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Dinotefuran

Human Health and Ecological Risk Assessment

Final Report

Submitted to:
Paul Mistretta, COR
USDA/Forest Service, Southern Region
1720 Peachtree RD, NW
Atlanta, Georgia 30309

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Submitted by:
Patrick R. Durkin
Syracuse Environmental Research Associates, Inc.
5100 Highbridge St., 42C
Fayetteville, New York 13066-0950

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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
calc	calculated value
CBI	confidential business information
CDPR	California Department of Pesticide Regulation
ChE	cholinesterase
CI	confidence interval
cm	centimeter
CNS	central nervous system
DAA	days after application
DAT	days after treatment
DBH	diameter at breast height
DER	data evaluation record
DFR	dislodgeable foliar residues
d.f.	degrees of freedom
EAB	emerald ash borer
EC_x	concentration causing X% inhibition of a process
EC_{25}	concentration causing 25% inhibition of a process
EC_{50}	concentration causing 50% inhibition of a process
EFED	Environmental Fate and Effects Division (U.S. EPA/OPP)
ExToxNet	Extension Toxicology Network
F	female
FH	Forest Health
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FQPA	Food Quality Protection Act
g	gram
GLP	Good Laboratory Practices
ha	hectare
HED	Health Effects Division (U.S. EPA/OPP)
HQ	hazard quotient
HWA	hemlock woolly adelgid
IARC	International Agency for Research on Cancer
IRED	Interim Reregistration Eligibility Decision
IRIS	Integrated Risk Information System
k_a	absorption coefficient
k_e	elimination coefficient
kg	kilogram
$K_{o/c}$	organic carbon partition coefficient
$K_{o/w}$	octanol-water partition coefficient
K_p	skin permeability coefficient
L	liter
lb	pound
LC_{50}	lethal concentration, 50% kill

LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LOC	level of concern
m	meter
M	male
mg	milligram
mg/kg/day	milligrams of agent per kilogram of body weight per day
mL	milliliter
mM	millimole
MOS	margin of safety
MRID	Master Record Identification Number
MSDS	material safety data sheet
MW	molecular weight
nAChRs	nicotinic acetylcholine receptors
NAWQA	USGS National Water Quality Assessment
NCI	National Cancer Institute
NCOD	National Drinking Water Contaminant Occurrence Database
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOEL	no-observed-effect level
NOS	not otherwise specified
NRC	National Research Council
NTP	National Toxicology Program
OM	organic matter
OPP	Office of Pesticide Programs
OPPTS	Office of Pesticide Planning and Toxic Substances
OSHA	Occupational Safety and Health Administration
PBPK	physiologically-based kinetic
ppm	parts per million
QSAR	Quantitative structure-activity relationships
RBC	red blood cells
RED	re-registration eligibility decision
RfD	reference dose
SERA	Syracuse Environmental Research Associates
SLN	Special Local Need
TEP	typical end-use product
T.G.I.A.	Technical grade active ingredient
TIPA	Triisopropanolamine
TRED	Tolerance Reassessment Eligibility Decision
UF	uncertainty factor
U.S.	United States
USDA	U.S. Department of Agriculture
U.S. EPA	U.S. Environmental Protection Agency
USGS	U.S. Geological Survey
WHO	World Health Organization

COMMON UNIT CONVERSIONS AND ABBREVIATIONS

To convert ...	Into ...	Multiply by ...
acres	hectares (ha)	0.4047
acres	square meters (m^2)	4,047
atmospheres	millimeters of mercury	760
centigrade	Fahrenheit	1.8℃+32
centimeters	inches	0.3937
cubic meters (m^3)	liters (L)	1,000
Fahrenheit	centigrade	0.556℉-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
1×10^{-10}	0.0000000001	One in ten billion
1×10^{-9}	0.000000001	One in one billion (nano-)
1×10^{-8}	0.00000001	One in one hundred million
1×10^{-7}	0.0000001	One in ten million
1×10^{-6}	0.000001	One in one million (micro-)
1×10^{-5}	0.00001	One in one hundred thousand
1×10^{-4}	0.0001	One in ten thousand
1×10^{-3}	0.001	One in one thousand (milli-)
1×10^{-2}	0.01	One in one hundred
1×10^{-1}	0.1	One in ten
1×10^{0}	1	One
1×10^{1}	10	Ten
1×10^{2}	100	One hundred
1×10^{3}	1,000	One thousand
1×10^{4}	10,000	Ten thousand
1×10^{5}	100,000	One hundred thousand
1×10^{6}	1,000,000	One million
1×10^{7}	10,000,000	Ten million
1×10^{8}	100,000,000	One hundred million
1×10^{9}	1,000,000,000	One billion
1×10^{10}	10,000,000,000	Ten billion

EXECUTIVE SUMMARY

Dinotefuran is a relatively new pesticide that the Forest Service is considering as a possible alternative to imidacloprid for the control the hemlock woolly adelgid (*Adelges tsugae*) and the emerald ash borer (*Agrilus planipennis*). The U.S. EPA/OPP (2005e) has designated dinotefuran as a *Reduced Risk* alternative. The focus of the current risk assessment is to determine if the presumption of reduced risk appears to be applicable to both the human health risk assessment as well as the nontarget species included in the ecological risk assessment.

The potential for risks to humans in the normal use of dinotefuran appear to be low. Based on a generally conservative and protective set of assumptions regarding both the toxicity of dinotefuran and potential exposures to dinotefuran, there is no basis for suggesting that adverse effects are likely in workers. For members of the general public, the only exposure scenarios of concern involve the upper bound estimates for the longer-term consumption of contaminated vegetation after either one or two broadcast foliar applications. Although foliar broadcast application methods are considered in this risk assessment, foliar broadcast is not an application method that is likely to be used in Forest Service programs. While the hazard quotient (HQ) values for these exposure scenarios only modestly exceed the RfD, these exceedances are of concern because the available data on dinotefuran are insufficient to propose a formal dose-severity relationship for potential human health effects.

The potential for risks to nontarget species also appear to be low, except for terrestrial insects. Dinotefuran foliar sprays are likely to kill insects that are sprayed directly, while drift associated with foliar sprays may also involve risk to insects, depending on their distance from the application site and the extent of foliar interception. Herbivorous insects appear to be at greatest risk, with HQ values ranging from about 60 to greater than 7000.

The risk to foraging honeybees is less certain, and data to support a risk analysis are scant. For certain types of dinotefuran applications (e.g., tree injections to wind-pollinated trees), exposure may be minimal for foraging bees. A worse-case assessment results in risks ranging from marginal (HQs from 0.95 to 1.8) to substantial (HQs from 12 to 53), depending on the application method. A less conservative analysis consistent with an extremely brief summary of an incomplete field study indicates that risks to foraging bees could range from insubstantial to marginal (HQs from 0.2 to 2). Without additional data to support a less speculative assessment, (i.e., one that relies less heavily on the use of surrogate chemicals), the risk characterization for the potential effects of dinotefuran on honeybees cannot be further refined.

This risk assessment encompasses several different application methods including foliar and soil broadcast as well as more focused and localized application methods – i.e., soil injection, bark application, and tree injection. Broadcast applications lead to exposures that are likely to occur over a wide area. For all other application methods, the levels and likelihood of exposure could be much lower, particularly for nontarget species, depending on the species of the treated tree, the time of treatment, and the specific conditions of the treatment. These factors are not reflected in the HQ values but should be considered in the interpretation of the consequences of the HQ values.

1. INTRODUCTION

This risk assessment addresses the consequences of dinotefuran use in Forest Service programs as it relates to human health and ecological effects. Dinotefuran is a relatively new pesticide that the Forest Service is considering for the control the hemlock woolly adelgid (*Adelges tsugae*) and the emerald ash borer (*Agrilus planipennis*). The hemlock woolly adelgid is a fluid-feeding insect that preys on hemlock (*Tsuga spp.*) trees in the eastern United States (USDA/FS 1994; Webb et al, 2003). The emerald ash borer is an insect that preys on ash trees (*Fraxinus spp.*) in several mid-west and Eastern states (Michigan, Ohio, Indiana, Illinois, Maryland, Pennsylvania, West Virginia) as well as Ontario, Canada (FHTET 2007). Both of these insects are non-native, aggressive, tree-killing pests.

This risk assessment for dinotefuran differs from other risk assessments prepared for the Forest Service in that several key components of the risk assessment are based on information on other pesticides, primarily imidacloprid and dimethoate. This approach is taken because, as noted above, dinotefuran is a relatively new pesticide and the database on dinotefuran is limited. Thus, information on other chemicals is used as a surrogate for dinotefuran. This use of surrogate data is similar to the approach taken by U.S. EPA/OPP (2004f) to estimate the dermal absorption of dinotefuran (Section 3.1.3.2). In addition, the California Department of Pesticide Regulation (2009) has indicated that surrogate monitoring data for neonicatinoids may be used to satisfy some testing requirements for dinotefuran. In the current risk assessment, surrogate data are used in the current risk assessment to assess the potential effects on nontarget terrestrial invertebrates.

The use of surrogate data is necessary in order to address the major impetus for the current risk assessment on dinotefuran – the assessment of whether or not dinotefuran will present lower risks to key nontarget species than other chemicals, particularly imidacloprid, that have been previously evaluated in Forest Service risk assessments (SERA 2005a). The U.S. EPA/OPP (2005e) has designated dinotefuran as a *Reduced Risk* alternative. The focus of the current risk assessment is to determine if the presumption of reduced risk appears to be applicable to both the human health risk assessment as well as the nontarget species included in the ecological risk assessment.

While data on surrogate chemicals are used, data specifically on dinotefuran are used whenever possible. Typically, Forest Service risk assessments will use only studies that are classified as acceptable by the U.S. EPA or studies that have been published in the open literature. Because of the limited data available on dinotefuran, some exceptions to this approach are made in the current risk assessment. Information from personal communications, unpublished studies not reviewed by the U.S. EPA, and other information sources that would not be used in a typical Forest Service risk assessment are used occasionally in order to avoid using data on surrogate chemicals. These instances are identified as they occur in the current risk assessment and the reasons for using atypical data sources are given.

Much of the peer-reviewed literature on dinotefuran involves mechanistic considerations (e.g., Tomizawa and Casida 2005), the development of resistance (e.g., Nauen and Denholm 2005; Prabhaker et al. 2005), or quantitative structure-activity relationships for neonicotinoids (Yamamoto et al. 1998; Kiriyama and Nishimura 2002). In addition to information published in the open literature, a limited amount of information on dinotefuran is available on the Internet. For the most part, data derived from the Internet are not used in this risk assessment, unless the information is well documented (e.g., FHTET 2007).

This risk assessment also focuses on the several different application methods that the Forest Service will consider for applications of dinotefuran. These range from general broadcast foliar applications to much more localized applications such as bark treatment and tree injection. When possible, the Forest Service plans to use and anticipates using more localized application methods to limit exposures to both members of the general public and nontarget species. Broadcast applications are considered in the current risk assessment and may be used by the Forest Service in some instances. This is an important consideration in the current risk assessment. While the different application methods often lead to similar numeric estimates of risk, the likelihood and extent of exposures differ among the application methods that are considered. This is particularly important and is emphasized in the ecological risk assessment (Section 4).

While data from the open literature are relevant to the assessment of dinotefuran, the current risk assessment is driven, at least quantitatively, by the unpublished studies submitted to the U.S. EPA in support of the registration of this pesticide. The U.S. EPA's Office of Pesticide Programs granted a conditional registration for dinotefuran (U.S. EPA/OPP 2004a) and established tolerances for its use on agricultural commodities (U.S. EPA/OPP 2004b). A list of studies submitted to U.S. EPA/OPP as of 2004 in support of the registration of dinotefuran is provided in U.S. EPA/OPP (2004a).

In the preparation of this risk assessment, the list of registrant-submitted studies was reviewed, and 108 study summaries/evaluations made by the U.S. EPA/OPP were requested from and provided by Landis International Inc. As discussed further in Section 2.2, Landis is the regulatory agent in the U.S. for Mitsui Chemicals, the registrant for dinotefuran. The EPA summaries/evaluations of the registrant-submitted studies are referred to as DERs or data evaluations records, and are the basis of the current risk assessment. In addition, EPA reviews of the registrant-submitted studies (U.S. EPA/OPP 2004a-f, 2005a-d, 2006a,b) were consulted during the preparation of this risk assessment, and they are discussed in the body of this report, as appropriate.

The Forest Service is aware of and is sensitive to concerns about risk assessments based chiefly on studies submitted to the U.S. EPA in support of product registration. The general concern can be expressed as follows:

If the study is paid for and/or conducted by the registrant, the study may be designed and/or conducted and/or reported in a manner that will obscure any adverse effects that the compound may have.

This type of concern is largely without foundation. While any study (published or unpublished) can be falsified, concerns with the design, conduct, and reporting of studies submitted to the U.S. EPA for pesticide registration are minor. Studies submitted for pesticide registration are designed in accordance with strict guidelines regarding the manner in which the studies are conducted and reported. These guidelines are developed by the U.S. EPA and not by the registrants. Full copies of the guidelines for these studies are available at http://www.epa.gov/opptsfrs/home/guidelin.htm. All studies are conducted under Good Laboratory Practices (GLPs). GLPs are an elaborate set of procedures that involve documentation and independent quality control and quality assurance, which substantially exceed the levels typically seen in open literature publications. Furthermore, the EPA reviews each of the submitted studies for adherence to the relevant study guidelines. These reviews most often take the form of Data Evaluation Records (DERs). While the nature and complexity of DERs will vary with the nature and complexity of the differing studies, each DER involves an independent assessment of the study to ensure that the EPA Guidelines are followed. In addition, each DER undergoes internal review (and sometimes several layers of review).

There are real and legitimate concerns with risk assessments based largely on registrant-submitted studies; however, it is the nature and diversity of the available studies, and not data quality or data integrity, that constitute the major limitation of risk assessments based largely on registrant-submitted studies. The studies required by the U.S. EPA are based on a relatively narrow set of studies in a relatively small subset of species. For some pesticides (e.g., picloram, clopyralid, and triclopyr), the number of published studies is substantial, many of which are generated by academics who have a fundamental interest in understanding both the toxicology of a compound as well as underlying biological principles (e.g., physiology, biochemistry, ecology, etc.). Such studies tend to be non-standard but highly creative and can substantially contribute to or even form the basis of a risk assessment. For dinotefuran, however, the information available in the open literature is admittedly limited, due to its status as a relatively new pesticide, and it is likely that as the open literature on dinotefuran develops, the risk assessment will be updated.

The Forest Service welcomes input from all interested parties 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 assessment.

Like other Forest Service risk assessments, this document has four chapters: the introduction, program description, risk assessment for human health effects, and risk assessment for ecological effects or effects on wildlife species. Each of the two risk assessment chapters has four major sections, including hazard identification, an assessment of potential exposures, a dose-response assessment, and a characterization of the risks.

Although this is a technical support document and addresses some specialized technical areas, an effort was made to ensure that the document can be understood by individuals who do not have specialized training in the chemical and biological sciences. Certain technical concepts, methods, and terms common to all parts of the risk assessment are described in plain language in a separate document (SERA 2007a).

As with all Forest Service risk assessments, almost no risk estimates presented in this document are given as single numbers. Usually, risk is expressed as a central estimate and a range, which is sometimes quite large. Because of the need to encompass many different types of exposure as well as the need to express the uncertainties in the assessment, this risk assessment involves numerous calculations, most of which are relatively simple. They are included in the body of the document.

Some of the calculations, however, are cumbersome. For those calculations, EXCEL workbooks (sets of EXCEL worksheets) are included as attachments to this risk assessment. The worksheets provide the detail for the estimates cited in the body of the document. Documentation for the use of these workbooks is presented in SERA (2007b). Six standard workbooks are included with this risk assessment:

- Attachment 1a: Aerial broadcast, single application at 0.2 lb a.i./acre
- Attachment 1b: Aerial broadcast, 0.2 lb a.i./acre, two applications with a 14 day application interval.
- Attachment 2: Ground broadcast, 0.54 lb a.i./acre
- Attachment 3: Bark applications, 0.54 lb a.i./acre
- Attachment 4: Soil injection, 0.54 lb a.i./acre
- Attachment 5: Tree injection, 0.54 lb a.i./acre

The rationale for each of these separate workbooks is discussed in Section 2.3.4 (Relationship of Application Methods to Workbooks) of the program description. Additional details for the specific exposure scenarios are provided in Section 3.2 (Exposure Assessment for the Human Health Risk Assessment) and Section 4.2 (Exposure Assessment for the Ecological Risk Assessment). A seventh custom workbook, **`Landis 2009 Field Study in Bees.xls`**, is also included with this risk assessment. This workbook is used in the evaluation of a field study on dinotefuran (Landis 2009) and is discussed in Section 4.4.2.3.4 (risk characterization for nectar foraging honeybees).

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

2. PROGRAM DESCRIPTION

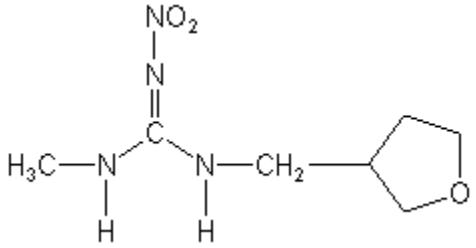
2.1. OVERVIEW

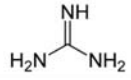
Dinotefuran is a relatively new insecticide used in Forest Service programs to control the hemlock woolly adelgid (HWA) and the emerald ash borer (EAB). Both uses involve the application Safari formulations, either Safari 20 SG or Safari 2 G, which are granular formulations distributed in the United States by Valent U.S.A. Safari 2 G is always applied by broadcast granular application (i.e., the formulation is not mixed in a liquid vehicle). In addition, both ground and aerial applications are permitted. It is likely that the major use of Safari 2 G will involve broadcast aerial applications in areas that are not amendable to other application methods. The application methods for Safari 20 SG, however, are more diverse. Safari 20 SG may be applied by ground or aerial broadcast applications as an aqueous solution of the formulation (i.e., broadcast foliar applications). In addition, Safari 20 SG is labeled for soil drench and soil injection. The U.S. EPA granted a Special Local Need label for bark applications of Safari 20 SG. Although dinotefuran is not currently labeled for tree injection, since the Forest Service is contemplating this application method, it is considered in this risk assessment.

Application rates for dinotefuran are typically expressed in units of amount per inch DBH (tree size in terms of diameter at breast height). This practice somewhat complicates the exposure assessments in this risk assessment in so far as the application rates must be converted to units of lb a.i./acre. Nonetheless, the maximum cumulative application rate for all formulations of dinotefuran is 0.54 lb a.i./acre, which is used as the upper bound rate for most dinotefuran applications considered in this risk assessment. The only exception relates to broadcast applications, for which the highest labeled application rate is 0.2 lb a.i./acre with a second application permitted in no fewer than 14 days.

2.2. CHEMICAL DESCRIPTION AND COMMERCIAL FORMULATIONS

Dinotefuran is the common name for (RS)-1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine:



The chemical and physical properties of dinotefuran are summarized in Table 1. Structurally, dinotefuran consists of a methyl- and nitro- substituted guanidine moiety () linked to a furan moiety () by a methyl bridge (–CH_2–). Dinotefuran is classified as a neonicotinoid, a group of insecticides that are highly neurotoxic to insects (Fishel 2005). More specifically,

dinotefuran is classified as a furanicotinyl third-generation neonicotinoid and differs from most neonicotinoids in that it has a furan moiety rather than a halogenated aromatic ring (Wakita et al. 2003).

