	Adverse effects at 1 mg/L: abdominal swelling, spinal deformations, reduced number of eggs, and reduced fertilization in the F1 and F2 generations.	Bresch et al. 1990
Zebra fish *Brachydanio rerio*	Flow-through	3 weeks	NOEC for Mortality and other effects = 1.8 mg/L	WHO 2003
Bioconcentration				
Medaka, *Oryzias latipes* (Killifish)	Static aqueous exposures to [^{14}**C]-chloroaniline** (8.9-17 mCi/ mmol; >98% pure) for up to 320 minutes	up to 320 minutes	Due to low elimination rates, 20% of the absorbed dose remained within the fish through 330 minutes after exposure. N-acetylation was the dominant route of *in vivo* metabolism, with no indication of ring hydroxylation.	Bradbury et al. 1993
Carp, *Cyprinus carpio*	continuous flow-through exposure to 0.30±0.07 or 10.4±0.4 µg/L **p-chloroaniline**	up to 335 hours (about 14 days)	average BCF in whole body were 1.7 (low concentration) and 0.8 (high concentration).	Tsuda et al. 1993

[a] Values in parentheses are the 95% confidence limits.

Appendix 7: Toxicity of diflubenzuron to aquatic invertebrates

Species	Exposure Time	Effects[a]	Reference
Grass shrimp, *Palaemonetes pugio*	Subchronic exposure to measured concentrations of 0.70, 1.73, 5.51, 6.79, or 16.4 µg/L for 35 days in flowing seawater	No survival to day 7 among zoea exposed to initial measured concentrations of 5.5, 6.8, or 16.4 µg/L; survival among shrimp exposed to 0.70 or 1.73 µg/L was significantly less than survival among controls; no significant difference in size of shrimp exposed to 0.70 or 1.73 µg/L, compared with controls.	Bionomics-EG&G 1975 MRID 00038612
Grass shrimp, *Palaemonetes pugio*	Acute exposure to nominal concentrations of ≤1.0 mg/L TH-6040 in static seawater	96-hour LC_{50} = 0.64 mg/L (0.13-3.1 mg/L)	Bionomics-EG&G 1975 MRID 00038612
Hydropsychidae (Trichoptera)	Dimilin 25-WP, 15 days at 0.0025 to 0.25 mg/L	No adult emergence from treated tanks and only 31.6% emergence from control tanks	Bradt and Williams 1990
Mysid shrimp, *Mysidopsis bahia*, F_1 second generation	mean measured concentration of 123 ng/L (0.123 µg/L) diflubenzuron (97.6% pure) for up to 5 days	upon removal of treated water, juvenile second generation mysids completely recovered and had survival and reproductive success similar to that of the controls.	Breteler 1987 MRID 40237501
Mysid shrimp,*Mysidopsis bahia*, juvenile	Continuous exposure to mean measured concentrations of 29, 45, 86, 140 or 210 ng/L diflubenzuron through entire life cycle over a 28-day test period. Juvenile mysids produced during the test at the lowest four test concentrations (29-140 ng/L) were continuously exposed for the 8 days of the 28-day test.	F_0 survival at 86, 140, and 210 ng/L was significantly reduced ($p \leq 0.05$) compared with controls; treatment caused significant reduction in growth and development (as measured by dry weight) in F_0 males (210 ng/L) and F_0 females (140 and 210 ng/L); reproduction of F_0 mysids was significantly reduced at 86, 140, and 210 ng/L. The NOEC = 86 ng/L for growth LOEC = 140 ng/L for growth. Survival of the second generation (F_1) mysids was not affected by continuous exposure to any of the mean measured concentrations tested (21, 33, 83, or 123 ng/L). The NOEC after 8 days of exposure of F_1 generation mysids was >83 ng/L.	Breteler 1987 MRID 40237501 Note: This summary is of the ***primary study*** on which the studies discussed below are based.