As discussed further in Section 3.1.6 (Effects on the Nervous System) and Section 4.3.2.3 (Terrestrial Invertebrates), dinotefuran interferes with a neural pathway in insects much more efficiently than in mammals.

In addition to dinotefuran, neonicotinoids include acetamiprid, clothianidin, imidacloprid, nitenpyram, thiacloprid, and thiamethoxam. These neonicotinoids are also designated as *4A* insecticides (IRAC 2007). Each dinotefuran product label considered in this risk assessment (see below) specifies that dinotefuran and other 4A insecticides should not be applied repeatedly over a period of years. This purpose of this limitation is to reduce the potential development of insect resistance to this class of insecticides (e.g., Liu et al. 2006; Nauen and Denholm 2005; Prabhaker et al. 2005).

Dinotefuran is a relatively new pesticide. It was developed in 1998 and registered to Mitsui Chemicals Incorporated in Japan in 2002 (Tomlin 2004). The U.S. EPA granted conditional registrations for the use of products containing dinotefuran to control numerous pest insects on (U.S. EPA/OPP 2004a). Dinotefuran is also an ingredient in pet products (U.S. EPA/OPP 2005a,b,c,d, 2006a); however, this risk assessment addresses only the use of dinotefuran to control insect pests on vegetation and not the veterinary uses of dinotefuran.

Within the United States, Landis International (http://www.landisintl.com/index.htm) acts as a regulatory agent for Mitsui Chemicals, and the agricultural and forestry formulations of dinotefuran are provided by Valent U.S.A. Corporation (http://www.valentusa.com/).

Notwithstanding, the availability of several different formulations of dinotefuran, only two formulations are included in the current risk assessment: Safari 20 SG and Safari 2 G. As summarized in Table 2, both Safari 20 SG and Safari 2 G are granular formulations. Safari 20 SG is formulated by Landis/Mitsui and is redistributed by Valent. Safari 2G is both formulated and distributed by Valent (Chamberlain 2008).

Safari 20 SG is a 20% a.i. formulation and Safari 2 G is a 2% a.i. formulation. As discussed further in Section 2.3.1, Safari 20 SG, which may be applied using a number of different application methods, is the formulation that is most likely to be used in Forest Service programs.

The use of Safari 2 G is included in this risk assessment because this formulation does not require pre-mixing with water and thus might be more suitable for application in areas with limited access to water. Nonetheless, soil applications of dinotefuran require either natural rainfall or irrigation so that the dinotefuran is transported into the soil and taken up by plant roots.

Both Safari formulations contain other ingredients, in addition to dinotefuran, the active ingredient (a.i.). The publically available information about these other ingredients, which comes primarily from the Material Safety Data Sheets for the formulations, is summarized in Table 3. The potential contribution of these other ingredients to the toxicity of Safari formulations is discussed further in Section 3.1.14 (Inerts and Adjuvants).

2.3. APPLICATION METHODS

2.3.1. Soil Applications (Broadcast, Drench and Injection)

As summarized in Table 2, Safari 2 G may be applied to soil by broadcast application and Safari 20 SG may be applied to soil by soil drench or soil injection. All of these application methods involve an attempt to achieve a concentration of dinotefuran in the soil. As noted above, the dinotefuran will then be transported from the roots to the leaves or twigs where the target insects will feed.

Soil broadcast applications of Safari 2 G involve spreading the formulation under the plants to be protected. Either rainfall or direct irrigation may be used to "activate" the dinotefuran (i.e., to transport the dinotefuran from the surface of the soil into the root zone of the plant).

Soil drench applications of Safari 20 SG involve a process similar to that of soil broadcast applications. The formulation is applied to the soil (either as a granular or liquid) and then watered in. The product label for Safari 20 SG specifies a soil drench volume of 0.5 inches after soil application to move the pesticide into the root zone. The requirement for irrigation limits the use of this application method to areas where water is readily available.

Safari 20 SG is also labeled for soil injection. This type of application involves using a solution or suspension of the formulation and placing the liquid in an injection pump designed to insert or inject a metered volume of the liquid into the soil, typically to a depth of about 2-4 inches (Onken 2008). The number and volume of the injections varies according to the size of tree. Applications of 3-12 g formulation/ inch DBH (tree size in terms of diameter at breast height) are recommended for Safari 20 SG. Because soil injection does not require the use of artificial irrigation, this method may be used in forestry (as opposed to nursery) applications where water resources are limited.

2.3.2. Foliar Applications

Safari 20 SG is labeled for both directed and broadcast foliar applications by ground or aerial application methods. All of these application methods involve the preparation of aqueous solutions of the formulation, as detailed further in Section 2.4. Aerial applications are made under meteorological conditions that minimize the potential for spray drift. Although the product label does not specify droplet size, it specifically notes that small droplets (i.e., from <150 to 200 microns) will favor drift. In practice, the Forest Service considers droplets less than 100 microns to be "small" in terms of favoring drift. The product label for Safari 20 SG specifically recommends that applications be made at wind speeds of 3-10 miles/hour.

Ground foliar broadcast applications involve spray equipment mounted on tractors or trucks, and airblast sprayers may be used to apply dinotefuran to the tree canopy. The Forest Service is not likely to use ground-based broadcast spray application of dinotefuran (Onken 2008); accordingly, this application method is not further considered in this risk assessment.

2.3.3. Bark Applications

The U.S. EPA recently released a FIFRA Section 24(c) Special Local Need labels for Georgia, New Jersey, and Virginia. These labels encompass bark applications of Safari 20 SG to control hemlock wooly adelgid and elongated hemlock scale on hemlocks in forested areas. The USDA/Forest Service is also evaluating the efficacy of bark applications for the control of the emerald ash borer (e.g., McCullough et al. 2007).

In these applications, Safari 20 SG is mixed with an adjuvant (e.g., Pentra-Bark) to facilitate penetration of the insecticide into the bark. This mixture is then sprayed onto the bark of the tree over an area from about 0.2 to about 1.6 meters above the ground. Based on the Georgia label, the application rate for bark application is identical to that for soil injection (i.e., 0.6-2.4 g a.i./inch of truck diameter at breast height (DBH).

In bark applications, dinotefuran is absorbed by the bark and translocated to the leaves. The applications are made prior to oviposition by the emerald ash beetle, which must feed for about 2 weeks prior to oviposition. This application method has the potential to substantially reduce offsite loses of dinotefuran. The ability to quantify estimates of offsite losses associated with bark applications of dinotefuran is discussed further in Section 2.4.

2.3.4. Tree Injection

Although, dinotefuran currently is not labeled for tree injection, imidacloprid, another neonicotinoid, is. As noted by Onken (2008) and Cowles (2009a), the physical properties of dinotefuran and the Safari 20 SG formulation suggest that tree injection might be a useful treatment method, particularly in small areas that are close to surface water. Consequently, tree injection is included in the current risk assessment to illustrate the plausible risks associated with this application method.

2.3.5. Relationship of Application Methods to Workbooks

This risk assessment considers a greater number of application methods than are typical in most Forest Service risk assessments. This matter complicates the exposure assessments and requires a more elaborate set of worksheets than are typically included with Forest Service risk assessments.

This risk assessment is accompanied by five EXCEL workbooks:

- Attachment 1a: Aerial broadcast, single application at 0.2 lb a.i./acre
- Attachment 1b: Aerial broadcast, 0.2 lb a.i./acre, two applications with a 14 day application interval.
- Attachment 2: Ground broadcast, 0.54 lb a.i./acre
- Attachment 3: Bark applications, 0.54 lb a.i./acre
- Attachment 4: Soil injection, 0.54 lb a.i./acre
- Attachment 5: Tree injection, 0.54 lb a.i./acre

Broadcast applications could involve either Safari 20 SG or Safari 2 G. As detailed further in Section 2.4, Safari 20 SG will be applied as a liquid after mixing with water. Safari 2 G, however, is more likely to be applied in granular form. While these two types of applications involve a similar set of exposure scenarios, different workbooks are required because the two application methods must be handled differently due to the nature of the initial residues on vegetation, which will be higher after liquid applications, compared with granular applications.

An additional difference between broadcast foliar and broadcast soil applications involves the application rates. The maximum annual application rate for both Safari 20 SG and Safari 2 G is 0.54 lb/acre. For foliar broadcast applications, however, the maximum labeled application rate is 0.2 lb a.i./acre and two applications may be made per year with a minimum application interval of 14 days. Thus, two attachments are provided for foliar broadcast applications, one for a single application at 0.2 lb a.i./acre (Attachment 1) and the other for two applications at 0.2 lb a.i./acre with an application interval of 14 days (Attachment 2). For ground broadcast application, only a single application at the maximum labeled rate is considered (Attachment 3).

As discussed further in Section 2.4, operational rates for bark applications, soil injection, and tree injection are commonly expressed as an amount of formulation or a.i. based on the size of the tree, specifically the diameter at breast height (DBH). In the workbooks that accompany this risk assessment, the A01 Worksheets gives the operational application rate in units of grams a.i./inch DBH but also converts these rates into units of lb a.i./acre based on assumptions regarding the number of trees to be treated per acre and the size of the trees. The inputs for these workbooks are manipulated, somewhat artificially, to result in an application in units of lb a.i./acre equivalent to the maximum application rate of 0.54 lb a.i./acre.

The Forest Service considers a relatively standard set of exposure scenarios in all risk assessments. For some application methods, however, not all of the exposure scenarios are

relevant. For example, broadcast foliar applications consider drift to offsite vegetation. This type of exposure, however, is not relevant for application methods like soil or tree injection. The specific exposure scenarios used in the workbooks for each application method are discussed in Section 3.2 (exposure assessment for the human health risk assessment) and Section 4.2 (exposure assessment for the ecological risk assessment).

2.4. MIXING AND APPLICATION RATES

Typically, risk assessments conducted for the USDA Forest Service express application rates in units of lbs a.i./acre. These application rates are then used in the risk assessment to estimate exposure levels for workers (Section 3.2.2), members of the general public (Section 3.2.3), as well as various groups of non-target species (Section 4.2). An application rate expressed in units of lbs a.i./acre is a particularly significant and, in some respects, a controlling parameter as input for environmental fate models to estimate pesticide concentrations in ambient water (Section 3.2.3.4). As noted in Section 2.3, two of the application methods used for dinotefuran (i.e., soil injection and bark treatment) are not amenable to simple assessments of application rates expressed in units of lbs a.i./acre; therefore, assumptions are needed in order to make such estimates.

2.4.1. Soil Applications

Safari 2 G is labeled only for granular application (i.e., the product is not mixed with water prior to application). Both granular broadcast and single plant treatments are specified on the product label. Application rates for soil broadcast treatments are expressed in relatively standard units (i.e., up to 0.54 lb a.i./acre).

In treatments of individual trees, Safari 2 G is broadcast evenly around the base of the tree within about 18 inches of the trunk. The specific amount of Safari 2 G to be applied to individual trees will depend on the size of the tree. The product label specifies 2-4 ounces (presumably referring to a unit of weight using the avoirdupois system) for each inch of trunk diameter at trunk breast height. Thus, in any particular application to a stand of trees that are treated individually, the functional application rate in units of lb a.i./acre will depend on the size of the trees to be treated as well as the distribution of trees to be treated within a given area. As with soil broadcast applications, however, the maximum application rate is 0.54 lb a.i./acre.

Safari 20 SG is labeled for soil injection but not broadcast soil application. Soil injections are always made to individual trees, based on the size of the trees. As specified on the product label, 1.05-4.2 ounces of formulation should be applied for each 10 inches of trunk diameter at breast height. The product label also gives rates in terms of grams, and it is clear that the term *ounces* refers to avoirdupois ounces. The application rates in units of active ingredient are given as 0.6-2.4 g a.i./inch DBH. As with granular applications to individual trees, the maximum application rate for Safari 20 SG, by any application method, is 0.54 lb a.i./acre.

The application volume for soil injection is not specified on the product label. Chamberlain (2009) indicates that forestry applications generally involve injection volumes of about 1 fl oz/inch DBH. Thus, application rates of 0.6-2.4 g a.i./inch DBH and an application volume of 1

fl oz (0.0283 L)/inch DBH correspond to field solutions ranging from about 21.2 to 85 mg/mL [0.6-2.4 g a.i./0.0283 L = 21.2-84.8 g/L].

2.4.2. Liquid Broadcast Applications

Safari 20 SG is labeled for liquid broadcast applications, which is a standard and relatively uncomplicated application method. As specified on the product label, Safari 20 SG may be applied as a foliar spray in single application rates of 0.1-0.2 lb a.i./acre at a dilution of 0.05-0.2 lb a.i./100 gallons, and a second application may be made after 14-21 days. The labeled maximum cumulative annual application rate for Safari 20 SG is 0.54 lb a.i./acre. Given the specific limitations on single foliar broadcast applications (i.e. 0.1-0.2 lb a.i./acre) it appears that the maximum annual application rate for foliar broadcast applications would be 0.4 lb a.i./acre.

As a convention in the worksheets that accompany Forest Service risk assessments, the concentration in a field solution is calculated as the application rate (lb/acre) divided by the application volume (the amount of liquid applied per acre). Based on the label directions, the application volumes for Safari 20 SG are in the range of 50 gallons/acre [(100 gallons/0.2 lb a.i.)/0.1 lb a.i./acre] to 400 gallons/acre [(100 gallons/0.05 lb a.i.) x (0.2 lb a.i./acre)].

2.4.3. Bark Applications

As noted in Section 2.3.3, the U.S. EPA recently released a FIFRA Section 24(c) Special Local Need label for bark applications of Safari 20 SG to hemlocks to control the hemlock woolly adelgid. Bark application rates are identical to the application rates for soil injection—i.e., 3-12 g formulation (0.6-2.4 g a.i.)/inch DBH. As with other application methods, the maximum application rate is 0.54 lb a.i./acre.

The Special Local Need label for bark applications specifies an application volume of 2-3 oz/inch DBH. At the maximum application rate of 2.4 g a.i/inch DBH, this value corresponds to a field concentration of about 27 g/L or 27 mg/mL [2.4 g a.i/inch DBH ÷ (3 fl. oz × 0.0296 L/fl. oz) = 27.027 g/L].

In a recent Forest Service risk assessment on carbaryl (SERA 2008), data were available suggesting that worker exposure rates for bark applications of carbaryl are likely to be comparable to those associated with backpack applications. This matter is considered further in Section 3.2.2.1 (Exposure Assessment for Workers).

For exposures to nontarget species as well as contamination of adjacent vegetation and surface water, some estimate of the proportion of the nominal amount that actually stays on the bark (or conversely, a proportion of the applied amount that is splashed onto the soil and the proportion that might be deposited on adjacent vegetation) is also needed. Based on the brief description of bark applications of dinotefuran in McCullough et al. (2007), it seems that bark applications of dinotefuran might be much more controlled than applications of carbaryl, both because it appears that a much smaller part of the tree is treated and because the pressure of the applied spray is probably much lower and much better directed than is the case with carbaryl applications. Onken (2009) suggests that a maximum of 10% of the dinotefuran applied to bark might be

splashed onto the ground adjacent to the treated tree. Cowles (2009a) suggests that a value of 5% might be more typical but that a lower rate could be achieved under favorable conditions. This information is considered in Section 3.2.3.7 (Oral Exposure from Contaminated Vegetation).

2.4.4. Tree Injection

As noted in Section 2.3.4, dinotefuran is not currently labeled for tree injection; however, since the method is under consideration by the Forest Services, it is considered in this risk assessment. This risk assessment assumes that the maximum labeled rate for dinotefuran would be the same as that for other application methods (i.e., 0.54 lb a.i./acre). Based on estimates from Cowles (2009a), the treatment rate for an individual tree is taken as 0.24 g a.i./inch DBH—i.e., one 10^{th} the highest rate used for soil injection (2.4 g a.i./inch DBH)—and the concentration in the injected solution is taken as 3% a.i. (w/v), equivalent to 30 g/L or 30 mg/mL.

2.5. USE STATISTICS

Forest Service risk assessments typically attempt to characterize the use of a pesticide in Forest Service programs relative to the use of the pesticide by other organizations or in agricultural applications. The information on Forest Service use is taken from Forest Service pesticide use reports (http://www.fs.fed.us/foresthealth/pesticide/ reports.shtml), and information on agricultural use is typically taken from use statistics compiled by the U.S. Geological Survey (http://water.usgs.gov/nawqa/pnsp/) and detailed pesticide use statistics compiled by the state of California (http://www.calepa.ca.gov/).

The most recent year for Forest Service use statistics is 2004, and no use of dinotefuran is listed. Similarly, no use statistics for dinotefuran are available at the USGS web site. California reports a total use of about 3779 pounds of dinotefuran in California during 2006, the most recent year for which use statistics are available (CDPR 2007). About two thirds of the applications in California appear to involve greenhouse crops or outdoor applications to container plants or transplants. Specific forestry applications are not identified.

Based on this very limited information, it is not possible to assess the extent to which Forest Service use of dinotefuran might be substantial relative to other non-forestry uses.

3. HUMAN HEALTH RISK ASSESSMENT

3.1. HAZARD IDENTIFICATION

3.1.1. Overview

Dinotefuran is a neonicotinoid insecticide that causes neurotoxicity through binding or partial binding to specific areas of the nicotinic acetylcholine receptor. Although dinotefuran activates nicotinic acetylcholine receptors, it appears to do so in a manner that is different from nicotine, which may be the basis for the differential toxicity of dinotefuran in mammals and insects (i.e., unlike nicotine, dinotefuran is much more toxic to insects than to mammals).

Dinotefuran is rapidly absorbed and rapidly excreted in mammals and will not accumulate in mammals with long-term exposure. The mammalian metabolism of dinotefuran is complex, but there is no information indicating that the metabolites of dinotefuran are more toxic than dinotefuran itself.

Most of the information used in the hazard identification for dinotefuran is based on studies submitted to the U.S. EPA in support of the registration of dinotefuran. The U.S. EPA's Office of Pesticide Programs (U.S. EPA/OPP) classifies potential acute hazards based on a number of standard tests using a system that goes from Category I (most hazardous) to Category IV (least hazardous). U.S. EPA/OPP reviewed the information on dinotefuran and classified it as Category IV, based on acute dermal and inhalation toxicity, skin and eye irritation, and skin sensitization, and Category III, based on oral toxicity.

A standard battery of subchronic and chronic toxicity studies were conducted in rats, mice, and dogs. Based on chronic toxicity studies, U.S. EPA/OPP determined that dinotefuran is … *Not likely to be carcinogenic to humans*. Standard developmental and reproduction studies found no indication that dinotefuran is likely to cause birth defects or adverse effects on the fetus that preclude normal development.

While dinotefuran is neurotoxic, neurotoxicity does not appear to be the most sensitive endpoint in longer-term exposures. The most sensitive endpoints (i.e., those occurring at the lowest doses) are apparently associated with changes in endocrine or immune function. The most commonly observed effect is a decrease in body weight and/or body weight gain. Other adverse effects include signs of damage to the adrenal cortex, changes in uterine morphology, effects on normal estrous cycling, and decreases in organ weights in the testes, spleen, and thymus.

3.1.2. Mechanism of Action

Dinotefuran belongs to a class of insecticides referred to as neonicotinoids. Although the general mechanism of action for this class of insecticides has been characterized, there is little information specific to mechanism of action of dinotefuran. Neonicotinoids—like dinotefuran and other insecticides including acetamiprid, clothianidin, imidacloprid, nitenpyram, thiacloprid, and thiamethoxam—are neurotoxins that act by binding to specific sub-sites or protein subunits

of the nicotinic acetylcholine receptor (nAChR), which in turn activates nAChR activity (Tomizawa and Casida 2005).

Acetylcholine is an important neurotransmitter in both insects and mammals. It is released at the nerve synapse in response to a membrane depolarization which is the hallmark of nerve transmission. The acetylcholine then binds to a protein receptor in the membrane of the nerve synapse, which then opens/alters an ion channel, which in turn causes changes in the fluxes of ions (sodium, potassium, calcium, chloride), ultimately perpetuating the nerve impulse. The acetylcholine is subsequently destroyed by acetylcholinesterase, and the membrane returns to its normal resting state.

There are different types of acetylcholine receptors. One type of receptor is called the nicotinic acetylcholine receptor (nAChR), which is activated by nicotine. Nicotine binds at or near the location where acetylcholine binds, causing the cascade of events leading to nerve transmission. Nicotine and other substances which stimulate acetylcholine-like behavior by binding to nAChRs are called nAChR agonists. Dinotefuran and other neonicotinoids act as nAChR agonists. The compounds mimic the action of nicotine in the nervous system, binding at or near the site on the nAChR where nicotine binds, producing an unregulated barrage of nerve impulses, resulting in something akin to a nervous breakdown, and ultimately, death (Tomizawa and Casida 2003, 2004).

Although dinotefuran and other neonicotinoids activate nAChRs, they do so in a manner dissimilar to that of nicotine, which seems to account for the differences in toxicity between nicotine and neonicotinoids: nicotine is more toxic to mammals than to insects, and neonicotinoids are more much toxic to insects than to mammals (Yamamoto et al. 1995). One aspect of the differential toxicity of nicotine and neonicotinoids involves receptor binding. As a class, neonicotinoids have a low binding affinity for vertebrate nicotinic receptors but a much higher binding affinity for insect nicotinic receptors (Debnath et al. 2003; Ihara et al. 2007). Differential binding affinities have been demonstrated specifically for dinotefuran, which binds to insect $\alpha 4\beta 2$ nicotinic receptors with an affinity that is over 100 times greater than binding to mammalian receptors (Tomizawa and Casida 2005, p. 257).

It is unclear that differences in binding affinity alone account for the greater degree of dinotefuran *in vivo* toxicity to insects, compared with mammals. Furthermore, it is possible that the difference between the metabolic pathways of insects and humans is also a factor in the apparent disparities in dinotefuran toxicity to insects and mammals. In mammals, the metabolism of dinotefuran and other neonicotinoids is generally viewed as a detoxification reaction (Section 3.1.15.1); however, the metabolic pathways of insects might entail the generation of metabolites that are more toxic, at least to insects, than the dinotefuran itself (Tomizawa and Casida 2003).

3.1.3. Pharmacokinetics and Metabolism

Pharmacokinetics concerns the behavior of chemicals in the body, including their absorption, distribution, alteration (metabolism), and elimination as well as the rates at which these

processes occur. The focus of this section of the risk assessment is the available information on the pharmacokinetic processes for dinotefuran, including a general discussion about metabolism (Section 3.1.3.1), with a focus on the kinetics of absorption (Section 3.1.3.2) and excretion (Section 3.1.3.3). Absorption kinetics, particularly the kinetics of dermal absorption, are important to this risk assessment because many of the included exposure assessments (Section 3.2) involve dermal exposure. Rates of excretion are generally used in Forest Service risk assessment to evaluate the likely body burdens associated with repeated exposure.

In addition to the general consideration about how dinotefuran behaves in the body, it is important to consider how dinotefuran behaves in the environment and the extent to which the metabolism of dinotefuran in the environment must be considered quantitatively in the risk assessment. The consideration of environmental metabolites is discussed in Section 3.1.15.1.

3.1.3.1. General Considerations

Several relatively standard metabolism studies were submitted to the U.S. EPA Office of Pesticide Programs in support of the registration of dinotefuran, including metabolism studies in adult rats (Cheng 2000), neonatal rats (Cheng and Howard 2000), lactating goats (Hatzenbeler and Lentz 2002a), and egg laying hens (Hatzenbeler and Lentz 200b). While the latter two studies are relevant to the ecological risk assessment (Section 4), they are considered in this section of the risk assessment to facilitate interspecies comparison. In addition, the published literature on dinotefuran includes two metabolism studies: Dick et al. (2006) and Ford and Casida (2006a).

The chemical structure of dinotefuran and it metabolites designated as metabolites of concern by the U.S. EPA/OPP (2004f) are illustrated in Figure 1. Figure 1 also includes illustrations of the structure of guanidine and urea. Guanidine and urea are not metabolites of dinotefuran, *per se*, but are included in Figure 1 to simplify the discussion of dinotefuran metabolism. Dinotefuran may be viewed as a guanidine derivative with a methyl group (—CH_3) as well as a furan moiety () connected to the guanidine moiety by a methyl bridge (–CH_2–).

Although the molecular structure of dinotefuran is not particularly complicated, virtually all of its subcomponents are readily subjected to metabolism in mammals, which is a relatively complex process involving multiple pathways. The most detailed discussion about the metabolism of dinotefuran in mammals, including the identification of specific metabolites, is provided in the published study by Ford and Casida (2006a). These investigators identified a total of 29 metabolites formed by reduction of the nitro (–NO_2) group of the guanidine moiety, demethylation of the methyl group on the guanidine moiety, cleavage of furan moiety at the methyl or amine groups followed by hydroxylation, and hydroxylation of the carbons in the furan group. These metabolic changes can occur in various combinations, leading to the formation of numerous metabolites, as illustrated in Figure 7 of the Ford and Casida (2006a) publication. Chen (2000) also notes that hydroxylation is a major metabolic pathway in rats.

As noted by Ford and Casida (2006a) and others, both metabolism and excretion of dinotefuran are rapid. The kinetics of excretion, based on data from this and other studies, are discussed further in Section 3.1.3.3. The extent of metabolism appears to be variable. Approximately 55% of dinotefuran was excreted unchanged in the urine of mice following administration of the compound by intraperitoneal injection (Ford and Casida 2006a). In rats, about 75-93% of the administered dose was excreted unchanged after intravenous or oral dosing (Cheng 2000). The extent of metabolism in neonatal rats appears to be somewhat less than that in adult rats (Cheng and Howard 2000); whereas, the extent of metabolism in goats and hens appears to be similar to that in adult rats, with dinotefuran in excreta accounting for about 40% in goats (Hatzenbeler and Lentz 2002a) and 57% in eggs from laying hens (Hatzenbeler and Lentz 200b).

3.1.3.2. Absorption

Dinotefuran appears to be rapidly and almost completely absorbed after oral administration (Cheng 2000; Cheng and Howard 2000). This is a common pattern for many pesticides and is consistent with the general assumption used in this risk assessment that dinotefuran will be completely absorbed after oral administration.

Complete absorption, however, is not a reasonable assumption for dermal exposure scenarios. Limited dermal absorption is important in the current risk assessment because most of the occupational exposure scenarios and many of the exposure scenarios for the general public involve the dermal route of exposure. For these exposure scenarios, dermal absorption is estimated and compared to an estimated acceptable level of oral exposure based on subchronic or chronic toxicity studies in animals. Thus, it is necessary to assess the consequences of dermal exposure relative to oral exposure and the extent to which dinotefuran is likely to be absorbed from the surface of the skin.

The extent of dermal absorption has been addressed in a recent EPA risk assessment on dinotefuran (U.S. EPA/OPP 2004e). Based on analogy to other compounds, the U.S. EPA used a dermal absorption factor of 30% per day. Based on a standard first-order absorption model, the proportion (P_t) of a compound absorbed by a given time (t) is:

$$P_t = 1 - e^{-k\,t}$$

where k is the first order dermal absorption rate in units of reciprocal time. Solving for k,

$$k = \frac{Ln(1 - P_t)}{t}$$

and using the proportion of 0.3 from U.S. EPA/OPP (2004e), the estimated first-order dermal absorption rate would be 0.356 day^{-1} or about 0.015 $hour^{-1}$.

In the absence of experimental data on dermal absorption rates, Forest Service risk assessments generally adopt a somewhat different approach to estimating dermal absorption rates based on quantitative structure activity relationships (QSAR), as documented in SERA (2007a). Using

this algorithm, the estimated first-order dermal absorption rates are 0.0017 (0.00058-0.005) $hour^{-1}$. The calculation of these rates is detailed in Worksheet B06 in each of the EXCEL workbooks accompanying this risk assessment. The central estimate of the first-order dermal absorption rate using the QSAR approach is a factor of about 10 less than the rate used by the EPA.

In some cases, relative differences in oral and dermal toxicity may help, at least crudely, to assess plausible rates of dermal absorption. The acute toxicity studies on dinotefuran are not particularly useful because all of the acute dermal studies are limit tests—i.e., they are based on a single dose at which adverse effects were not observed (Section 3.1.12). As also discussed in Section 3.1.12, a 29-day subchronic toxicity study in rats indicates that adverse effects were not observed at doses up to 1000 mg/kg bw/day (Henwood 2001a,b). Based on a daily dermal absorption rate of 0.356 day^{-1} taken from U.S. EPA/OPP (2004e), the equivalent oral dose for the NOAEL would be about 350 mg a.i./kg bw/day.

In a comparable 90-day oral toxicity study in rats (Weiler 1997a), discussed in Section 3.1.5, the NOAEL in male rats was 38 mg/kg bw/day and the corresponding LOAEL was 384 mg/kg bw/day. The oral NOAEL in female rats was 384 mg/kg bw/day with a corresponding LOAEL of 1871 mg/kg bw/day. Thus, the dermal NOAEL of 1000 mg/kg bw/day is not consistent with the relatively high dermal absorption rate proposed by U.S. EPA. If the dermal absorption rate were about 0.356 day^{-1}, dermal exposure to 1000 mg a.i./kg bw would be expected to cause adverse effects in the male rats, given the oral LOAEL of 384 mg/kg bw/day. The relationship between the dermal and oral toxicity studies is, however, consistent with a lower dermal absorption rate, such as the one based on the standard QSAR relationships used in most Forest Service risk assessments.

Comparisons between oral and dermal toxicity studies, however, are tenuous at best. As a matter of standard practice, Forest Service risk assessments generally use assumptions which are at least as conservative or protective as those used by the EPA, unless there is a compelling reason to do otherwise. In terms of the first-order dermal absorption rates, there is little reason to assume that QSAR values are necessarily more accurate than the judgmental estimate in U.S. EPA/OPP (2004e). Consequently, in the current risk assessment, the first-order dermal absorption rates by the QSAR estimates (Worksheet B06) are multiplied by a factor of 10—i.e., first-order 0.017 (0.0058-0.05) $hour^{-1}$. These adjusted estimates are entered in Worksheet B04 of the EXCEL workbooks accompanying this risk assessment and are used in all exposure assessments based on the assumption of first-order dermal absorption. As discussed further in Section 3.4 (Risk Characterization), this more conservative approach has no material impact on the risk assessment because all hazard quotients for exposure scenarios involving the assumption of first-order dermal absorption lead to hazard quotients that are far below the level of concern.

Another set of exposure scenarios used in this risk assessment involves the assumption of zero-order absorption (i.e., the dermal absorption rate is constant over time). This type of assumption is reasonable when the skin is in constant contact with the amount or concentration of the pesticide, and is fundamental to exposure scenarios that involve wearing contaminated gloves.

In this scenario, the assumption is that the amount of pesticide saturating the inside of the gloves is greater than the amount that could be dermally absorbed.

As also discussed in SERA(2007a), Forest Service risk assessments generally use a QSAR algorithm developed by the EPA (U.S. EPA 1992, 2007), when experimental data are not available to estimate a zero-order dermal absorption rate (i.e., typically referred to as a K_p in units of cm/hour). As detailed in Worksheet B05 of all EXCEL workbooks which accompany this risk assessment, the QSAR algorithm developed by the EPA results in an estimated zero-order dermal absorption rate of 0.000044 (0.00002-0.000099) cm/hour. The EPA human health risk assessments on dinotefuran (U.S. EPA/OPP 2004c, 2004e) do not use exposure scenarios that involve zero-order absorption, and the EPA has not proposed a zero-order dermal absorption rate for dinotefuran. Nonetheless, the current Forest Service risk assessment takes the same approach with the zero-order rates that that is taken with the first-order rates and assumes that the zero-order rates derived from QSAR may underestimate dermal absorption. Thus, 10-fold higher zero-order dermal absorption rates—i.e., 0.00044 (0.0002-0.00099) cm/hour—are given in Worksheet B04 and are used in all exposure scenarios involving the assumption of zero-order absorption. As with the first-order rates and for the same reason, this extremely conservative assumption has no impact on the risk characterization.

3.1.3.3. Excretion

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

$$\frac{X_{Inf}}{X_0} = \frac{1}{1 - e^{-kt^*}}$$

where ***t**** is the interval between dosing and k is the first-order excretion rate.

Based on the study by Ford and Casida (2006a), the plasma half-life of dinotefuran is about 35 minutes, and the half-lives in brain and liver are 20 and 15 minutes, respectively (Ford and Casida 2006a, Table 4, p. 1554). These very short half-lives are consistent with observations by Chen (2000) indicating whole body excretion half-lives ranging from 3.64 to 15.2 hours. For estimates of body burden, whole body excretion half-lives are more relevant than plasma half-lives. The half-life of 15.2 hours or about 0.63 days corresponds to a whole-body excretion rate of 1.1 day^{-1} [$k = \ln(2)/t_{½}$]. Using the above equation from Goldstein et al. (1974) and assuming a daily dose interval, the increase in body burden would plateau at a factor of about 1.5. Consistent with the review by White and Williams (2002) as well as the metabolism studies summarized in Section 3.1.3.1, dinotefuran appears to have a very low potential to bioaccumulate in mammals as a result of chronic exposure.

3.1.4. Acute Oral Toxicity

Studies on the acute toxicity of dinotefuran are summarized in Appendix 1. As is true for other types of toxicity studies, the only information on the acute oral toxicity of dinotefuran comes from studies conducted as part of the registration process.

Two standard oral toxicity studies were conducted on technical grade dinotefuran, one in rats (Glaza 1997a) and the other in mice (Glaza 1997b). In both studies, the LD_{50} values for dinotefuran were greater than 2000 mg/kg bw, and slightly lower for males (i.e., a factor of 1.4 lower in rats and a factor of about 1.1 in mice). Nonetheless, based on the confidence intervals for the LD_{50} values reported in the studies, the differences between males and females do not appear to be statistically significant. One study is available on the 20% SG formulation, presumably corresponding to Safari 20 SG in which no mortality was noted at a dose of 2000 mg/kg bw (Oda 2001a). While not specified in the DER for Oda (2001a), the dose 2000 mg/kg bw dose appears to refer to the formulation—i.e., the technical end-use product.

Based on these studies, the. EPA has classified dinotefuran as having low acute oral toxicity—i.e., Category III (U.S. EPA/OPP 2004e, p. 13). In the EPA's categorization scheme, Category III designates the second lowest toxicity category for pesticides. As discussed in SERA (2007, Table 3-2), these classifications have an impact on the labeling requirements of pesticides, with progressively less severe warning notices (referred to as signal words) going from Category I (*Danger*) to Category IV (no signal word required). A Category III classification triggers the signal word *Caution*.

3.1.5. Subchronic or Chronic Systemic Toxic Effects

Studies on the subchronic and chronic oral toxicity of dinotefuran are summarized in Appendix 2, including standard subchronic dietary studies on rats (Weiler 1997a,b), mice (Weiler 1997c,d), and dogs (Weiler 1999a); chronic oral studies on rats (Weiler 2000b), mice (Weller 2000a), and dogs (Weiler 1999b); and standard repeated-dosing studies on developmental and reproductive effects (Edwards et al. 2001; Sakurai 1998b; Sakurai 2002), discussed in Section 3.1.9 (Reproductive and Teratogenic Effects). Because dinotefuran is a member of a class of neurotoxins (i.e., the neonicotinoids) specialized studies on neurotoxicity are also available (Weiler 2001a,b) and are discussed in Section 3.1.6 (Neurotoxicity).

Decreased body weight or body weight gain was observed in all of the subchronic oral toxicity studies in all species tested. This is a very common observation in toxicity studies (i.e., intoxicated animals tend to consume less food than control animals and will either losse weight or not gain as much weight as control animals). Decreases in body weight or body weight gain may also be caused by changes in metabolism resulting in a decrease in food conversion efficiency. Decreased food conversion efficiency was noted in the subchronic rat feeding study by Weiler (1997a) as well as the subchronic feeding study in dogs (Weiler 1999a). In dogs, the decrease in food conversion efficiency may have been associated with vomiting and diarrhea. In the rat study, the decrease in food conversion efficiency was observed only during week 1 of the study and attributed to food spillage that precluded an accurate measure of food consumption

(Weiler 1997a). In one of the subchronic studies in mice (Weiler 1997d), slight increases in total urinary protein and albumin were noted at the highest dietary concentration (50,000 ppm): however, there was no sign of kidney pathology. Although organ weights were generally decreased, most changes corresponded to decreases in body weight. The only statistically significant changes in organ weight included decreases in the right kidney and left testis of male mice in the 50,000 ppm dose group. Since these changes were noted in only one of the two sides of these organs, the decreases may have been incidental. In the subchronic study in rats (Weiler 1997a,b), the only remarkable change in tissue histology was vacuolization of cells in the adrenal cortex.

Decreased body weight was also observed in the chronic oral toxicity studies. In the chronic dog study (Weiler 1999b), the decrease in body weight was associated with a significant decrease in food conversion efficiency over the first 16 weeks of the study. While poor documentation of food spillage may have been a factor in the apparent decreases in food conversion efficiency, this effect was judged to be compound-related in the EPA review of this study. In the chronic studies in rats and mice, decreased body weights were noted only at the highest test concentrations—i.e., 25,000 ppm in the study in mice (Weller 2000a) and 20,000 ppm in the study in rats (Weller 2000b)—and the decreases were not substantial. Changes in organ weights included a decrease in thymus and testes weights in dogs (Weiler 1999b), a decrease in spleen weights in mice (Weller 2000a), and an increase in ovary weights in rats (Weller 2000b).

All of the chronic toxicity studies were classified as acceptable by the EPA. The chronic dog study failed to identify a NOAEL in males. The lowest dietary concentration of 640 ppm was classified as a LOAEL in male dogs based on a decrease in thymus weight. This dietary concentration corresponded to a dose of 20 mg/kg bw/day in male dogs. As detailed in Section 3.3.2, U.S. EPA/OPP (2004e) uses the LOAEL from the chronic dog study to derive the chronic RfD. The EPA classified the dietary concentration of 640 ppm as a NOAEL in female dogs, which corresponds to a dose of 22 mg/kg bw/day in female dogs. Furthermore, the NOAEL is used to derive a toxicity value for intermediate oral exposures, as discussed further in Section 3.3.4 (Dose-Response Assessment for Occupational Exposures).

3.1.6. Effects on Nervous System

As discussed in Section 3.1.2, dinotefuran is clearly neurotoxic, and the mechanism of action—i.e., activation of nicotinic acetylcholine receptors—is generally well understood. For neurotoxins, the EPA requires specialized tests for neurotoxicity, and the registrant submitted two neurotoxicity assays using dinotefuran: a single-dose gavage study (Weiler 2001b) and a 13-week dietary study (Weiler 2001a). Both of these studies are summarized in Appendix 2.