Appendix 7: Toxicity of diflubenzuron to aquatic invertebrates

Species	Exposure Time	Effects[a]	Reference
Mysid shrimp, *Mysidopsis bahia*	24-hour exposure to mean concentration of 298 ng/L diflubenzuron (97.6% pure), followed by transfer to clean control water for 27 days.	Survival, growth, and reproductive success similar to that of controls.	Breteler 1987 MRID 40237501
Marine crabs, *Pontonia pinnophylax*, larvae	≤10 ppb diflubenzuron	larvae of four different crab species appeared normal during inter-molt periods and adverse effects were apparent until molting (similar to effect of DFB on insect larvae). Treatment deformed both the exocuticle and the endoculticle and was lethal to all four species of marine crabs.	Christiansen 1987
Mixed aquatic invertebrates (i.e., cladocerans, rotifers, and adult amphipods)	Microcosm 1: nominal concentrations of 0.3, 0.7, 1.4, 3.4, 6.8, or 13.6 µg/L Dimilin 25W Microcosm 2: nominal concentrations of 1.4. 3.4. 6.8, or 20.0 µg/L Dimilin 25W	Major effect of diflubenzuron in the microcosms was on the cladocerans. Population density was decreased within 3-4 days after treatment at ≥0.7 µg/L and remained consistently low, compared with controls throughout the study duration. Statistically significant ($p \leq 0.05$) differences in population density at ≥1.4 µg/L in Microcosm 1 between days 3 and 10 and at ≥0.7 µg/L in Microcosm 2 between days 4 and 14. Cladoceran population densities did not generally increase in either microcosm at ≥0.7 µg/L. Rotifers were no adversely affected by treatment at any concentration. The numbers of adult amphiphods (*Hyalella azteca*) were significantly different from controls ($p \leq 0.05$) at 13.6 µg/L (Microcosm 1) and 20 µg/L (Microcosm 2). *Amphipods exposed to concentrations <13.6 µg/L were not different (p≤0.05) from controls in either experiment.* NOEC for cladocerans = 0.3 µg/L LOEC for cladocerans = 0.7 µg/L	Corry et al. 1995 ***In***: Moffett 1995 MRID 44386201

Appendix 7: Toxicity of diflubenzuron to aquatic invertebrates

Species	Exposure Time	Effects[a]	Reference
Fiddler crabs, *Uca pugilator*, juveniles	repetitive 24-hours weekly exposures to 0.2, 2, 20, or 200 µg/L Dimilin in static seawater systems for 10 weeks.	NOEC (time to first molt) =20µg/L NOEC (survival) = 2 µg/L NOEC (ability to escape from test container) = 0.2 µg/L Behavioral effect caused by DFB exposure (≥2 µg/L) was most sensitive indicator of DFB toxicity. Investigators conclude that survival, molting, and behavior of juvenile fiddler crabs are significantly affected by exposure to repetitive applications of DFB.	Cunningham and Meyers 1987
Barnacles, *Balanus eburneus*, Cirripede crustaceans.	Exposure to1-1000 µg/L technical grade, air-milled diflubenzuron w/acetone as carrier solvent (preliminary studies showed no mortality in acetone controls) for 28 days	Dose-dependent mortality, with drastic mortality observed during the second week of exposure. Lethal and sublethal effects were observed at concentrations as low as 50 µg/L Disruption of the exoskeleton caused by diflubenzuron was similar to that observed in insects. Development of barnacles exposed to diflubenzuron for 10 days or more at 750 and 1000 µg/L was delayed in the pre-molt phase of cuticle secretion	Gulka et al. 1980
Ceriodaphnia dubia, neonates, <12 hours old	Exposure to 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, or 4.0 ng/mL Dimilin for 48 hours.	48-hr NOEC = 0.75 ng/mL [0.75 µg/L] 48-hr LC_{50} =1.7 ng/mL (95% CI = 1.36-2.02 ng/mL) [1.7 µg/L]	Hall 1986 MRID 40130601
Ceriodaphnia dubia	Chronic exposure to 0, 0.05, 0.1, 0.25, 0.5, 0.75, or 1.0 ng/mL (µg/L). Used methanol carrier with carrier control.	NOEC = 0.25µg/L At ≥0.5 µg/L, significant decrease in numbers of neonates produced, compared with controls; at 0.75 and 1.0 µg/L, adults produced no viable young; mortality increased at exposures to >0.1 µg/L. No carrier effect: 31.7 (28.4-34.9) neonates/female with 20% mortality in adults in untreated control and 30.9 (26.9-35) in carrier control with 10% mortality in adults.	Hall 1986 MRID 40130601