As would be expected, both studies demonstrate signs of neurotoxicity, at least at high doses. In the single-dose study, decreased motor activity was noted in males and females at a gavage dose of 1500 mg/kg bw and also in female rats at a gavage dose of 750 mg/kg bw (Weiler 2001b). In the 13-week dietary study, increases in motor activity were noted at dietary concentrations of 5000 and 50,000 ppm, equivalent to doses of 337 and 3413 mg/kg bw/day in male rats.

The lowest dose associated with signs of neurotoxicity, however, did not occur in either of the two neurotoxicity studies. As noted in U.S. EPA/OPP (2004e), the lowest dose associated with neurotoxicity occurred in the developmental toxicity study in rabbits (Sakurai 1998b) in which dams evidenced signs of neurotoxicity—i.e., prostration and tremors—at a dose of 300 mg/kg bw on Days 6-7 of gestation.

As discussed in Section 3.1.2, the neurotoxicity of dinotefuran is much less pronounced in mammals than in insects. Notwithstanding the evidence from neurotoxicity studies, neurotoxicity is not the most sensitive endpoint in studies involving longer-term exposure to dinotefuran—i.e., adverse effects other than neurotoxicity occur at doses lower than those associated with neurotoxicity. Consequently, none of the longer-term toxicity values used in the current Forest Service risk assessment or in the EPA risk assessment (U.S. EPA/OPP 2004e) for human health effects is based on neurotoxicity (Section 3.3).

3.1.7. Effects on Immune System

There are various methods for assessing the effects of chemical exposure on immune responses, including assays of antibody-antigen reactions, changes in the activity of specific types of lymphoid cells, and assessments of changes in the susceptibility of exposed animals to resist infection from pathogens or proliferation of tumor cells. With the exception of skin sensitization studies (Section 3.1.11.2), specific studies regarding the effects of pesticides on immune function are not required for pesticide registration.

Although specific studies regarding immunological effects from exposure to dinotefuran are not available, limited information is available from the standard subchronic and chronic studies (Section 3.1.5). Typical subchronic or chronic animal bioassays conduct morphological assessments of the major lymphoid tissues, including bone marrow, major lymph nodes, spleen and thymus (organ weights are sometimes measured as well), and blood leukocyte counts. These assessments can detect signs of inflammation or injury indicative of a direct toxic effect of the chemical on the lymphoid tissue. Changes in morphology/cellularity of lymphoid tissue and blood, indicative of a possible immune system stimulation or suppression, can also be detected.

As noted in Section 3.1.5, decreases in both spleen and thymus weights were observed in longer-term toxicity studies in dogs, rats, and mice. Consequently, U.S. EPA/OPP (2004c,e) identified potential effects on immune function as an endpoint of concern. As discussed further in Section 3.3 (Dose-Response Assessment), the longer-term toxicity values derived by the EPA and used in the current Forest Service risk assessment are based on NOAELs for potential effects on immune function.

3.1.8. Effects on Endocrine System

Assessment of the direct effects of chemicals on endocrine function are most often based on mechanistic studies on estrogen, androgen, or thyroid hormone systems (i.e., assessments on hormone availability, hormone receptor binding, or post-receptor processing). In addition, changes in structure of major endocrine glands (i.e., the adrenal, hypothalamus, pancreas, parathyroid, pituitary, thyroid, ovary, and testis) may also be indicative of effects on the

endocrine system. Disruption of the endocrine system during development may give rise to effects on the reproductive system which may be expressed only after maturation. Consequently, multigeneration exposures are recommended for toxicological assessment of suspected endocrine disruptors. The endocrine system is also important in normal growth and development, and changes in growth can be an indicator of effects on the endocrine system.

As discussed in Section 3.1.5, several standard subchronic toxicity studies indicate changes that might be associated with an impact on endocrine function, including decreases in body weight or body weight gain (all subchronic studies), histopathological changes in the adrenal cortex of rats (Weiler 1997a,b), changes in the testes weights of dogs (Weiler 1999b) and ovaries in rats (Weiler 2000b). As discussed in the following subsection (Reproductive and Developmental Effects), additional effects which might be associated with the disruption of normal endocrine function include a decrease in ovarian primordial follicles and an alteration in the estrous cycle in adult female rats in the reproduction study by Becker (2002). So, although there are no mechanistic studies to clearly indicate that dinotefuran interferes with normal endocrine function, the potential impact of dinotefuran on the endocrine system is, nonetheless, an endpoint of concern, based on responses in standard toxicity studies that may be related to changes in endocrine function.

3.1.9. Reproductive and Developmental Effects

3.1.9.1. Developmental Studies

Developmental studies are used to assess whether a compound has the potential to cause birth defects—also referred to as teratogenic effects—as well as other effects during development or immediately after birth. These studies typically entail gavage administration to pregnant rats or rabbits on specific days of gestation. Teratology assays as well as studies on reproductive function (Section 3.1.9.2) are generally required for the registration of pesticides. Very specific protocols for developmental studies are established by U.S. EPA/OPPTS and are available at http://www.epa.gov/opptsfrs/publications/OPPTS_Harmonized.

As detailed in Appendix 2, two developmental studies involving gavage dosing were submitted to the U.S. EPA in support of the registration of dinotefuran: one study in rabbits (Sakurai 1998b) and the other in rats (Sakurai 2002). In both studies, the highest dose tested resulted in some signs of maternal toxicity; however, adverse effects on fetuses were not observed. Thus, there is no basis for asserting that dinotefuran is likely to cause developmental effects. The signs of toxicity noted in the dams and does were consistent with the signs noted in standard subchronic toxicity studies (i.e., primarily signs of neurotoxicity as well as decreased body weight). In the rabbit study, gross pathological changes were observed in the liver (pale brown discoloration) and the stomach (gray white plaques in the fundus). These effects are not reported in the subchronic or chronic studies on dinotefuran. Although the effects on the stomach and liver are dose-related (Sakurai 1998b), they are not otherwise associated with dinotefuran; thus, their significance is unclear.

3.1.9.2. Reproduction Studies

Reproduction studies involve exposing one or more generations of the test animal to a chemical compound. Generally, the experimental method involves dosing the parental (P or F0) generation (i.e., the male and female animals used at the start of the study) to the test substance prior to mating, during mating, after mating, and through weaning of the offspring (F1). In a 2-generation reproduction study, this procedure is repeated with male and female offspring from the F_1 generation to produce another set of offspring (F_2). During these types of studies, standard observations for gross signs of toxicity are made. Additional observations often include the length of the estrous cycle, assays on sperm and other reproductive tissue, and number, viability, and growth of offspring.

The EPA requires only one acceptable multi-generation reproduction study, and the registrant submitted a single study (Becker 2002): a two-generation reproduction study in rats. Unlike the developmental studies, all of which included gavage dosing, the study by Becker (2002) involved dietary exposures at concentrations of 0, 300, 1000, 3000, or 10,000 ppm (mg a.i./kg diet). Adverse effects in the parental generation and offspring were noted only at the highest dietary concentration. In females, changes in the estrous cycle along with alterations in uterine morphology were noted in the parental and F_1 generation and a 40% decrease in ovarian primordial follicles were noted only in the F_1 generation. In males of the parental and F_1 generations, abnormalities in sperm morphology and sperm activity were noted.

3.1.10. Carcinogenicity and Mutagenicity

In terms of a quantitative significance to the human health risk assessment, carcinogenicity is an issue only if the data are adequate to support the derivation of a cancer potency factor. A cancer potency factor is typically derived based on a dose-related increase in malignant tumors from a chronic toxicity study that encompasses a significant portion of the test animals' lifespan. Two such bioassays were conducted on dinotefuran: the chronic (78-week) study in mice (Weiler 2000a) and the chronic (2-year) study in rats (Weiler 2000b). Although the 52-week feeding study in dogs (Weiler 1999b) is classified as a chronic study in terms of assessing toxicity, this type of study does not encompass a substantial portion of the lifespan of beagles and is not typically used to assess potential carcinogenicity. Neither the chronic study in rats nor the chronic study mice noted significant or dose-related increases in the incidence of malignant tumors. In addition, none of the mutagenicity screening assays submitted to the EPA noted any remarkable mutagenic activity (e.g., Takeda 1006a,b). Based on lack of carcinogenic or mutagenic activity, U.S. EPA/OPP (2004c,e) classifies dinotefuran as: *Not likely to be carcinogenic to humans*. This determination is reflected in a more recent summary of EPA's classification of the carcinogenicity of pesticides (U.S. EPA/OPP 2006c).

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

3.1.11.1. Skin Irritation

Two dermal irritation studies in rabbits are available: one on technical grade dinotefuran (Glaza 1998b) and the other on the 20% SG formulation (Ukon 2002b). Both of these follow the same very standard protocol required by the EPA for pesticide registration, and both are classified by

the EPA as *Acceptable*. Neither study noted marked dermal irritation. Based on slight erythema with no edema, the study on technical grade dinotefuran resulted in a classification of the dermal irritancy of dinotefuran as Category IV—the lowest categorization of irritancy in the ranking scheme used by U.S. EPA. Somewhat greater irritancy was noted in the study using the formulation—i.e., more severe erythema and slight edema—and the irritancy of the formulation was classified as Category III, a moderate skin irritant.

3.1.11.2. Skin Sensitization

As for dermal irritation, there are two available dermal sensitization studies: one on technical grade dinotefuran (Glaza 1997d) and the other on the 20% SG formulation (Ukon 2002c). Both of these studies were conducted using guinea pigs and followed a standardized protocol. Both studies are classified as *Acceptable* by U.S. EPA/OPP (2004c,e). Moreover, both studies showed no evidence of dermal sensitization.

In the formulation study (Ukon 2002c), however, slight decreases in body weight were noted in 5/20 test animals and 2/10 control animals, and these effects were not attributed to treatment. Although weight loss is an unusual finding in a skin sensitization study, weight loss is an effect commonly seen in toxicity studies with dinotefuran (Section 3.1.5). Nonetheless, the assessment made in the DER for this study, which is that the weight loss is incidental and not related to treatment, appears to be reasonable. The magnitude of the weight loss in the study, according to the DER, is only *2 to 13 grams*. The initial body weights of the test animals ranged from 305 to 381 g; thus, the proportion of body weight lost was very small (i.e., about 0.6-3.4%). Furthermore, the differences in the incidence of weight loss between the control and test groups are not statistically significant or even marginally so, using the Fisher Exact Test (p=0.571176).

3.1.11.3. Ocular Effects

There are three available eye irritation studies for dinotefuran, as summarized in Appendix 1. Like the dermal irritation and sensitization studies, the eye irritation studies follow very standard protocols and all are classified by the EPA as *Acceptable*. Based on the results of the study by Kuhn (2004) using technical grade dinotefuran, U.S. EPA/OPP (2004, p. 13) classifies dinotefuran as minimally-irritating to the eyes (i.e., Category IV). This classification, however, does not address the study by Glaza (1998a) in which technical grade dinotefuran caused corneal opacity that persisted in the unwashed, treated eyes of rabbits for up to 7 days after exposure. The third eye irritation study was performed with the 20% SG formulation which caused transient corneal opacity in the unwashed treated eyes of rabbits (Ukon 2002a). The effect of exposure to the formulated product was less severe than that observed in the study by Glaza (1998a) involving exposure to technical grade dinotefuran, and would generally warrant a Category III classification. According to the study results, dinotefuran is not a severe eye irritant; nevertheless, at least mild or possibly moderate irritation could result from accidental eye exposure to either the technical grade product or the 20% SG formulation.

3.1.12. Systemic Toxic Effects from Dermal Exposure

Two acute dermal toxicity studies, both of which are limit tests, are available in rats, one involving exposure to technical grade dinotefuran (Glaza 1997c), and the other involving

exposure to the 20% SG formulation (Oda 2001b). In addition, there is a 29-day subchronic dermal toxicity study in rats exposed to technical grade dinotefuran (Henwood 2001a,b). These studies are summarized in Appendix 1 (acute) and Appendix 2 (subchronic); in addition, the EPA classified each of these studies as *Acceptable* (U.S. EPA/OPP-HED 2005).

The results of the acute toxicity studies are unremarkable. Both studies involved a single 2000 mg/kg bw application of the test material to the skin for 24 hours. For the technical grade powder, this dose is equivalent to 2000 mg a.i./kg bw; for the formulation, the dose is equivalent to 400 mg a.i./kg bw. No signs of toxicity were noted in either acute study, although moderate skin irritation is noted in the study that used the technical grade powder (Glaza 1997c), consistent with the rabbit studies designed specifically to detect skin irritation (Section 3.1.11.1).

The subchronic dermal toxicity study involved four doses, including the control: 0, 40, 200, or 1000 mg/kg bw/day applied to the shaved skin of rats for 6-7 hours/day, 7 days/week for 29 days (Henwood 2001a,b). In the 40 mg/kg bw dose group, 1/10 male rats died; however the incidence is not statistically significant or the effect is not dose-related. No signs of toxicity or dermal irritation were noted at any dose level.

3.1.13. Inhalation Exposure

Information on inhalation exposure to dinotefuran includes two acute inhalation studies and one subchronic inhalation study. The acute toxicity studies, one on technical grade dinotefuran (Shepherd 1999) and the other on the 20% SG formulation (Decker 2002), are summarized in Appendix 1. The subchronic inhalation toxicity study (Mita 2002) is summarized in Appendix 2.

A transient decrease in body weight was noted in 1/5 males and 1/5 females in the acute toxicity study using the 20% SG formulation (Decker 2002). The magnitude of the weight loss is specified in the DER for this study only as *slight*. It is unclear whether these changes were attributable to treatment. As noted in Section 3.1.5, weight loss is a common response to dinotefuran exposure. Based on these acute studies, the U.S. EPA/OPP (2004e) classifies the inhalation toxicity of dinotefuran as Category IV.

The subchronic inhalation study involved nose-only exposures of rats to concentrations of 0, 0.22, 0.66, or 2.08 mg/L, 6 hours/day for 29 days (Mita 2002). The DER for this study specifies that these exposures were equivalent to daily doses of approximately 60, 179, or 565 mg/kg/day. The basis for the route extrapolation is not given in the DER. These dose estimates are presumably estimates of exposed dose (i.e., the amount of material inhaled) rather than absorbed dose. The observed effects include alopecia and protruding eyes at all but the lowest dose.

While it is reasonable to assert that high concentrations of dinotefuran in air would likely be of concern, the proposed uses of dinotefuran in Forest Service programs are not likely lead to inhalation exposure.

3.1.14. Inerts and Adjuvants

3.1.14.1. Inerts

The EPA is responsible for regulating inerts and adjuvants in pesticide formulations. As implemented, these regulations affect only pesticide labeling and testing requirements. The term *inert* is used to designate compounds that do not have a direct toxic effect on the target species. Although the term *inert* is codified in FIFRA, some inerts may be toxic; therefore, the EPA now uses the term *Other Ingredients* instead of the term *inerts*.

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

The information available on the specific inerts in both Safari 2G and Safari 20 SG is summarized in Table 3. Hydrated amorphous silica as well as the material referred to in the MSDS for Safari G as *wood or particle board* are classified as List 4A inerts (i.e., an inert of minimal concern). The bulk of the inerts in both Safari 2G (98%) and Safari 20 SG (80%) are not identified.

While inerts can be viewed with substantial concern by some individuals simply because the identity of the inerts is not disclosed, there appears to be little basis for asserting that inerts are a substantial concern in dinotefuran formulations. As noted in previous subsections, acute toxicity studies are available on a 20% formulation of dinotefuran. This material presumably refers to Safari 20 SG. Based on these toxicity studies, there is no basis for asserting that the inerts in this formulation are likely to increase the toxicity of the formulation substantially. Dinotefuran itself appears to be the agent of primary concern. Since there are no available toxicity studies on Safari 2G, there is no basis for assessing the potential hazards posed by inerts in Safari 2G other than the general practice of the EPA to ban inerts that are hazardous. Although the identities of all of the inerts in the Safari formulations are not publically available, all inerts are disclosed to the U.S. EPA (MacDonald and Graham 2001).

3.1.14.2. Adjuvants

Adjuvants may be used in some applications of dinotefuran formulations. The most common adjuvant is likely to be water. As noted in Section 2.3.3, bark applications of dinotefuran may involve adjuvants such as Pentra-Bark to enhance the absorption of dinotefuran through the bark. As with most Forest Service risk assessments as well as pesticide risk assessments conducted by the EPA, the current risk assessment does not specifically attempt to assess the risks of using adjuvants, unless specific information is available suggesting that the risks may be substantial. For example, some adjuvants used in glyphosate formulations may be as toxic as, and possibly

more toxic than, glyphosate itself; accordingly, these risks are addressed in the Forest Service risk assessment on glyphosate.

No information is available on the hazards which might be associated with the use of Pentra-Bark or other adjuvants with dinotefuran. Pentra-Bark is a surfactant used to enhance the absorption of water soluble pesticides into vegetation (AgBio 2008). The impact, if any, on the use of Pentra-Bark or other surfactants with dinotefuran cannot be assessed based on available information.

3.1.15. Impurities and Metabolites

3.1.15.1. Metabolites

The *in vivo* mammalian metabolism of dinotefuran is considered in Section 3.1.3. This section is concerned with the metabolism of dinotefuran in the environment. The environmental metabolism of a pesticide may need to be considered quantitatively if the metabolites are more toxic and more persistent than the parent compound. For example, malathion is metabolized to malaoxon both *in vivo* and in the environment. The environmental metabolism of malathion to malaoxon must be considered quantitatively because malaoxon may be more persistent than malathion and malaoxon is much more toxic than malathion (SERA 2008b).

Very little information is available on the toxicity of the metabolites of dinotefuran; moreover, no information is available on the toxicity of any of the metabolites of dinotefuran in mammals. Some very limited information is available on the toxicity of DN and MNG metabolites to aquatic organisms. As illustrated in Figure 1, DN is structurally similar to dinotefuran and is formed by removal of the nitro (–NO2) group of the guanidine moiety. MNG is a metabolite formed by the cleavage of the methyl-furan moiety. Based on toxicity tests in green algae, both MNG (Kelly and Ferguson 2002a) and DN (Kelly and Ferguson 2002b) are less toxic than dinotefuran (Seyfried 2000) with the NOEC value for the two metabolites at about 100 ppm and the NOEC for dinotefuran at 25 ppm. Bioassays also were conducted with *Daphnia magna* exposure to dinotefuran (Peither 2000a) and DN (Kelly et al. 2002), but each of these bioassays involved only a single concentration. While DN was tested at a lower concentration than dinotefuran, and a low incidence of immobility was noted in the DN study, U.S. EPA/OPP (2004f, p. 81) classifies both DN and dinotefuran as practically nontoxic to freshwater invertebrates.

Another indication from the ecotoxicology literature that the metabolism of dinotefuran is a detoxification process involves the impact of piperonyl butoxide (an inhibitor of oxidative metabolism) and propargyl propyl benzenephosphonate (an inhibitor of hydrolytic metabolism) on the toxicity of dinotefuran. Studies in both the cockroach and housefly by Kiriyama and coworkers (Kiriyama and Nishimura 2002; Kiriyama et al. 2003) indicate that pre-treatment of these organisms with the two metabolic inhibitors enhance the toxicity of subsequent exposures to dinotefuran. If the metabolism of dinotefuran in these species lead to the toxicologically significant formation of more toxic metabolites, the opposite pattern would be expected – i.e., the metabolic inhibitors would be expected to diminish rather than enhance the toxicity of dinotefuran.

The lack of data on dinotefuran metabolites in mammals does not, of course, indicate that the metabolites are nontoxic. As discussed in U.S. EPA/OPP (2004f, p. 93 ff), several metabolites of dinotefuran have been identified as *residues of concern* in water or vegetation. Although there may be some basis for concern about the metabolites of dinotefuran, it cannot be addressed quantitatively in the current risk assessment due to the lack of toxicity data on the metabolites. As discussed further in Section 3.2, all exposure assessments developed in the current Forest Service risk assessment are based on dinotefuran. As discussed in further detail in Section 3.4, the risk characterization for all longer-term dinotefuran exposures leads to hazard quotients that are far below a level of concern. Given the very limited toxicity data on the metabolites of dinotefuran, a residual concern for metabolites is not unreasonable; however, there is no basis for asserting that the concern is substantial.

3.1.15.2. Impurities

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

Impurities can be a substantial concern in a risk assessment, if the impurities pose risks that are qualitatively different from the active ingredient. For example, both picloram and clopyralid contain hexachlorobenzene as an impurity. Hexachlorobenzene is a concern in the risk assessments on picloram and clopyralid because hexachlorobenzene is a persistent carcinogen. Thus, full exposure assessments, dose-response assessments, and risk characterizations are given for the hexachlorobenzene impurity in the risk assessments on picloram and clopyralid. No information is available, however, to suggest that technical grade dinotefuran contains impurities that cause effects which are qualitatively different from dinotefuran itself.

3.1.16. Toxicological Interactions

Given the relatively complex metabolic pathways for dinotefuran (Section 3.1.3.1) and the general importance of pharmacokinetic mechanisms in toxicological interactions (e.g., ATSDR 2004), it is reasonable to suppose that compounds that alter the uptake, metabolism, or excretion of dinotefuran could influence the toxicity of dinotefuran. These types of interactions might either enhance or reduce the toxicity of dinotefuran. There is, however, no information to permit more specific statements concerning toxicological interactions of dinotefuran with other compounds.

As noted in Section 2 and discussed further in Section 3.1.2, dinotefuran is a neonicotinoid that causes neurotoxicity by binding to nicotinic acetylcholine receptors. In general, combinations of compounds that act by the same or similar mechanisms will display additive toxicity rather than synergism (e.g., U.S. EPA/ORD 2000). Thus, it seems reasonable to suggest that other

neonicotinoid pesticides (e.g., acetamiprid, clothianidin, imidacloprid, nitenpyram, thiacloprid, and thiamethoxam) are likely to evidence additive toxicity with dinotefuran.

3.2. EXPOSURE ASSESSMENT

3.2.1. Overview

Exposure assessments in most Forest Service risk assessments are based on a relatively standard set of exposure scenarios for workers and members of the general public. Details of the exposure scenarios and subsequent risk estimates are provided in EXCEL workbooks. While the exposure assessments vary depending on the characteristics and data relevant to a specific pesticide, their organization and the assumptions on which they are based are standard and consistent in Forest Service risk assessments.

The exposure assessments for dinotefuran are somewhat complicated by the number of different application methods to be considered. To accommodate the different application methods, this risk assessment is accompanied by six EXCEL workbooks designated as attachments:

Attachment 1a: Broadcast foliar, single application
Attachment 1b: Broadcast foliar, two applications
Attachment 2: Broadcast soil
Attachment 3: Bark Applications
Attachment 4: Soil Injection
Attachment 5: Tree Injection

The workbooks for broadcast foliar applications are based on the maximum broadcast foliar application rate of 0.2 lb a.i./acre. Attachment 1b is based on two broadcast foliar applications each at 0.2 lb a.i./acre with the minimum application interval of 14 days. All other workbooks are based on the maximum labeled application rate of 0.54 lb a.i./acre. The consequences of using lower application rates are discussed in the risk characterization.

Table 4 summarizes the specific exposure scenarios used in this risk assessment for the various application methods. Not all exposure scenarios are relevant to all application methods. For example, in broadcast foliar applications of pesticides in a liquid carrier, exposure scenarios are developed for the accidental spill of the liquid onto a worker's hands and legs as well as the accidental direct spray of a child and the accidental direct spray of the lower legs and feet of a young woman. For dinotefuran, broadcast soil applications are made with granular formulations. Although granular formulations might be spilled onto an individual, there are no reasonably reliable methods for estimating exposures from such scenarios; accordingly, no quantitative exposure scenarios are developed. For other types of application methods, such as soil or tree injections, the nature of the application method suggests that the direct spray of members of the general public are simply implausible; therefore, these exposure scenarios are omitted for those application methods.

In some cases, the same exposure scenario may be used for different application methods, but the implementation of the scenario may be different. For example, the consumption of contaminated fruit or vegetation is considered in exposure assessments for members of the general public in both broadcast foliar and broadcast ground applications. Nevertheless, available data indicate

that plausible residues on fruit or vegetables will be much different after liquid applications than after granular applications. These differences are reflected in the specific workbooks for each of the application methods.

Specifics regarding the assumptions used for each of the application methods and the rationale for including or excluding different exposure scenarios for the various application methods are addressed in the remaining sections of this exposure assessment.

3.2.2. Workers

Exposure assessments for workers are summarized in Worksheet E01 of each of the EXCEL workbooks 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 exposures involving absorbed dose estimates based on handling a specified amount of chemical during specific types of applications. The accidental/incidental exposure scenarios involve specific events that may occur during any type of application.

3.2.2.1. General Exposures

As described in SERA (2007a), worker exposure rates in Forest Service risk assessments 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. A summary of these exposure rates, taken from Table 3-3 in SERA 2007a, is given below:

Application Method	Exposure Rate (mg/kg bw per lb a.i.)
Directed foliar	0.003 (0.0003 to 0.01)
Broadcast foliar, boom spray	0.0002 (0.00001 to 0.0009)
Aerial	0.00003 (0.000001 to 0.0001)

There are no available studies involving worker exposure to dinotefuran, regardless of the application method. Accordingly, the rates for aerial applications summarized above are used to characterize worker exposure rates for aerial applications of dinotefuran (Attachments 1a, 1b, and 2). Exposure rates are also not available for workers involved in bark applications, soil injection, or tree injection of dinotefuran; however, worker exposure studies on carbaryl included in a recent Forest Service risk assessment (SERA 2008a), suggest that worker exposure rates for bark application would be comparable to those for directed foliar/backpack applications. In the absence of additional data on dinotefuran, the above worker exposure rates for directed foliar applications are used for bark application, soil injection, and tree injection of dinotefuran. This approach is taken because bark application, soil injection, and tree injection appear to be more closely related to directed foliar applications, in terms of the nature of the worker exposure. Furthermore, it is a general practice in Forest Service risk assessments to use the most conservative assumption in the absence of data. As noted above, the worker exposure rates for directed foliar application are more than a factor of 10 greater than the worker exposure rates for other application methods.

Sometimes, Forest Service pesticide risk assessments incorporate a protection factor for the use of personal protective equipment (PPE) in worker exposure assessments. For dinotefuran, the use of extraordinary PPE is neither required on the product label nor specified by the Forest Service. Consequently, the worksheets for worker exposures (i.e., C01 in the workbooks that accompany this risk assessment) use a clothing protection factor of 0 (i.e., no protection). As documented in Section 3.4.2 (Risk Characterization for Workers), all of the HQ values for workers are substantially below the level of concern, and the use of extraordinary PPE does not have an impact the risk characterization.

3.2.2.2. Accidental Exposures

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

There are various methods for estimating absorbed doses associated with accidental dermal exposure (SERA 2007a). Two general types of exposures are modeled in this risk assessment: those involving direct contact with a pesticide solution and those associated with accidental spills of the pesticide onto the surface of the skin. Any number of specific exposure scenarios could be developed for direct contact or accidental spills by varying the amount or concentration of the chemical on or in contact with the skin surface and by varying the surface area of the affected skin.

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

Exposure scenarios involving direct contact with chemical solutions of dinotefuran are characterized either by immersion of the hands in a field solution for 1 hour or wearing pesticide contaminated gloves for 1 hour. Although generally, it is unreasonable to assume that the hands or any other part of a worker will be immersed in a chemical solution for any given period of time, it is, however, quite plausible to assume that the gloves or other articles of clothing worn by a worker may become contaminated with pesticide. For these exposure scenarios, the key assumption is that wearing gloves grossly contaminated with a chemical solution is equivalent to immersing the hands in a chemical solution. In both cases, the concentration of the chemical solution in contact with the skin and the resulting dermal absorption rate are basically constant.

For both scenarios (hand immersion and contaminated gloves), the assumption of zero-order absorption kinetics is appropriate. For these types of exposures, the rate of absorption is estimated, based on a zero-order dermal absorption rate (K_p). Details regarding the derivation of the K_p value for dinotefuran are provided in Section 3.1.3.2. The amount of the pesticide

absorbed per unit time depends directly on the concentration of the chemical in solution. For aerial liquid applications, the concentrations will vary, ranging from about 0.045 to 0.36 mg/mL (Worksheet A01, Attachment 1a,b). For other application methods, like soil injection, the concentration of dinotefuran may exceed the nominal water solubility (i.e., a nominal concentration of 81 mg/mL) (Worksheet A01, Attachment 4). The specific concentrations used for each application method are based on the program parameters discussed in Section 2.4 (Mixing and Application Rates) of the program description, and details regarding the calculations are given in Worksheet A01 of the attachments to this risk assessment.

Exposure scenarios involving chemical spills onto the skin are characterized by a spill on to the lower legs as well as a spill on to the hands. In these scenarios, it is assumed that a chemical solution is spilled on to a given surface area of skin and that a certain amount of the chemical adheres to the skin. The absorbed dose is then calculated as the product of the amount of the chemical on the surface of the skin (i.e., the amount of liquid per unit surface area multiplied by the surface area of the skin over which the spill occurs and the concentration of the chemical in the liquid), the first-order absorption rate, and the duration of exposure. As with the zero-order dermal absorption rate, the first-order absorption rate (k_a) is derived in Section 3.1.3.2.

3.2.3. General Public

3.2.3.1. General Considerations

3.2.3.1.1. Likelihood and Magnitude of Exposure

The likelihood that members of the general public will be exposed to dinotefuran in Forest Service programs appears to be highly variable, depending on which of the various application methods is used. In broadcast aerial applications, dinotefuran could be applied in or near recreational areas like campgrounds, picnic areas, and trails. Under such circumstances, it is plausible that members of the general public would be exposed to dinotefuran. Conversely, members of the general public are less likely to be exposed to dinotefuran under the circumstances of bark application, soil injection, or tree injection. Moreover, the magnitude of the exposures under those circumstances is likely to be less than anticipated for broadcast applications.

Because of the conservative exposure assumptions used in the current risk assessment, neither the probability of exposure nor the number of individuals who might be exposed has a substantial impact on the characterization of risk presented in Section 3.4. As noted in Section 1 (Introduction) and detailed in SERA (2007a, Section 1.2.2.2), the exposure assessments developed in this risk assessment are based on ***Extreme Values*** rather than a single value. Extreme value exposure assessments, as the name implies, bracket the most plausible estimate of exposure (referred to statistically as the central or maximum likelihood estimate and more generally as the typical exposure estimate) with extreme lower and upper bounds of plausible exposures.

This Extreme Value approach is essentially an elaboration on the concept of the *Most Exposed Individual* (MEI), sometime referred to as the *Maximum Exposed Individual* (MEI). As this

name also implies, exposure assessments that use the MEI approach are made in an attempt to characterize the extreme but still plausible upper bound on exposure. This approach is common in exposure assessments made by U. S. EPA, other government agencies, and the International Commission on Radiological Protection (e.g., ATSDR 2002; ICRP 2005; Payne-Sturges et al. 2004). In the current risk assessment, the upper bounds on exposure are all based on the MEI.

In addition to this upper bound MEI value, the Extreme Value approach used in this risk assessment provides a central estimate of exposure as well as a lower bound on exposure. While not germane to the assessment of upper bound risk, it is significant that the use of the central estimate and especially the lower bound estimate is not intended to lessen concern. To the contrary, the central and lower estimates of exposure are used to assess the feasibility of mitigation—e.g., protective measures to limit exposure. If lower bound exposure estimates exceed a level of concern (which is not the case in the current risk assessment), this is strong indication that the pesticide cannot be used in a manner that will lead to acceptable risk.

Thus, the Extreme Value approach in the exposure assessment is part of an integrated approach designed to encompass plausible upper limits of risk for the most exposed and most sensitive individuals, regardless of the specific probabilities or number of exposures.

3.2.3.1.2. Summary of Assessments

As summarized in Table 4, three types of exposure scenarios are developed for the general public: acute accidental, acute non-accidental, and longer-term or chronic exposures. The accidental exposure scenarios assume that an individual is exposed to the compound either during or shortly after its application. What is more, the nature of the accidental exposures is intentionally extreme. Non-accidental exposures involve dermal contact with contaminated vegetation as well as the consumption of contaminated fruit, vegetation, water, and fish. The longer-term or chronic exposure scenarios parallel the acute exposure scenarios for the consumption of contaminated fruit, water, and fish. All of the non-accidental exposure scenarios are based on levels of exposure to be expected in the routine uses of dinotefuran. Nonetheless, the upper bounds of the exposure estimates for the non-accidental scenarios involve conservative assumptions intended to reflect exposure for the MEI (*Most Exposed Individual*).

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

3.2.3.2. Direct Spray

Direct spray scenarios for members of the general public 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 field solution of the compound and that some amount of the compound remains on the skin and is absorbed by first-order kinetics. Two direct spray scenarios are given, one for a young child (D01a) and the other for a young woman (D01b).

For the young child, it is assumed that a naked child is sprayed directly during a broadcast application and that the child is completely covered with pesticide (i.e., 100% of the surface area of the body is exposed). This exposure scenario is intentionally extreme. As discussed in Section 3.2.3.1.1, the upper limits of this exposure scenario are intended to represent the *Extreme Value* of exposure for the *Most Exposed Individual* (MEI).

The exposure scenario involving the young woman (Worksheet D01b) is somewhat less extreme, but more plausible, and assumes that the woman is accidentally sprayed over the feet and lower legs. By reason of allometric relationships between body size and dose-scaling, a young woman would typically be subject to a somewhat higher dose than the standard 70 kg man. Consequently, in an effort to ensure a conservative estimate of exposure, a young woman rather than an adult male is used in many of the exposure assessments.

For the direct spray scenarios, assumptions are made regarding the surface area of the skin and the body weight of the individual, as detailed in Worksheet A03 of the attachments. The rationale for and sources of the specific values used in these and other exposure scenarios are provided in the documentation for the worksheets (SERA 2008c) and in the methods document for preparing Forest Service risk assessments (SERA 2007a). As with the accidental exposure scenarios for workers (Section 3.2.2.2), different application methods involve different concentrations of dinotefuran in field solutions, and details of the calculations for these concentrations are given in Worksheet A01of the attachments to this risk assessment.

3.2.3.3. Dermal Exposure from Contaminated Vegetation

As discussed in detail in SERA (2007a), the exposure scenario involving dermal exposure from contaminated vegetation assumes that the pesticide is sprayed at a given application rate and that a young woman comes in contact with sprayed vegetation or other contaminated surfaces at some period after the spray operation (D02). For these exposure scenarios, there must be chemical-specific data from which to estimate dislodgeable residue (the amount of chemical released from the vegetation) and its rate of transfer from the contaminated vegetation to the skin. As noted in Durkin et al. (1995), dermal transfer rates are reasonably consistent for a number of pesticides. Accordingly, the methods and rates derived in Durkin et al. (1995) are used as defined in Worksheet D02. The exposure scenario assumes a contact period of 1 hour and further assumes that the chemical is not effectively removed by washing until 24 hours after exposure.

Other estimates used in this exposure scenario involve estimates of the first-order dermal absorption rate and dislodgeable foliar residue. The first order dermal absorption rate for dinotefuran is discussed in Section 3.1.3.2.

Most Forest Service risk assessments use a default assumption of 0.1, as a proportion of the application rate, to estimate dislodgeable foliar residues for broadcast foliar applications. Thus, the estimated dislodgeable foliar residue immediately after application of 1 lb a.i./acre (equivalent to 11.21 $\mu g/cm^2$) is 1.121 $\mu g/cm^2$.

There are dislodgeable residue data for foliar applications of dinotefuran to ornamental plants (Hatterman 2002a), turf (Hatterman 2002b), and leafy vegetables (Hummel 2002a). Hatterman (2002b) indicates that maximum initial dislodgeable foliar residues ranged from 0.0281 to 0.0393 μg/cm^2, after dinotefuran was applied at the maximum labeled rate of 0.54 lb a.i./acre (6.05 μg/cm2). These rates correspond to proportions of about 0.0046-0.065 of the nominal application rate. The studies by Hatterman (2002a) and Hummel (2002a) involved two applications at 13- to 14-day intervals. As a proportion of the nominal cumulative application rates, the maximum dislodgeable residues in these studies are much higher, ranging from about 0.087 to 0.22. Since dislodgeable residue on turf is the most likely contact exposure scenario for members of the general public, a case could be made for reducing the standard proportion of 0.1. Conversely, the studies by Hatterman (2002a) and Hummel (2002a) could be used to increase the proportion. These considerations are incidental to the current risk assessment. Using the default assumption of 0.1, the upper bound of the HQ value for this exposure scenario for broadcast foliar applications is below the level of concern by factors of 1000 or more. Nonetheless, in order to better reflect the dinotefuran specific data, the dislodgeable residue is taken as a range from 0.005 to 0.22, with a central value of 0.1.

3.2.3.4. Contaminated Water

3.2.3.4.1. Accidental Spill

The accidental spill scenario assumes that a young child consumes contaminated water from a small pond (1000 m^2 in surface area and 1 meter deep) shortly after an accidental spill of a pesticide into the water. This is an arbitrary scenario in the sense that the concentration in the pond simply depends on the amount of pesticide spilled. For liquid formulations, the amount spilled is taken as 100 gallons with a range from 20 to 200 gallons of a field solution. For granular applications, the amount spilled is taken as 40 pounds with a range of 16 to 80 pounds.

The specifics of the accidental spill scenario are provided in Worksheet D05. Because this scenario is based on the assumption that exposure occurs shortly after the spill, no dissipation or degradation is considered. This scenario is dominated by arbitrary variability. The actual concentration in the water would depend greatly on the amount of pesticide spilled, the size of the water body into which the pesticide is spilled, the time at which water consumption occurs relative to the time of the spill, and the amount of contaminated water consumed.

3.2.3.4.2. Accidental Direct Spray/drift for a Pond or Stream

The exposure scenarios for accidental direct spray/drift for a pond or stream are less severe but more plausible than the accidental spill scenario described above. Although dinotefuran used in Forest Service programs will not be applied directly to surface water, direct applications may be made inadvertently to small ponds or streams unseen during aerial applications. In addition, unintentional contamination of surface water could occur due to drift.

The exposure scenarios for the contamination of a small pond and a small stream are given in Worksheets 10a and 10b, respectively, and consider both direct application and drift at distances from 25 to 900 feet. The resulting concentration depends on the application rate as well as the

nature of the water body. For ponds, U.S. EPA typically uses a 2-meter-deep pond to develop exposure assessments (SERA 2007a), and this approach is used in Worksheet D10a. For small streams, the resulting water concentration depends on the surface area of the stream and the rate of water flow within the stream. The stream modeled using GLEAMS (see below) is about 6 feet wide (1.82 meters), and it is assumed that the pesticide is applied along a 1038-foot (316.38 meters) length of the stream with a flow rate of 710,000 L/day.