Appendix 7: Toxicity of diflubenzuron to aquatic invertebrates

Species	Exposure Time	Effects[a]	Reference
CRITICAL NOTE on HALL 1986: Hall (1986) reports concentrations as nanograms/mL. These are converted above to µg/L.			
Daphnia magna	Diflubenzuron under static conditions for 48 hours	LC_{50} = 1.84 µg/L (95% CI = 0.05-3.71 µg/L)	Hansen and Garton 1982a
Midges, *Tanytarsus dissimilis*, 2nd to 3rd larval instar	Diflubenzuron under flow-through conditions for 5 days; effect criteria = molting success	LC_{50} = 1.02 µg/L (95% CI = 0.56-1.47 µg/L)	Hansen and Garton 1982a
Midges, *Cricotopus*, sp, 4th larval instar to pupae	Diflubenzuron under flow-through conditions for 7 days; effect criteria = molting success	LC_{50} = 1.79 µg/L (95% CI = 1.48-2.13 µg/L)	Hansen and Garton 1982a
Daphnia magna	Survival and reproduction in full life cycle after exposure to diflubenzuron (conditions not specified)	LC_{50} = 0.062 µg/L (95% CI = 0.051-0.071 µg/L)	Hansen and Garton 1982a
Freshwater molluscs (two species of snails)	Diflubenzuron under flow-through conditions for 96 hours; effect criteria for chronic exposure (3 weeks) = survival, growth and reproduction	NOEC 45 µg/L (highest concentration tested)	Hansen and Garton 1982a
Stream invertebrates (most abundant), including Ephemeroptera, Plecoptera, Diptera, Tricoptera, and Coleoptera.	Technical diflubenzuron in dimethlformamide at 0.1, 1, 10, and 50 µg/L added continuously to complex laboratory stream channels supplied periodically with field-collected microorganisms for 5 months	Invertebrates were most adversely affected undergoing rapid and permanent reductions in biomass and diversity at diflubenzuron concentrations of ≥1.0 µg/L. These effects were the results of major in reductions in many of the aquatic insect populations, primarily among mayflies, stoneflies and diptera.	Hansen and Garton 1982a

Species	Exposure Time	Effects[a]	Reference

Additional Notes on Hansen and Garton 1982a: Diversity in all groups of stream invertebrates was clearly dose-related with little or no reductions observed at 0.1 µg/L, intermediate reductions observed at 1.0 µg/L (some dipteran tax were relatively insensitive at this concentration but eliminated at higher concentrations), and maximal reductions observed at ≥10.0 µg/L.

Algal, fungal, and bacterial functional groups were also adversely affected by exposure to diflubenzuron. Generally the adverse effects observed among these organisms was variable and transient alterations in biomass and diversity with algae and bacteria affected at 1.0 µg/L and fungi affected at as little as 0.1 µg/L.

Species	Exposure Time	Effects[a]	Reference
Total biological community in 8 stream microcosms	8- month continuous exposure to 0.1, 1.0, 10, or 50 µg/L diflubenzuron dissolved in dimethylformamide	Insects were directly affected at ≥1.0 µg/L (stoneflies and mayflies were the most sensitive with adverse effects apparent at 1.0 µg/L, dipterans affected at 10.0 µg/L, and coelopterans were not affected at any test concentrations); Algae and fungi were mildly affected at ≥1.0 µg/L, but the effects were considered indirect in response to the decreases in herbivore and shredder components of the insects; No effects were observed in bacteria, oligochaetes, or gastropods at any test concentration.	Hansen and Garton 1982b
Gammarid, *Hyallela azteca* (Benthic crustacea)	Diflubenzuron under flow-through conditions for 96 hours	LC_{50} = 1.84 µg/L (95% CI = 0.05-3.71 µg/L)	Hansen and Garton 1982a
Stoneflies, *Peltoperla arcuata* and *Pteronarcys proteus*	DFB-treated yellow poplar leaves via ingestion for 24-hours with 60- and 90-day observation periods.	*Peltoperla*: survival significantly different from controls at day 60; however survival of *Pteronarcys* was not significantly different from controls at 90 days, although the low number of molts that occurred during that time may have influenced the results.	Harrahy et al. 1994