Accidental sprays of a small pond or stream apply only to broadcast applications; these exposure scenarios are not relevant to bark treatment, soil injection, or tree injection. A summary of these scenarios is included in Table 5, along with other estimates of dinotefuran concentrations in surface waters, as discussed below.

3.2.3.4.3. GLEAMS Modeling

The Forest Service developed a program, Gleams-Driver, to estimate expected peak and longer-term pesticide concentrations in surface water. Gleams-Driver serves as a preprocessor and postprocessor for GLEAMS, a field scale model developed by the USDA/ARS and a program used for many years in Forest Service and other USDA risk assessments (SERA 2007b).

Gleams-Driver offers the option of conducting general exposure assessments using site-specific weather files from Cligen, a climate generator program developed and maintained by the USDA Agricultural Research Service (http://horizon.nserl.purdue .edu/Cligen). Gleams-Driver was used in the current risk assessment to model dinotefuran concentrations in a small stream and small pond. The generic site parameters used in the Gleams-Driver runs are summarized in Table 6 and additional details are available in the documentation for Gleams-Driver (SERA 2007b).

Table 7 summarizes the chemical-specific values used in GLEAMS, which, for the most part, are similar to those used by U.S. EPA (U.S. EPA/OPP 2004a). The EPA modeling efforts are discussed below (Section 3.2.3.4.4). In the current risk assessment, the modeling input values are based on the environmental fate studies submitted to the EPA by the registrant as well as standard values for GLEAMS modeling recommended by Knisel and Davis (2000). The notes to Table 7 indicate the chemical-specific sources of information used in the GLEAMS modeling effort.

The locations selected for modeling include a total of nine sites, as summarized in Table 8. As discussed in SERA (2007b), these locations are standard sites for the application of Gleams-Driver in Forest Service risk assessments and are intended to represent combinations of precipitation (dry, average, and wet) and temperature (hot, temperate, and cool). For each site, Gleams-Driver was used to simulate 100 replicate applications of dinotefuran at a unit application rate of 1 lb/acre, and each of the simulations was followed for a period of more than 1½ years post application. For each of the nine sites, three sets of simulations were conducted with soil characteristics for clay, loam, and sand.

Because dinotefuran may be applied twice per year in foliar broadcast applications, two sets of Gleams-Driver runs were conducted for this application method: a single application and two applications conducted with the minimum application interval of 14 days.

The results of the Gleams-Driver simulations are summarized in Table 5. Additional details are given in Appendix 8 for each of the Gleams-Driver runs that were conducted:

- Foliar broadcast, single application
- Foliar broadcast, two applications
- Ground broadcast
- Soil injection

Since GLEAMS (hence Gleams-Driver) cannot be used to model tree injection, no estimates of dinotefuran in surface water following tree injection are provided in this risk assessment. Given the extremely low hazard quotients associated with surface water exposures, this limitation has no significant impact on the risk characterization for human health (Section 3.4) or ecological effects (Section 4.4).

3.2.3.4.4. Other Modeling Efforts

In addition to Gleams-Driver, PRZM-EXAMS runs were conducted using the USA Express v. 1.03.02 EXAMS-PRZM Exposure Simulation Shell (Burns 2006). Simulations were conducted for the EPA standard farm pond (similar to the pond used in Gleams-Driver modeling) as well as the standard EPA Index Reservoir. Most of the scenarios built into the Express program involve agricultural crops. One scenario, however, involves a pine nursery in Oregon, and this scenario was used in the simulations conducted for this risk assessment.

In the EPA risk assessments on dinotefuran, Tier 1 screening models were used, GENEEC in U.S. EPA/OPP (2006b) as well as FIRST and SCIGROW in U.S. EPA/OPP (2004g). The results of the EPA modeling are summarized at the bottom of Table 5 and are normalized for an application rate of 1 lb a.i./acre so that the results are comparable to the other values summarized in Table 5.

3.2.3.4.5. Monitoring Data

Due to the lack of surface water monitoring data, modeling, as discussed in previous subsections is not plausible. The lack of monitoring data is both a limitation in this risk assessment and a source of uncertainty; however, as noted in Section 1, dinotefuran is a relatively new insecticide and the lack of monitoring data is to be expected.

3.2.3.4.6. Concentrations in Water Used for Risk Assessment

Table 9 summarizes the concentrations of dinotefuran in surface water used in this risk assessment for each of the application methods considered quantitatively.

The concentrations are given as water contamination rates (WCRs), the concentrations in water expected at a normalized application rate of 1 lb a.i./acre, converted to units of ppm or mg/L per

lb a.i./acre. While units of ppb or µg/L are used in Tables 5 as a convenience, the conversion from ppb to ppm in Table 9 is made because ppm and mg/L are the units of measure used in the EXCEL workbook for contaminated water exposure scenarios in both the human health and ecological risk assessments. The water contamination rates are entered in Worksheet B04 in each of the EXCEL workbooks that accompany this risk assessment. The values in Worksheet B04 are linked to the appropriate scenario-specific worksheets in the EXCEL workbooks.

All of the values summarized in Table 9 are based on the Gleams-Driver simulations summarized in Table 5 and detailed in Appendix 8. This approach is taken because the Gleams-Driver simulations resulted in somewhat higher estimates of concentrations in surface water than did the simulations based on PRZM-EXAMS or the Tier 1 screening models used by U.S. EPA (i.e., GENEEC, FIRST, and SCIGROW). This pattern is a quite common in Forest Service risk assessments. While the estimates based on Gleams-Driver are comparable to estimates from the other models, the estimates from Gleams-Driver tend to be higher than those based on applications of other models because of the highly conservative input values used for clay (i.e., a very high runoff potential) and sand (i.e., a very high potential for percolation). The upper bound estimates also tend to be higher than those of other modeling efforts simply because of the nature of the simulations. The Gleams-Driver runs are all based on 100 simulations per run and the upper bound of the concentrations given in Appendix 8 reflect the empirical 0.05 upper bound from each simulation. The simulations using the PRZM-EXAMS shell are based on a single 20-year simulation.

As also summarized in Table 5 and detailed in Appendix 8, the modeled concentrations of dinotefuran in ponds generally exceed those in streams, and this difference is most pronounced for longer-term exposures. To some extent, the differences in the modeled peak concentrations may be an artifact of the characteristics of the pond and stream that are modeled (Table 6). In other words, if a larger pond or a smaller drainage area were modeled, the concentration in the pond would decrease. For this generic exposure assessment, the concentrations used in the risk assessment (Table 9) are based on the higher concentration estimate (pond vs stream) for each application method summarized in Table 5.

3.2.3.5. Oral Exposure from Contaminated Fish

This risk assessment includes three sets of exposure scenarios for the consumption of contaminated fish, and each set includes separate estimates for the general population and subsistence populations. These exposure scenarios consist of one set for acute exposures following an accidental spill (Worksheets D08a and D08b), another set for acute exposures based on expected peak concentrations (Worksheets D08c and D08d), and the third set for chronic exposures based on estimates of longer-term concentrations in water (Worksheets D09a and D09b). The two worksheets in each of these three sets are intended to account for different rates of wild-caught fish consumption in both general and subsistence populations. Details of exposure scenarios involving the consumption of contaminated fish are provided in Section 3.2.3.5 of SERA (2007a).

The water concentrations of dinotefuran are based on the accidental spill scenario (Section 3.2.3.4.1) for Worksheets D08a and D08b, and the peak and longer-term expected concentrations in water are based on the Gleams-Driver modeling, as summarized in Table 9 and discussed in Section 3.2.3.4.6. The specific concentrations will vary among the different application methods; accordingly, the water concentrations for the various application methods will differ in the EXCEL workbooks that accompany this risk assessment.

The concentration of the pesticide in fish (C_F) is taken as the product of the concentration of the chemical in water (C_W) and the bioconcentration factor (BCF):

$$C_{Fish_{mg/Kg}} = C_{W\,mg/L} \times BCF_{L/kg}$$

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 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.

No experimental BCF values are available for dinotefuran. The U.S. EPA/OPP (2004f, p. 35) waived the requirement for a bioconcentration factor in fish because of the low K_{ow} for dinotefuran. In other words, no bioconcentration would be expected because the physical properties of dinotefuran suggest that it will not partition from water into fish, due to its highly hydrophilic and lipophobic nature. Thus, using a bioconcentration factor of 1 (no bioconcentration) is justified.

As with dermal absorption rates (Section 3.1.3.2), various algorithms, are available for estimating the BCF based on the structure and physical properties of a chemical. One such program, EPI Suite, was developed by the EPA (Meylan and Howard 2007). As summarized in Table 2, the BCF for dinotefuran, as estimated by EPI Suite, is 3.162. For the current risk assessment, this value is rounded to 3 and used for all exposure scenarios involving the consumption of contaminated fish.

3.2.3.6. Dermal Exposure from Swimming in Contaminated Water

Some geographical sites maintained by the Forest Service or Forest Service cooperators contain surface water in which members of the general public might swim. To assess the potential risks associated with swimming in contaminated water, an exposure assessment is developed for a young woman swimming in surface water for 1 hour (Worksheet D11).

Conceptually and computationally, this exposure scenario is virtually identical to the contaminated gloves scenario used for workers (Section 3.2.2.2)—i.e., a portion of the body is immersed in an aqueous solution of the compound at a fixed concentration for a fixed period of time. The major differences in the two scenarios involve the pesticide concentration in water and the exposed surface area of the body. For the worker wearing contaminated gloves, the assumption is made that both hands are exposed to the field solution—i.e., the concentration of

the compound in the applied solution. For the swimmer, the assumption is made that the entire surface area of the body is exposed to the expected peak concentrations in ambient water (Table 9). Also, like the exposure scenario involving contaminated gloves, the swimming scenario is conservative in that it assumes zero-order absorption directly from the water to the systemic circulation. While the swimmer will not be immersed for 1 hour, the entire body surface is used both as a conservative approximation (i.e., the MEI) and to consider intermittent episodes during which the whole body might be immersed or at least wet.

As in the corresponding worker exposure scenario, the 1-hour period of exposure is somewhat, but not completely, arbitrary, given that longer periods of exposure are plausible. Nonetheless, the 1-hour period is intended as a unit exposure estimate. In other words, the exposure and consequently the risk will increase linearly with the duration of exposure, as indicated in Worksheet D11. Thus, a 2-hour exposure would lead to a hazard quotient that is twice as high as that associated with an exposure period of 1 hour. In cases in which this or other similar exposures approach a level of concern, further consideration is given to the duration of exposure in the risk characterization (Section 3.4). For dinotefuran, the levels of exposure are well below the level of concern.

3.2.3.6. Oral Exposure from Contaminated Vegetation

Although none of the Forest Service applications of dinotefuran will involve crop treatment, Forest Service risk assessments typically include standard exposure scenarios for the acute and longer-term consumption of contaminated vegetation. Two sets of exposure scenarios are provided: one for the consumption of contaminated fruit and the other for the consumption of contaminated vegetation. These scenarios are detailed in Worksheets D03a and D03b for acute exposure and in Worksheets D04a and D04b for chronic exposure.

For broadcast foliar applications, the concentration of the pesticide on contaminated fruit and vegetation is estimated using the empirical relationships between application rate and concentration on different types of vegetation (Fletcher et al. 1994). The rates given by Fletcher et al. (1994) are based on a reanalysis of data originally compiled by Hoerger and Kenaga (1972) and represent estimates of the concentration in different types of vegetation (mg chemical/kg vegetation) after a normalized application rate of 1 lb a.i./acre. Although the human health risk assessments conducted by the EPA (U.S. EPA/OPP 2004c,e) do not consider this exposure scenario, the residue rates recommended by Fletcher et al. (1994) are used by U.S. EPA/OPP in their ecological risk assessment of dinotefuran (U.S. EPA/OPP 2004f, 2006b).

The residue rates recommended by Fletcher et al. (1994) are given in Table 10 of the current Forest Service risk assessment. Note that Fletcher et al. (1994) as well as Hoerger and Kenaga (1972) give only central estimates and upper bound estimates of residue rates. In Table 10, lower bound estimates are given under the assumption that the ratio of the central estimate to the upper bound estimate will be identical to the ratio of the lower bound to the central estimate (i.e., the variability will be log-symmetrical).

The residue rates recommended by Fletcher et al. (1994) are based on foliar applications and may not be appropriate for granular broadcast soil applications. Intuitively, it seems that granular broadcast applications would result in lower initial concentrations in vegetation because less of the applied granular formulation would adhere to leaf or fruit surfaces than would be the case with liquid foliar applications. This issue is further complicated by the lack of data regarding dinotefuran residues on vegetation after granular applications of the pesticide. As summarized in the Forest Service risk assessment of hexazinone (SERA 2005b, Table 3-3), Michael (1992) assayed concentrations of hexazinone on vegetation after applications of a liquid formulation of hexazinone (Velpar L) and a granular application of hexazinone (Velpar ULV). For the liquid formulation, the initial residues normalized for application rate are in the range of those recommended by Fletcher et al. (1994). For the granular formulation, however, the residues are lower by factors ranging from about 26 (grass) to over 400 (blueberries). Again, this is to be expected because granular formulations do not tend to adhere to the surface of vegetation. Thus, for granular applications, estimates of residue rates are based on 0.04 of the rates recommended by Fletcher et al. (1994) for liquid applications. The specific rates for granular applications are given in Table 10 immediately below those for broadcast foliar (liquid) applications.

An additional complication with dinotefuran involves the applicability of the residue rates recommended by Fletcher et al. (1994). In general, the application of a pesticide or any chemical to vegetation seems to entail a simple physical process unaffected by the chemical-specific properties of the applied compound, with the obvious exception of high volatile chemicals or chemicals that degrade rapidly. In most cases, field data regarding pesticide residue rates after foliar applications are reasonably consistent with the residue rates recommended by Fletcher et al. (1994). As noted above, this consistency is true for the study by Michael (1992) for the liquid formulation of hexazinone; furthermore, similar consistencies between field data the residue rates recommended by Fletcher et al. (1994) are documented in many other Forest Service risk assessments.

On the other hand, results from Hummel (2003b) suggest that the residue rates recommended by Fletcher et al. (1994) may somewhat overestimate plausible residue rates for dinotefuran. In the Hummel (2003b) study, dinotefuran—a 20 SG formulation in an aqueous solution—was applied by broadcast foliar application to head lettuce, leaf lettuce, and spinach. Two applications were made at rates of about 0.14 lb a.i./acre with a 14-day application interval for a cumulative application rate of about 0.28 lb a.i./acre. The mean residues reported by Hummel (2003b) after the second application include dinotefuran as well as the DN and UF metabolites. These metabolites are discussed in Section 3.1.15.1 and are illustrated in Figure 1. The total mean residues of dinotefuran and the DN and UF metabolites were 0.419 ppm for head lettuce, 2.39 ppm for leaf lettuce, and 2.20 ppm for spinach. The maximum combined residue reported by Hummel (2003b) is 3.13 ppm.

Even ignoring the first application (i.e., the residue rates are based on a single application rate of 0.14 lb a.i./acre) the maximum normalized residue rate is only about 17 ppm per lb a.i./acre, based on mean residues [2.39 ppm ÷ 0.14 lb a.i./acre ≈ 17.071 ppm per lb a.i./acre]. Based on

the maximum residue, the normalized application rate is about 22.4 ppm per lb a.i./acre, based on the maximum reported residue [3.13 ppm ÷ 0.14 lb a.i./acre ≈ 22.357 ppm per lb a.i./acre].

All of the vegetation treated by Hummel (2003b) may be generally classified as broadleaf vegetation. As noted in Table 10, the expected residue rate from Fletcher et al. (1994) is 45 ppm with a range from 15 ppm to 135 ppm. The rates derived from Hummel (2003b) are lower than those recommended by Fletcher et al. (1994) by a factor of about 2.6 based on mean residues [45 ÷ 17 ≈ 2.647] and 6 based on maximum residues [135 ÷ 22.4 ≈ 6.027].

Although the residues rates from the Hummel (2003b) study suggest that the standard rates from Fletcher et al. (1994) may overestimate dinotefuran exposure levels, particularly at the upper bound, the residue rates recommended by Fletcher et al. (1994) are maintained in the current risk assessment, because the data from Hummel (2003b) do not completely contradict the standard rates from Fletcher et al. (1994) but simply fall within the lower range of values used originally by Hoerger and Kenaga (1972) and reanalyzed by Fletcher et al. (1994). Furthermore, decreasing the residue rates based on only a single study—i.e., Hummel (2003b)—does not seem justified. Moreover, as noted previously, Forest Service risk assessments seldom use assumptions which are less conservative than those used by U.S. EPA without a compelling reason. U.S. EPA/OPP (OPP 2004f, 2006b) elected to use the residue rates from Fletcher et al. (1994), and the single study by Hummel (2003b) is not a sufficiently compelling basis for using an exposure assumption that is less protective than that used by the EPA.

From a practical perspective, the use of the Fletcher et al. (1994) recommended residue rates has no impact on the human health risk assessment. As discussed in Section 3.4 (Risk Characterization), none of the exposure scenarios for vegetation consumption in the human health risk assessment approaches a level of concern. That is not the case in the ecological risk assessment concerning the potential effects of dinotefuran on herbivorous insects, as discussed further in Section 4.4.2.3.2.

The exposure scenarios for broadcast foliar applications use the residue rates recommended by Fletcher et al. (1994), as specified in the upper section of Table 10. For broadcast applications of granular formulations, however, the lower residue rates derived from the study by Michael (1992) are used. As indicated in Table 4 (Summary of Exposure Scenarios for the HHRA), exposure scenarios for the consumption of contaminated vegetation are omitted in the EXCEL workbooks for bark application, soil injection, and tree injection. These application methods do not involve the treatment of crops or other forms of vegetation meant for human consumption.

For the longer-term exposure scenarios (Worksheets D04a,b) as well as the acute exposure scenarios involving two applications (Worksheets D03a,b), some estimate of the half-life of dinotefuran on vegetation is necessary. As noted in Table 7, the Gleams-Driver modeling uses the 90% upper bound value from the half lives reported by Hattermann 2002a,b and Hummel 2002a – i.e., 11.6 days. While only the upper bound value is used in the Gleams-Driver simulation, the scenarios for the consumption of contaminated vegetation used the mean value as the central estimate – i.e., 6 days – as well as the 10% lower bound of 0.36 days.

3.3. DOSE-RESPONSE ASSESSMENT

3.3.1. Overview

Table 11 provides an overview of the toxicity values used in the current Forest Service risk assessment for human health effects. When the EPA adopts toxicity values for human health, which is the case for dinotefuran, those values are typically adopted and used directly in Forest Service risk assessments. The EPA derived an acute RfD of 1.25 mg/kg bw, based on a NOAEL for neurotoxicity in rabbits and an uncertainty factor of 100, and a chronic RfD of 0.02, based on a LOAEL of 20 mg/kg bw/day for decreased thymus weights in dogs and an uncertainty factor of 1000. The EPA does not derive RfDs for occupational exposure, and instead recommends an experimental toxicity value and a margin of exposure (MOE), which is analogous to an uncertainty factor. For dinotefuran, the EPA uses a NOAEL of 22 mg/kg bw/day for reduced body weight in dogs and recommends an MOE of 100. This approach is used in the current Forest Service risk assessment to derive an equivalent surrogate occupational RfD of 0.22 mg/kg bw/day.

3.3.2. Acute RfD

The acute RfDs derived by the EPA apply only to a single exposure in a single day. Thus, the EPA derives an acute RfD only when the effect observed in a study is associated with a chemical exposure level or dose administered on a single day.

As discussed in Section 3.1.2, dinotefuran is neurotoxin, which affects the nervous system by binding to nicotinic acetylcholine receptors. Therefore, as part of the registration process, the EPA required specific neurotoxicity studies on dinotefuran. These studies are discussed in Section 3.1.6 and summarized in Appendix 2 of this risk assessment. In the single dose study by Weiler (2001b) the NOAEL for neurotoxicity is 325 mg/kg bw in female rats and 750 mg/kg bw in male rats. Although the lower dose of 325 mg/kg bw could be used to derive an acute RfD, U.S. EPA/OPP (2004e, p. 27 ff) notes that the female rats in the developmental study by Sakurai (1998b) exposed to 300 mg/kg bw showed signs of neurotoxicity on Days 6-7 of gestation. Thus, it is appropriate to derive an acute RfD from the single 325 mg/kg bw dose from the Weiler (2001b) study.

Alternatively, U.S. EPA/OPP (2004e) bases the acute RfD on the 300 mg/kg bw/day NOAEL for neurotoxicity from the developmental study by Sakurai (1998b). As indicated in Table 11 and summarized in Appendix 2, the 300 mg/kg bw/day dose is the LOAEL, not the NOAEL in the study. Dams exposed to 300 mg/kg bw/day evidenced decreased weight gain over the course of the 13-day exposure period (i.e., Days 6-18 of gestation, and, U.S. EPA/OPP (2004e) associates the weight loss with the 13-day exposure period and not with a single dose. Consequently, the dose of 300 mg/kg bw/day is treated as single-day LOAEL, and the next lower dose of 125 mg/kg bw/day is treated as a single-day NOAEL because signs of neurotoxicity were not observed at that dose level on any time over the course of the 13-day exposure period.

To derive the acute RfD, the single-day NOAEL 125 mg/kg bw/day is divided by an uncertainty factor of 100—the product of a factor of 10 for species-to-species extrapolation and a factor of 10 for extrapolation to sensitive individuals—resulting in the acute RfD of 1.25 mg/kg bw. This derivation may be somewhat atypical, in that the distinction between the study LOAEL of 125 mg/kg bw and the single-dose NOAEL of 125 mg/kg bw must be clearly understood; nevertheless, the derivation of the 1.25 mg/kg bw acute RfD is clearly and appropriately articulated by U.S. EPA/OPP (2004e) and is used directly in the current Forest Service risk assessment for acute exposure scenarios, all of which encompass an event that occurs on only a single day.

3.3.3. Chronic RfD

The chronic RfD for dinotefuran is also unusual in that it is based on a LOAEL rather than a NOAEL and is not based on responses in the most sensitive species. As described in U.S. EPA/OPP (2004e, p. 28), the chronic RfD is based on 52-week feeding study in dogs by Weiler (199b) in which male and female dogs were administered dinotefuran in the diet at concentrations of 0, 640, 3200, or 16,000 ppm. The lowest dietary concentration caused no adverse effects in females. In males, however, decreases were noted in thymus weights by the end of the study. Although not statistically significant, the thymus weight decreases in the 640 ppm group males are below the control range in three of the four dogs tested (p. 13, Table 5b of the DER for the study by Weiler 1999b). Moreover, the magnitude of decrease, which is designated as treatment related in the DER, is about 68% of control weight (p. 12, Table 5a of the DER for the study by Weiler 1999b). As discussed in Section 3.1.7, effects on the thymus may have an impact on immune function. While no histopathological changes in the thymus were noted in the 640 ppm group, cysts were noted in three of four dogs in the 3200 ppm group and two of four dogs in the 16,000 ppm group. Thus, based in the decreased thymus weights in the male dogs in the 640 ppm group, U.S. EPA/OPP (2004e, p. 28) designates the 640 ppm group as a LOAEL for male dogs, and this designation seems appropriate.

In the 640 ppm group, the estimated dose based on measured food consumption was 20 mg/kg bw/day. This dose was divided by an uncertainty factor of 1000 to arrive at the chronic RfD of 0.02 mg/kg bw/day. The uncertainty factor is the product of three factors of 10: 10 for species-to-species extrapolation, 10 for extrapolation to sensitive individuals, and 10 for using a LOAEL rather than a NOAEL. The application of these uncertainty factors is standard in the EPA's derivation of RfDs.

In a lifetime feeding study in mice, Weiler (2000a) noted decreased spleen weights in males and increased ovarian weights (week 53) in females at the lowest dietary concentration tested, 25 ppm, corresponding to average daily doses of 3 mg/kg bw for males and 4 mg/kg bw for females (Appendix 2). Typically, the most sensitive species and the most sensitive endpoint are used to derive the RfD. The disposition of the EPA regarding the lower LOAEL in the mouse study as it pertains to the derivation of an RfD is as follows:

> *Effects seen in the mouse oncogenicity study at a lower dose were not considered appropriate for use in a chronic dietary risk*

> *assessment (there was no dose-response, the standard deviations were large, and no corroborative findings were seen in the histopathology evaluations).*
>
> U.S. EPA/OPP 2004e, p. 28

In the DER prepared for the mouse study, the EPA indicates that the reduced spleen weight among treated males is substantial but no dose-response relationship is apparent—i.e., the reduction in the low dose group (about 53.5% of controls) is about the same as the reduction in the high dose group (about 53.7% of controls). Similarly, the increased ovarian weights are substantial but not dose-related, with an increase in relative weight of 263% at the low dose and 233% at the high dose. As noted by U.S. EPA/OPP (2004e), the standard deviations for the changes in both spleen and ovary weights are remarkably large, with some coefficients of variation exceeding 200%. Nonetheless, it is notable that the increased ovary weights are statistically significant ($p<0.05$) in all but the mid-dose group (Weiler 2000a, p. 10, Table 4).

Forest Service risk assessments sometimes propose surrogate RfDs that are lower than those used by the EPA but only if the Forest Service risk assessment has compelling data that was not available to the EPA (e.g., a more recent study) or if the EPA did not consider relevant data. The lower LOAEL in mice is considered in U.S. EPA/OPP (2004e) and is considered in great detail in the DER for the study by Weiler (2000a), which was prepared by U.S. EPA/OPP. Accordingly, the current Forest Service risk assessment defers to the analysis by U.S. EPA and uses the chronic RfD of 0.02 mg/kg bw/day to characterize risks associated with chronic exposure.

3.3.4. Surrogate RfD for Occupational Exposures

Instead of deriving RfDs for occupational exposure, the EPA will identify a longer-term NOAEL and recommend a margin of exposure (MOE). Often, the EPA uses the same longer-term toxicity value used to derive the chronic RfD, in which case, the recommended MOE will be identical to the uncertainty factor used to derive the chronic RfD. This, however, is not the case for dinotefuran. Rather than assessing occupational exposures based on a chronic/lifetime RfD, U.S. EPA/OPP (2004e) selected an intermediate-term exposure of 1-6 months.

For the assessment of occupational exposures to dinotefuran, U.S. EPA/OPP (2004e) does use the same study used to derive the chronic RfD—i.e., the 1-year feeding study in dogs by Weiler (1999b)—but selects an endpoint different from that used to derive the chronic RfD. Rather than using the LOAEL in male dogs from the 640 ppm exposure group, the U.S. EPA uses the NOAEL in female dogs from 640 ppm exposure group. As summarized in Appendix 2, no statistically significant effect on body weight gain was noted in females or males in the 640 ppm exposure group. Specifically, the terminal body weights of the male dogs in the 640 ppm were only slightly less than controls—i.e., 99.1% of the control group (Weiler 1999b, p. 7, Table 2 of the study DER). Thus, the dietary concentration of 640 ppm is considered a LOAEL in male dogs, based on decreases in thymus weight and a NOAEL for both male and female dogs, based on decreases in total body weight. In female dogs, the 640 ppm concentration is equivalent to a

dose of 22 mg/kg bw/day, which the EPA uses to assess occupational risks of exposure to dinotefuran.

The rationale for using body weight rather than thymus weight to derive the toxicity value is addressed as follows:

> *Histopathological endpoints (i.e. decreased thymus weight seen in males at the one-year study LOAEL of20 mg/kg/day) are not assumed to have occurred in the intermediate term time frame. This endpoint is protective of effects in males in the subchronic dog study, and of effects seen in rats and rabbits at higher doses (NOAEL = 33 mg/kg/day in the subchronic neurotoxicity study in rats, 52 mg/kg/day in the developmental toxicity study in rabbits). An MOE of 100 should be required (10x inter-species extrapolation and 10x intra-species variability).*
>
> U.S. EPA/OPP 2004e, p. 28

Forest Service risk assessments do not use the MOE approach. As with all other risk characterizations, Forest Service risk assessments use the HQ approach (Section 3.4). Thus, for assessing risks associated with occupational exposures, the current Forest Service risk assessment uses a surrogate RfD of 0.22 mg/kg bw/day—i.e., the experimental NOAEL of 22 mg/kg bw/day for female dogs divided by an uncertainty factor of 100. This approach is mathematically equivalent to the approach used by EPA.

3.3.5. Dose-Severity Relationships

Forest Service risk assessments will often attempt to define dose-severity relationships in order to more fully interpret the plausible consequences of exceeding the RfD. Dose-severity relationships are generally based on comparisons of human data to data on experimental animals or systematic patterns in toxicity among various species.

As discussed further in Section 3.4 (Risk Characterization), most but not all human exposures are below the level of concern. One non-accidental scenario – i.e., the longer-term consumption of contaminated vegetation after broadcast foliar applications – mostly exceeds the RfD. Consequently, a consideration of dose-severity relationships, particularly for the chronic RfD, would be useful. Nonetheless, no human data are available on dinotefuran. In addition and as detailed further in the dose-response assessment for mammalian wildlife (Section 4.3.2.1), the data on the toxicity of dinotefuran in mammals do not present a consistent pattern in species sensitivity that would be needed to propose dose-severity relationships for humans. Thus, for this pesticide, no formal dose-severity relationship is proposed. This limitation is addressed further in the following section (Section 3.4, Risk Characterization for Human Health).

3.4. RISK CHARACTERIZATION

3.4.1. Overview

Details of the risk characterization for workers and members of the general public are given in Worksheets E02 and E04, respectively, of the six attachments that accompany this risk assessment. In addition, copies of the E02 worksheets for workers are included in Appendix 9, and copies of the E04 worksheets for members of the general public are included in Appendix 10. These appendices are provided as a convenience to facilitate comparisons of risk among the several different application methods considered in this risk assessment.

The risk characterization for both workers and members of the general public is reasonably simple and unambiguous: based on a generally conservative and protective set of assumptions regarding both the toxicity of dinotefuran and potential exposures to dinotefuran, there is no basis for suggesting that adverse effects in workers are likely. For members of the general public, the only exposure scenarios of concern involve the upper bound estimates for the longer-term consumption of contaminated vegetation after either one or two broadcast foliar applications. Although foliar broadcast application methods are considered in this risk assessment, foliar broadcast is not an application method that is likely to be used in Forest Service programs. While the HQ values for these exposure scenarios only modestly exceed the RfD – i.e., HQ values of 2 and 4 for one and two applications, respectively – these exceedances are of concern because the available data on dinotefuran are insufficient to propose a formal dose-severity relationship for potential human health effects.

Some accidental exposure scenarios result in exposures that approach or modestly exceed the level of concern (i.e., an HQ of 1) but only at the upper bounds of the exposure estimates. For workers, the upper bound exposures for accidental exposure scenarios approach but do reach a level of concern (HQs of 0.1 to 0.8) for accidental exposures (i.e., from spills onto the legs or wearing contaminated gloves) to soil broadcast, bark treatment, soil injection, and tree injection applications.

For members of the general public, none of the accidental exposure scenarios reach or even approach a level of concern for aerial broadcast applications. The upper bound estimates of water consumption by a child after an accidental spill exceed the level of concern for soil broadcast application (HQ 3), bark application (HQ 1.8) and soil injection (HQ 5). The direct spray of a child during bark application also leads to an HQ that exceeds the level of concern—i.e., 1.3 (0.4 to 4). These types of scenarios are intentionally extreme and lead to exceedances in the level of concern for many pesticides. As with the application of any pesticide, severe accidental events involving spills or sprays with dinotefuran should be addressed using prudent measures to limit and mitigate exposures.

3.4.2. Workers

None of the hazard quotients for general exposures to workers exceeds the level of concern. As described in Section 3.2.2.1, the term *general exposure* refers to the range of exposures to be

expected during the normal application of the pesticide. For aerial broadcast applications (Attachments 1a and 1b), the hazard quotients are 0.01 (0.0002-0.07), below the level of concern by factors ranging from about 14 to greater than 5000. These HQ values are based on the maximum application rate and standard assumptions used in Forest Service risk assessments concerning the number of acres that might be treated in a single day (i.e., from 240 to 800 acres for an aerial application). Onken (2009) has suggested that the upper range for the number of acres that might be treated in 1 day of aerial application is closer to 400 acres per day. Thus, the HQ values in this risk assessment may somewhat overestimate plausible exposures in Forest Service programs involving the application of dinotefuran.

Notably, the hazard quotients for general worker exposures are identical for one broadcast foliar application (Attachment 1a) and two broadcast foliar applications (Attachment 1b). This is because HQ values for general exposures are based on the conservative assumption that the worker will apply the pesticide daily during an application season. Thus, the number of applications modeled in the EXCEL workbooks is not dependant on the number of applications modeled in the workbook.

The upper bound of the HQ values associated for general exposures based on other application methods are 0.2 for soil injection and soil broadcast application and 0.02 for bark applications and tree injection. The similarity of the upper bound HQ for soil injection and the upper bound HQ for aerial broadcast soil applications is incidental and reflects offsetting differences in the worker exposure rates and the number of acres treated per day by the different application methods.

The hazard quotients for bark applications and tree injection are not directly comparable to the HQ values for other application methods. For both bark application and tree injection, reliable estimates of the number of acres that a worker might treat in 1 day are not available. Consequently, the HQ values for bark application and tree injection are based on the treatment of 1 acre. Since the upper bound of the HQ is 0.02, a worker would need to treat 50 acres in 1day to reach the level of concern (HQ=1). A worker treating 50 acres in 1 day by either bark application or tree injection is not plausible. Thus, for all of the application methods considered for dinotefuran, there is no basis for asserting that risks to workers during routine applications are likely.

All of the accidental exposure scenarios lead to HQ values below the level of concern. For broadcast foliar applications, the HQ values for accidental exposures are below the level of concern by factors of 50-5000. For other application methods, the upper bounds of the HQ values for accidental exposures approach but do not reach a level of concern (i.e., the highest HQ is 0.8, the upper bound for wearing contaminated gloves for 1 hour during a soil injection).

3.4.3. General Public

The risk characterization for members of the general public suggests that expected peak exposures and most longer-term exposures will be below the level of concern. The only exceptions are the upper bounds of the hazard quotients associated with the consumption of

contaminated vegetation by an adult female over a 90-day period following either one foliar application (HQ=2) or two foliar applications (HQ=4) of dinotefuran at the maximum application rate 0.2 lb a.i./acre (Worksheet D04a Attachments 1a and 1b). As discussed in Section 3.3, the RfD is based on a chronic LOAEL in dogs and an additional uncertainty factor of 10 is used to approximate the NOAEL. HQ values of 2 to 4 would generally be regarded as only marginal excursions above of the RfD. Nonetheless, these HQ values are of concern because the data on dinotefuran are not sufficient to propose a formal dose-severity assessment. As also discussed in Section 3.3.3, modest excursions above the RfD are a concern because of the questionable effects seen in mice at dose of 3 mg/kg bw/day (Weiler 2000a), which is substantially below the dog LOAEL of 20 mg/kg bw/day on which RfD is based.

Some accidental exposure scenarios (i.e., the accidental spill into a small pond or the direct spray of a child) lead to HQ values of up to 5. As detailed in Section 3.2.3.2 (direct spray of a child) and Section 3.2.3.4.1 (accidental spill into a small pond), these exposure scenarios are used consistently in Forest Service risk assessments to provide a very general sense of the hazards that might be posed by a relatively serious accident. These scenarios are extremely conservative and usually result in exposures that exceed the RfD (i.e., an HQ > 1).

3.4.4. Sensitive Subgroups

For exposures to almost any chemical, there is particular concern for children, women who are pregnant or may become pregnant, the elderly, or individuals with any number of different diseases. Nonetheless, there are no reports in the literature suggesting subgroups that may be unusually sensitive to dinotefuran exposure.

Based on the low hazard quotients for workers (Section 3.4.2) and members of the general public (Section 3.4.3), it is not clear that any particular group would be at increased risk from plausible exposures to dinotefuran used in Forest Service programs.

Smokers, individuals on nicotine replacement therapy, or individuals taking smoking suppressant drugs might be considered a group at increased risk to dinotefuran as well as other neonicatinoids. These individuals will have higher levels of acetylcholine receptor agonists than most members of the general population. Nonetheless, the low hazard quotients for dinotefuran, the low binding affinity of dinotefuran to vertebrate nicotinic receptors (Tomizawa and Casida 2005), and the well-documented adverse health effects of smoking suggest that expected exposures to dinotefuran are not likely to pose a substantial or even detectable increase in risk to individuals with higher than normal levels of acetylcholine receptor agonists

3.4.5. Connected Actions

The Council on Environmental Quality (CEQ), which provides the framework for implementing NEPA, defines connected actions (40 CFR 1508.25) as actions which occur in close association with the action of concern; in this case, the use of a pesticide. Actions are considered to be connected if they: (i) Automatically trigger other actions which may require environmental impact statements; (ii) Cannot or will not proceed unless other actions are taken previously or simultaneously, and (iii) Are interdependent parts of a larger action and depend on the larger action for their justification. Within the context of this assessment of dinotefuran, “connected

actions" include actions or the use of other chemicals which are necessary and occur in close association with use of dinotefuran.

As discussed in detail in Sections 3.1.14 (Inerts and Adjuvants) and 3.1.15 (Impurities and Metabolites), dinotefuran formulations contain inert components, and the metabolism of dinotefuran may involve the formation of a large number of different compounds. Given the low HQ values associated with non-accidental exposure scenarios and the generally conservative assumptions on which these HQ values are based, there does not appear to be a plausible basis for suggesting that inerts, impurities, or metabolites will have an impact on the risk characterization for potential human health effects.

Adjuvants are a much more difficult issue to address, and it is beyond the scope of this risk assessment to address adjuvants in detail. This is a general issue in all Forest Service risk assessments but particularly in risk assessments of relatively new pesticides.

3.4.6. Cumulative Effects

Similar to the issues involved in assessing the use of adjuvants, it is beyond the scope of the current risk assessment to identify and consider all agents that might interact with, or cause cumulative effects with dinotefuran. To do so quantitatively would require a complete set of risk assessments on each of the other agents to be considered.

Addressing cumulative effects, within the context of the Food Quality Protection Act, requires the assessment of chemicals with a similar mode of action. In the recent human health risk assessment on dinotefuran, the U.S. EPA states:

> *...EPA has not made a common mechanism of toxicity finding as to dinotefuran and any other substances and dinotefuran does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that dinotefuran has a common mechanism of toxicity with other substances.*
>
> – U.S. EPA/OPP, 2004e, p. 73.