Appendix 7: Toxicity of diflubenzuron to aquatic invertebrates

Species	Exposure Time	Effects[a]	Reference
Stoneflies, *Peltoperla arcuata*	nominal concentrations of 0, 1.0, 10, 100, or 1000 ppb DFB in dechlorinated tap water for 96 hours and then transferred to glass chambers containing pesticide-free water and fed stream conditioned red maple and white oak leaves.	Survival at 10 and 1000 ppb was significantly different from controls; however, survival at 100 ppb was not significantly different from survival of controls. No behavioral changes were observed.	Harrahy et al. 1994
Mayflies, *Cyngmula subaequalis*, *Stenacron interpunctatum*, *Stenonema meririvulanum*, and *S. femaratum*	0, 0.6, 5.6, 55.7, or 557.2 ppb DFB (Dimilin 25% WP) in water for 96 hours then placed in pesticide-free water for 36-day observation period	after 4 days of exposure, mayflies were significantly lower than controls al all concentrations tested. At the lowest concentration, only about 45% survived to day 36. Many of the treated mayflies died while molting, while others died from incomplete hardening of the new cuticle. Behavioral changes observed included decreased swimming speed at higher concentrations, and no avoidance of pipet or hands during water replacement activities. Some mayflies were observed to shake sporadically before dying.	Harrahy et al. 1994
Daphnids, *Daphnia magna*	48-hour exposure to diflubenzuron (97.6% pure)	48-hour NOEC = 0.45 µg/L 48-hour EC_{50} = 7.1 µg/L (95% CI = 5.0-1.0 µg/L)	Kuijpers 1988 MRID 40840502
Fairy shrimp, *Streptocephalus sudanicus*, females	Dimilin (solvent-based, liquid ULV formulation) for 24 or 48 hours under static conditions	24-hour EC_{50} =13.3 µg/L (range = 12.8-14.0 µg/L) 48-hour EC_{50} =0.74 µg/L (range = 0.60-0.88 µg/L)	Lahr et al. 2001
Backswimmer, *Anisops sardeus*, females	Dimilin (solvent-based, liquid ULV formulation) for 24 or 48 hours under static conditions	24-hour EC_{50} =2123 µg/L (range = µg/L) 48-hour EC_{50} =1937 µg/L (range = 1800-2020 µg/L)	Lahr et al. 2001
Daphnia magna	Technical grade diflubenzuron (TH-6040)	LOEC for reproduction: 0.09 ppb	LeBlanc 1975

Appendix 7: Toxicity of diflubenzuron to aquatic invertebrates

Species	Exposure Time	Effects[a]	Reference
Blue crabs, *Callinectes sapdidus*, embryos	acute toxicity; diflubenzuron exposure in culture plates	hatching EC_{50} =1.8 µg/L	Lee and Oshima 1998
Littoral enclosure community of mixed insects	Dimilin at nominal treatment levels of 0.7, 2.5, 7.0, or 30 µg/L to littoral enclosures	EC_{50} = 1.2 µg/L (measured concentration) NOEC = 1.0 µg/L (measured concentration) LOEC = 1.9 µg/L (measured concentration)	Liber 1995 ***In***: Moffett 1995 MRID 44386201
Littoral zooplankton community dominated by cladocera, copepoda, rotifera, and ostracoda.	Dimilin at nominal treatment levels of 0.7, 2.5, 7.0, or 30 µg/L to littoral enclosures.	Cladocera were extremely sensitive to treatment, with mean population abundances significantly reduced, compared with controls, at all four treatment levels. Mean population densities at ≥2.5 µg/L were 92 to >99% lower than mean control values by day 6 and remained at those levels through day 56. None of the decreased populations at ≥2.5 µg/L showed any sign of recovery throughout the study. Copepoda were adversely affected by treatment at all concentration levels. LOEC = 0.7 µg/L. The measured peak diflubenzuron concentration in water was 1.0 µg/L. Copepoda were significantly affected at this level, not unlike the Cladocera. The NOEC for both Claodcera and Copepoda was defined as <0.7 µg/L; however the effects at 0.7 µg/L appeared to be transistory with recovery after a single application observed within 12-29 days. Ostracoda densities were reduced at the two highest concentrations. NOEC = 2.5 µg/L Rotifera were not affected by treatment at any concentration level. NOEC = >30 µg/L.	Liber and O'Halloran 1995 ***In***: Moffett 1995 MRID 44386201 Published as Liber et al. 1996 and as O'Halloran et al. 1996
Chironomus plumosus, 4th instar larvae	Dimilin 25-WP, 48 hour exposure	EC_{50} = 0.56 mg/L	Julin and Sanders 1978

Appendix 7: Toxicity of diflubenzuron to aquatic invertebrates

Species	Exposure Time	Effects[a]	Reference
Daphnia magna	Dimilin 25-WP® - 48 hour exposure	LC_{50} = 0.00075 mg/L (neonate) LC_{50} = 0.02345 mg/L (adult)	Majori et al. 1984
Dragonfly nymphs *Orthemis* spp., *Pantala* sp.	TH 6040 (diflubenzuron) - 168 hour exposure	LC_{50} = 50 µg/L	Miura and Takahashi 1974
Mayfly nymphs *Callibaetis* sp.	TH 6040 (diflubenzuron) - 168 hour exposure	LC_{90} = 10 µg/L	Miura and Takahashi 1974
Aedes nigromaculatum	TH 6040® (diflubenzuron) - 48 hour exposure	LC_{50} = 0.5 µg/L	Miura and Takahashi 1974
Water scavenger beetle larvae *Hydrophilus triangularis*	TH 6040® (diflubenzuron) - 48 hour exposure	LC_{50} = 100 µg/L	Miura and Takahashi 1974
Water scavenger beetle adults *Laccophilus* spp., *Thermonectus basillaris*, *Tropisternus lateralis*	TH 6040® (diflubenzuron) concentrations as high as 250 µg/L	no mortality	Miura and Takahashi 1974
Mysid shrimp,*Mysidopsis bahia*	life-cycle exposure under flow-through conditions	96-hour LC_{50} = 2.1 µg/L 21-day LC_{50} = 1.24 µg/L direct adverse effect on reproduction: the numbers of juveniles/female were significantly depressed at all nominal concentrations (0.075-0.75 µg/L)	Nimmo et al. 1979
Littoral enclosure community of mixed benthic marcroinvertebrates,predominantly, Chironomidae (midges), Oligochaeta (earthworms), and Mollusca	Dimilin at nominal treatment levels of 0.7, 2.5, 7.0, or 30 µg/L to littoral enclosures. Study duration = 71 days.	Reductions in abundance of Ephemeroptera (mayflies) and Odonata (damselflies and dragonflies) were observed at all nominal concentrations ≥2.5 µg/L. No adverse effects were observed on molluscs or earthworms at any of the four diflubenzuron test concentrations. Overall, the only benthic macroinvertebrate group that appeared to have been adversely affected by exposure to diflubenzuron was the Insecta.	O'Halloran and Liber 1995 ***In***: Moffett 1995 MRID 44386201

Appendix 7: Toxicity of diflubenzuron to aquatic invertebrates

Species	Exposure Time	Effects[a]	Reference
Stoneflies (*Pteronarcys proteus* and *Pteronarcys arcuata*)	fed leaves from treated poplar after conditioning in stream	No effect on survival.	Perry 1995a
Blue crabs, *Callinectes sapidus*, juveniles	Dimilin WP-25 in static renewal tests	both molt stage and renewal frequency affected toxicity: LC_{50} (random molt stages) = 3.5 mg/L LC_{50} (day of molt) = 300 µg/L LC_{50} (day of molt and repeated dosing) = 18.5 µg/L	Rebach 1996
Copepods, *Eurytemora affinis*, naupli	0.78 µg/L WP25 commercial DFB (25% DFB, 75% kaolin) and filtered river water for 5 or 6 days	0% survival at >1.69 µg/L; at 0.93 µg/L survival did not differ significantly from controls.	Savitz et al. 1994
Copepods, *Eurytemora affinis*, naupli	WP25 commercial DFB (25% DFB, 75% kaolin) and filtered river water.	48-hour LC_{50} =2.2 µg/L	Savitz et al. 1994
Daphnids, *Daphnia magna*	Continuous exposure to ^{14}-C-diflubenzuron nominal concentrations of 6.3-100 ng/L (mean measured concentrations of 5.6, 14, 23, 40, or 93 ng/L) under flow-through conditions for 21 days (one generation)	50% survival at 93 ng/L[0.093 µg/L]; survival at the other test concentrations ranged from 93 to 98%, comparable to controls. significant reduction in reproduction and body length at 93 ng/L, compared with controls ($p \leq 0.05$); at other test concentrations, reproduction and growth were comparable to controls. NOEC = 40 ng/L [0.04µg/L]	Surprenant 1988 MRID 40840501
Quahog clams, *Mercenaria mercenaria*	48-hour exposure to nominal concentrations of 100 or 500 µg a.i./L (mean measured concentrations of 79, or 320 µg a.i./L) of diflubenzuron (97.6% pure)	No adverse effects on development of quahog embryos and larvae NOEC >320 µg a.i./L	Surprenant 1989 MRID 41392001

Appendix 7: Toxicity of diflubenzuron to aquatic invertebrates

Species	Exposure Time	Effects[a]	Reference
Grass shrimp, *Palaemonetes pugio*	continuous exposure to 1-10 µg/L from inter-molt to molt (normally 7-14 days) and transfer to filtered seawater	Mortalities generally related to molt cycle with death occurring at the time of ecdysis or immediately after (LC_{50} = 0.65 µg/L); at concentrations of 7.5-10 µg/L, some shrimp did not die during the exposure period and displayed delayed progress in the molt cycle, and although these shrimp began progressing through the molt cycle when transferred to filtered seawater, they all failed to reach ecdysis and eventually died. Control shrimp were never observed in an arrested stage in the molt cycle during the experiment.	Tourat and Rao 1987 *In*: Technology Sciences Group 1998 MRID 44399307
Grass shrimp, *Palaemonetes pugio*	24-hour pulsed exposure with transfer to DFB-free medium	LC_{50} =3.4 µg/L (premolt animals D_1 - D_2)	Tourat and Rao 1987 *In*: Technology Sciences Group 1998 MRID 44399307
Grass shrimp, *Palaemonetes pugio*,	96 hours	LC_{50} =1.1 µg/L (premolt animals D_1 - D_2) very few or no mortalities among shrimp in very late premolt, early premolt, intermolt, or early postmolt stages during the 96-hour exposure.	Tourat and Rao 1987 *In*: Technology Sciences Group 1998 MRID 44399307
Horseshoe crabs, *Limulus polyphemus*, eggs	0, 5, or 50 µg/L DFB	at 5 µg/L, crabs showed a slight, but significant ($p<0.05$) delay in molt at 14 days, then molted at a rate comparable to controls and did not exhibit significant mortality. At 50 µg/L, molted at the same rate as controls but exhibited significant mortality immediately after ecdysis. Also, the prosomal width of the crabs in this group was smaller, compared with controls and crabs in the low dose group.	Weis and Ma 1987
snail *Physa* sp.	acute exposure	LC_{50} > 125 ppm	Wilcox and Coffey 1978

Appendix 7: Toxicity of diflubenzuron to aquatic invertebrates

Species	Exposure Time	Effects[a]	Reference
Grass shrimp, *Palaemonetes pugio*, ovigerous carrying 0.5-, 1-,3-, 6-, or 8-day old embryos	continuous exposure for 4 days to 0.3-5.0 µg/L DFB in static system with transfer after exposure to DFB-free seawater for rest of the embryonic development.	No correlation between age of the embryos at exposure and either hatchability or duration of larval development; severity of abnormality did not vary with the age of the embryos except at exposure concentration of 2.5 µg/L. Larval viability was significantly ($p<0.05$) affected by the age of the embryos at the time of exposure to DFB, with older embryos more sensitive to sublethal effects of DFB.	Wilson 1997b
Grass shrimp, *Palaemonetes pugio* at different life stages (embryos, larvae, postlarvae male and female non-spawning adults, and ovigerous females.	96 hours under static renewal conditions	larvae and post-larvae most sensitive to acute toxicity of DFB with LC_{50} values of 1.44 and 1.62 µg/L, respectively; ovigerous females (hence embryos) appeared to be the most resistant to the acute toxicity of DFB with a mean LC_{50} of 6985 µg/L.	Wilson and Costlow 1987
Grass shrimp, *Palaemonetes pugio*	chronic exposure to either technical grade DFB (98.4% a.i.) Or the wettable powder (WP-25) (25% a.i.)	72-hr and 96-hr calculated LC_{50} values were similar for the two formulations of DFB (WP-25 and TG): 72-hr LC_{50} = 2.95 µg/L (TG) 72-hr LC_{50} = 2.83 µg/L (WP-25) 96-hr LC_{50} = 1.84 µg/L (TG) 96-hr LC_{50} = 1.39 µg/L (WP-25) The investigators conclude that results from studies using technical grade DFB are applicable to the WP-25 formulation without the need for a “correction factor.”	Wilson and Costlow 1986

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Species	Exposure Time	Effects[a]	Reference
Copepods, *Eurytemora affinis*, naupli, 24- to 48-hours old, initially	0, 0.5, 0.78, or 0.93 ppb DFB under pulse (two 6.5 exposure periods) and continuous (14-day) exposure regimens.	In pulse exposures, copepods exposed in the first 6.5 days showed a significantly lower survival rate at 0.78 and 0.93 ppb; copepods exposed during the second half of the experiment showed no significant differences in mortality, compared with controls. In the 14-day continuous exposure, survival was significantly lower at 0.78 and 0.93 ppb, but was significantly higher than that in the early pulse exposure to 0.78ppb. Effects on brood production were observed at 0.8 ppb in individuals exposed only during the copepodite stages. Significant effects on production of naupli were observed only in the first 6.5 days of pulse exposure to 0.93 ppb. At salinities of 2, 10, and 15 ppt, survival from naupilar to adult stages was significantly reduced at 0.84 ppb and none survived to adulthood at 1.7 ppb.	Wright et al. 1996

[a]Values in parentheses are 95% confidence limits.

Appendix 8: Toxicity of diflubenzuron to aquatic plants

Species	Exposure	Effects [a]	Reference
ALGAE			
Phytoplankton communities in littoral enclosures	Dimilin at nominal treatment levels of 0.7, 2.5, 7.0, or 30 µg/L to littoral enclosures	Phytoplankton, as measured by cell size distributions and chlorophyll *a* in the enclosures, were not affected directly or indirectly by diflubenzuron treatment. No occasions of significant ($p \leq 0.05$) linear correlations between the nominal concentrations of diflubenzuron and phytoplankton measures. These results were consistent with the idea that diflubenzuron does not directly inhibit non-chitinous biota due to the specificity of its mode of action.	Moffett 1995 ***In***: Moffett 1995 MRID 44386201
Periphyton communities in littoral enclosures	Dimilin at nominal treatment levels of 0.7, 2.5, 7.0, or 30 µg/L to littoral enclosures	Late in the season (September), a 80 and 90% reduction in periphyton dry weight and 75 and 80% reduction in chlorophyll *a* at 7.0 and 30 µg/L treatment levels, respectively. Differences were statistically significant ($p=0.01$) on day 55 and nearly significant ($p=0.07$) on day 67.	Moffett 1995 ***In***: Moffett 1995 MRID 44386201
Macrophyte populations in littoral enclosures	Dimilin at nominal treatment levels of 0.7, 2.5, 7.0, or 30 µg/L to littoral enclosures	No adverse effects, direct or indirect, were observed on macrophyte species composition or total standing crop. There was no correlation between treatment concentrations and total macrophyte density throughout the study. The investigator indicates that direct effects were not anticipated because macrophytes do not have chitin.	Moffett 1995 ***In***: Moffett 1995 MRID 44386201
Blue-green algae, *Plectonema boryanum*	0.1 ppm TH-6040 in pure culture for 4 days	No growth inhibition, rapid metabolism of compound in water. Algae degraded 80T of compound in 1-hour incubation period to p-chlorophenyl urea and p-chloroaniline.	Booth and Ferrell 1977

Appendix 8: Toxicity of diflubenzuron to aquatic plants

Species	Exposure	Effects [a]	Reference
Freshwater algae *Selenastrum capricornutum*	300 µg/L diflubenzuron for 5 days	NOEC = 300 µg/L	Thompson and Swigert 1993b MRID 42940104
Freshwater algae, *Selenastrum capricornutum*	120 hour exposures; effect criteria = growth	NOEC 45 µg/L (highest concentration tested)	Hansen and Garton 1982a
Freshwater diatoms (*Navicula pelliculosa*)	380 µg/L for 5 days	NOEC = 380 µg/L	Thompson and Swigert 1993c MRID 42940105
Marine diatoms (*Skeletonema costatum*)	270 µg/L for 5 days	NOEC = 270 µg/L	Thompson and Swigert 1993d MRID 42940106
		MACROPHYTES	
Macrophyte populations in littoral enclosures	Dimilin at nominal treatment levels of 0.7, 2.5, 7.0, or 30 µg/L to littoral enclosures	No adverse effects, direct or indirect, were observed on macrophyte species composition or total standing crop. There was no correlation between treatment concentrations and total macrophyte density throughout the study.	Moffett 1995 ***In***: Moffett 1995 MRID 44386201
Duckweed (*Lemna gibba*)	190 µg/L diflubenzuron for 14 days	NOEL = 190 µg/L	Thompson and Swigert 1993a MRID 42940103