Notwithstanding the above statement, dinotefuran is a neonicotinoid, and it seems reasonable to suggest that the mechanism of action of dinotefuran, at least with respect to neurotoxicity, is likely to be similar to that of other neonicotinoids (Section 3.1.2).

The current Forest Service risk assessment does consider the effect of repeated exposures to dinotefuran for both workers and members of the general public. The chronic RfD is used as an index of acceptable longer-term exposures. Consequently, the risk characterizations presented in this risk assessment for longer-term exposures specifically address and encompass the potential impact of the cumulative effects of repeated exposures to dinotefuran.

4. ECOLOGICAL RISK ASSESSMENT

4.1. HAZARD IDENTIFICATION

4.1.1. Overview

Dinotefuran is an effective insecticide. Based on a limited number of toxicity studies in insect species, dinotefuran is likely to be highly toxic to target and many nontarget insects, including honeybees. Since dinotefuran is a relatively new insecticide, the available field studies are not sufficient to gauge its potential impact on nontarget insects, and the resulting data gap limits confidence in the hazard identification for nontarget insects.

The toxicity of dinotefuran to most other nontarget species or groups of organisms appears to be low, although the data supporting this assertion is highly variable among different groups of organisms. As described in the human health risk assessment, numerous standard toxicity bioassays were conducted in mammals, which are relevant to the ecological risk assessment. The most common effects noted in these studies involve decreased body weight and signs of neurotoxicity. Other effects noted (e.g., damage to the adrenal cortex, changes in uterine morphology, effects on normal estrous cycling, and decreases in organ weights in the testes, spleen and thymus) may be indicative of effects on the immune and/or endocrine systems. Fewer toxicity studies are conducted on birds than on mammals, due to differences in testing requirements for pesticide registration. Nonetheless, dinotefuran appears to be relatively nontoxic or only slightly toxic to birds, based on the general categorization system used by the EPA. Very little information is available on the toxicity of dinotefuran to terrestrial plants, which is not unusual for an insecticide. Based on the one toxicity study involving several different plant species, there is no basis for asserting that dinotefuran is phytotoxic.

Although information on the toxicity of dinotefuran to aquatic species is limited, mysid shrimp appear to be very sensitive to the effects of dinotefuran as well as other neonicotinoids. As for other aquatic species, the available data indicate that dinotefuran is not highly toxic to fish, aquatic invertebrates (other than mysids) or aquatic plants.

No information is available on the toxicity of dinotefuran to reptiles or amphibians. This is not uncommon for a new pesticide, because toxicity tests in reptiles and amphibians are not required for pesticide registration.

4.1.2. Toxicity to Terrestrial Organisms

4.1.2.1. Mammals

Several standard toxicity studies were conducted with experimental animals as part of the registration process. The most common effects noted in these studies involve decreased body weight and signs of neurotoxicity. Other effects noted (e.g., damage to the adrenal cortex, changes in uterine morphology, effects on normal estrous cycling, and decreases in organ weights in the testes, spleen and thymus) may be indicative of effects on the immune system (Section 3.1.7) and/or endocrine system (Section 3.1.8).

There are no field studies that address the impact of dinotefuran applications on mammalian wildlife communities. Standard experimental toxicity studies indicate the acute oral toxicity of dinotefuran is relatively low. A common measure of acute oral toxicity is the LD_{50}, the estimate of the dose that may be lethal to 50% of the exposed animals. As summarized in Section 3.1.4, the acute oral LD_{50} values in rats are equal to or greater than 2000 mg/kg. Based on the available LD_{50} values in mammals, the EPA classifies dinotefuran as *...slightly to practically nontoxic on an acute basis to surrogate wild mammal species* (U.S. EPA/OPP 2004f, p. 20).

For some pesticides, acute oral LD_{50} values in mammalian studies are useful for determining systematic differences in sensitivity among various mammals (e.g., allometric relationships based on body weight). For dinotefuran, however, estimated LD_{50} values are available only for rats and mice, and the differences are not remarkable (Appendix 1).

As also discussed in Section 3.1, there is a standard series of bioassays in mice, rats, rabbits, and dogs for subchronic and chronic toxicity (Section 3.1.5) as well as developmental and reproductive effects (Section 3.1.9). A comparison of these studies, which are summarized in Table 12, is somewhat more difficult to make, relative to the acute toxicity studies, because the endpoints for comparison involve NOAELs and LOAELs. Moreover, the chronic toxicity studies in mice and dogs failed to identify a clear NOAEL for one or both sexes.

Although species comparisons based on the longer-term studies summarized in Table 12 are not straightforward, the LOAEL of 3 mg/kg bw/day in mice, is remarkably lower than the chronic NOAEL of about 100 mg/kg bw/day in rats, the LOAEL of 20 mg/kg bw/day in male dogs, and the NOAEL of 22 mg/kg bw/day in female dogs. As discussed in Section 3.3.3 (Chronic RfD), the EPA reviewed the mouse study in some detail (U.S. EPA/OPP 2004e) and determined that it is inappropriate for deriving a chronic RfD for the human health risk assessment. Furthermore, species sensitivity, ranked from most sensitive to least sensitive, based on the 90-day LOAEL values for decreased body weight in the studies summarized in Table 12 is: dogs (58 mg/kg bw/day) > rats (366 mg/kg bw/day) > mice (10,635 mg/kg bw/day). Thus, the subchronic toxicity data do not support the assumption that mice are more sensitive than other species to the effects of dinotefuran. This matter is discussed further in the dose-response assessment for mammalian wildlife (Section 4.3.2.1).

4.1.2.2. Birds

Studies regarding the toxicity of dinotefuran to birds are limited to a single gavage study in quail (Burn 2000a), acute dietary studies in quail (Burn 2000b) and mallards (Burn 2000c), and reproduction studies in quail (Mitchell et al. 2002b) and mallards (Mitchell et al. 2002a). These studies were submitted to the EPA in support of the registration of dinotefuran and follow standard protocols required by the EPA. The potential impact of dinotefuran on birds has not been addressed in field studies, which is not an unusual circumstance for a new pesticide.

Based on the limit test in quail in which no adverse effects were observed over a 5-day dietary exposure to 4936 ppm dinotefuran (Burri 2000b), U.S. EPA/OPP (2004f) classifies dinotefuran as *practically nontoxic* to birds in acute exposures. As discussed in SERA (2007a, Table 4-1), this is the least hazardous classification used by U.S. EPA/OPP. In addition, based on dietary reproduction studies, U.S. EPA/OPP (2004f) classifies dinotefuran as slightly toxic to mallards based on the NOEC of 2150 ppm (Mitchell et al. 2002a) and slightly toxic quail based on the NOEC of 5270 ppm (Mitchell et al. 2002b).

The results of an acute toxicity study (Burri 2000a) suggest that birds are somewhat less sensitive than mammals to the toxicity of dinotefuran (i.e., adverse effects were not observed in birds exposed to single gavage doses of up to 2000 mg/kg bw). As shown in Appendix 1, 2000 mg/kg bw is the lowest LD_{50} value in mammals—i.e., for female rats in the Glaza (1997a) study.

The available subchronic toxicity studies suggest that birds and mammals are about equally sensitive to dinotefuran, The dietary NOEC values from the avian reproduction studies correspond to about 325 mg/kg bw/day for mallards (Mitchell et al. 2002a) and about 93 mg/kg bw/day for quail (Mitchell et al. 2002b). These values are comparable to the 90-day NOAEL values for mammals which range from 33 to 384 mg/kg bw/day (Table 12).

4.1.2.3. Reptiles

The database maintained by Pauli et al. (2000) on reptiles and amphibians does not include toxicity data for dinotefuran. Furthermore, no other sources of such data were identified in the dinotefuran literature. Generally, in the absence of toxicity data concerning reptile exposure to pesticides, the EPA recommends the use of birds as suitable surrogates (e.g., U.S. EPA/OPP 2004f, p. 66).

4.1.2.4. Terrestrial Invertebrates

Data regarding the toxicity of dinotefuran to terrestrial invertebrates is summarized in Appendix 4, which is divided into two sections: honeybees and other species. The honeybee is the standard test species used by the EPA to assess toxicity to nontarget terrestrial invertebrates, and is, therefore, handled separately from other terrestrial invertebrates.

The mechanism of action of dinotefuran in insects appears to be similar to that of other neonicotinoids: dinotefuran and other neonicotinoids activate nicotinic acetylcholine receptors (nAChR) through binding at or near the sites where nicotine and acetylcholine bind, resulting in dysfunction of the nervous system, immobilization, and death.

Several of the available studies examine the relationship between the chemical structure of neonicotinoids and the insecticidal efficacy of these compounds (e.g., Kagabu et al. 2002; Kiriyama and Nishimura 2002; Kiriyama et al. 2003; Matsuo et al. 1998; Millar and Denholm 2007; Miyagi et al. 2006; Mori et al. 2002; Nakayama and Sukekawa 1998; Nishiwaki et al. 2003). These types of studies, generally referred to as quantitative structure-activity relationships (QSAR), clearly demonstrate that apparently minor changes in the structure of neonicotinoids can lead to substantial changes in insecticidal activity. For example, Kagabu et al. (2002) note 100- to greater than 30,000-fold differences in neonicotinoids based on differences in ring substitutions. This information is relevant to the current risk assessment in terms of assessing the potential hazards of metabolites. As discussed in 3.1.15.1 (Metabolites), dinotefuran appears to undergo relatively minor changes during metabolism which lead to detoxification. Accordingly, dinotefuran is considered the agent of primary concern in the current risk assessment.

Specific information about dinotefuran toxicity from QSAR studies for neonicotinoids and other studies is included in Appendix 4. Although there is a great deal of information concerning the toxicity of neonicotinoids, a comparison of the toxicity of dinotefuran to other neonicotinoids, except for imidacloprid, is beyond the scope of the current risk assessment. As noted in Section 2 (Program Description), the Forest Service is considering dinotefuran as an alternative to imidacloprid for certain types of application to control insects. For that reason, some discussion about the comparative toxicity of dinotefuran and imidacloprid is provided in the following subsections.

4.1.2.4.1. Honeybees

4.1.2.4.1.1. Toxicity Studies

Available honeybee toxicity studies include an acute oral and a contact study using the technical grade active ingredient (TGAI) and two such studies using the 20% SG formulation. These studies are detailed in Appendix 4 and summarized in Table 13.

Based on the acute contact 48-hour LD_{50} of 0.047 µg a.i./bee for technical grade dinotefuran (Harnish 2000a), the EPA classifies dinotefuran as *highly toxic* to bees (U.S. EPA/OPP 2004d, 2006b). The comparable assay on imidacloprid yielded a 48-hour LD_{50} of 0.008 µg a.i./bee (Cole 1990), indicating that compared with dinotefuran, imidacloprid is more toxic to bees by a factor of about 6. As discussed further in Section 4.1.2.3.2, the relative toxicity of dinotefuran and imidacloprid to other insect species is variable.

All of the honeybee toxicity studies, including Harnish (2000a), were submitted to the EPA by the registrant, Mitsui Chemicals, in support of the registration of dinotefuran. Generally, U.S. EPA reviews and reanalyzes the registrant-submitted studies. Thus, as noted in Appendix 4, most of the submitted studies include analyses (i.e., LD_{50} and NOEC determinations) performed both by the study author and U.S. EPA. In many instances, the statistical analyses are reasonably concordant. For example, the LD_{50} and confidence limits of 0.047 (0.039-0.057) µg a.i./bee are based on the reanalysis by EPA; whereas, the original analysis by Harnish (2000a) resulted in an LD_{50} of 0.056 (0.044-0.072) µg/bee.

In some instances, however, the statistical analyses are not concordant, which complicates further assessment of the study. For example, Harnish (2000a) also assayed the oral toxicity of dinotefuran to honeybees and reported an LD_{50} of 0.023 (0.019-0.027) µg/bee. The oral LD_{50} is lower than the contact LD_{50} by a factor of about 2, and this difference may be regarded as significant in that the confidence intervals do not overlap. Based on the U.S. EPA analysis, however, the LD_{50} for the oral bioassay is 0.018 (0.0059-0.066) µg/bee. Based on the central estimate, the oral LD_{50} is lower than the contact LD_{50} by a factor of about 2.6 [0.047 ÷ 0.018]; however, the confidence limits for the two LD_{50} values do overlap.

Notably, some of the reported confidence intervals and NOEC values seem unusual. For example, the EPA reanalysis of the oral toxicity study by Thompson (1998) reports an upper bound for the oral LD_{50} of 7.7 µg/bee; whereas, the investigator reported an upper bound value of 0.12 µg/bee. Based on the dose-response data (Appendix 4), the latter value appears to be a more reasonable estimate.

Two additional honeybee studies were conducted involving contact and oral exposure to the 20% WG formulations, which presumably corresponds to Safari 20 SG (Harnish 2000b; Thompson 1998). As detailed in Appendix 4 and discussed further in Section 4.3.2.3 (Dose-Response Assessment for Terrestrial Invertebrates), the results of the formulation studies are consistent: dinotefuran is more toxic by the oral route than by the contact route of exposure. In the Harnish (2000b) study, oral exposure to dinotefuran, compared with contact exposure, is from 2 to 3 times more toxic to honeybees. In the Thompson (1998) study, the differences in toxicity are somewhat greater—i.e., a factor of about 3.8 [0.024 ÷ 0.0063], based on the EPA analysis and a factor of about 3 [0.023 ÷ 0.0076] based on the analysis reported by Thompson (1998). Thus, the toxicity data on dinotefuran consistently show that oral exposure levels may be somewhat more hazardous to bees than equivalent exposures by direct contact.

Remarkably, there is no consistent difference in the toxicity of the TGAI versus the end-use formulations. A comparison of the TGAI study by Harnish (2000a) to the formulation study by Thompson (1998), indicates that the formulation is somewhat more toxic by both oral exposure (TGAI LD_{50} of 0.018 mg/bw ÷ formulation LD_{50} of 0.0063 mg/bee ≈ 2.8) and direct contact (TGAI LD_{50} of 0.047 mg/bw ÷ formulation LD_{50} of 0.024 mg/bee ≈ 2.0). Basing the comparison to the TGAI on the more recent formulation bioassay by Harnish (2000b), the opposite pattern is apparent with both oral exposure (TGAI LD_{50} of 0.018 mg/bw ÷ formulation LD_{50} of 0.032 mg/bee ≈ 0.6) and direct contact (TGAI LD_{50} of 0.047 mg/bw ÷ formulation LD_{50} of 0.061 mg/bee ≈ 0.8).

NOEC values are provided for each of the honeybee acute toxicity bioassays discussed above. For comparing relative toxicities (i.e., oral versus contact or TGAI versus formulations) LD_{50} estimates are preferable to NOEC values in that LD_{50} estimates are based on the complete dose-response curve and are accompanied by estimates of confidence limits. NOEC values, on the other hand, are based on only a single dose used in a toxicity study. Nonetheless, the Forest Service prefers to use NOEC values rather than LD_{50} estimates for risk characterization. The

selection of NOEC values is discussed further in Section 4.3.2.3 (Dose-Response Assessment for Terrestrial Invertebrates).

In addition to the standard honeybee oral and contact acute toxicity studies, the EPA required a honeybee toxicity study involving exposure to dinotefuran residues on foliage (U.S. EPA/OPP 1985; U.S. EPA/PPTS 1996). In response, the registrant submitted the study by Hummel (2001), which is summarized in Appendix 4. The study involved the foliar application of a 20% SG formulation (presumably identical to Safari 20 SG) of dinotefuran to small plots of alfalfa at an application rate of about 0.15 a.i./acre using. Leaves from the treated plants were harvested at 3, 8, 24, and 48 hours after treatment, and groups of 150 bees (6 replicates of 25 bees/replicate) were exposed to the leaves in small test chambers for up to 100 hours. Mortality in matched control and treated groups did not differ in the assay of 48-hour post-treatment residues. The mortality rate among bees exposed to residues harvested 3, 8, and 24 hours after treatment was significantly higher than the mortality rate in matched control groups. In general, and as would be expected, the toxicity of the residues declined as the residue time (i.e., the time that the residue was sampled) increased. Based on estimates of the LT_{25} (i.e., time to 25% mortality) the 8-hour residue was somewhat more toxic than the 3-hour residue; however, the difference is not statistically significant.

4.1.2.4.1.2. Field Study

Based on the acute toxicity of dinotefuran to bees, U.S EPA has expressed substantial concern for the potential impact of dinotefuran on bees and has indicated that a field study should be conducted:

> *Because of these apparent risks to the bees, EFED needs a honeybee study (guideline 141-5) to properly assess these risks. The honeybee study should evaluate the effects of dinotefuran to the hive over time from a typical dinotefuran use pattern. The use pattern chosen should be one that will result in bee exposure from residues in the nectar or pollen. This study should include but not necessarily be limited to the following: a) an evaluation of two complete life cycles (~130 days) including egg, larvae, adult stages, and mortality of the honeybee colony; b) an evaluation of the exposure and effects to the queen during these life cycles; c) provide dinotefuran residue analysis of the stored nectar, honey, and pollen at the beginning of the study, at periodic intervals during the study and at the end of the study; and d) the study must include replicated data with statistical comparison to controls.*
>
> U.S. EPA/OPP 2004d, p. 2

The California Department of Pesticide Regulation (2009) has recently indicated that field studies should be conducted on dinotefuran as well as other neonicotinoids.

A field study on honeybee exposure to dinotefuran is currently in progress, and an abstract of the interim report was requested from and provided by Landis International (Landis 2009). The field study involved two applications of dinotefuran to cotton plants at rates of 40.5 g a.i./acre (about

0.0893 lb a.i./acre) and 60.65 g a.i./acre (about 0.134 lb a.i./acre). Notably, the application rate is given in the abstract as g a.i./acre and not as g a.i./hectare. The application interval is not specified in the abstract.

The highest application rate tested in this field study, 0.13 lb a.i./acre, is the highest labeled application rate Venom (EPA Reg. No. 59639-135), which is a dinotefuran formulation labeled for use on cotton. This application rate, however, is only about 65% of the maximum labeled rate for broadcast foliar applications of Safari 20 SG (i.e., 0.2 lb a.i./acre).

The endpoints examined in the field study varied with the number of days after treatment (DAT) and included:

- Dead bees (up to DAT 22)
- Foragers returning to the hive (up to DAT 22)
- Foraging bees in cotton plants (up to DAT 22)
- Mass of hive frames (up to DAT 78)
- Number of adults (up to DAT 78)
- Number of capped brood (up to DAT 189)

According to the abstract, adverse effects were not observed for any of the endpoints listed above. In addition, the abstract indicates that dinotefuran concentrations were monitored in pollen, nectar, honey, and wax but that analytical results were not available at the time that the interim report was prepared. The abstract also notes that by Day 189:

> *All hives were healthy, with a fecund queen and normal population of adult bees. No long term adverse effects were observed.*
>
> – Landis (2009)

No other study details are available. This study is discussed further in the risk characterization (Section 4.4.2.3).

4.1.2.4.2. Other Insects

In addition to the standardized honeybee toxicity studies, there are studies regarding the toxicity of dinotefuran to other insects. With the exceptions of the three plate-spray bioassays (Aldershof 2000a,b,c), all of the studies on other insects are published in the open literature. These studies are summarized in Table 14, and additional details are provided in Appendix 4. The published studies are much more diverse in experimental design, compared with the standardized studies submitted to the EPA for pesticide registration, which makes comparing of the published studies to one another as well as to the standardized bioassays on honeybees somewhat difficult.

As noted in the previous section, 48-hour oral LD_{50} values for honeybees range from about 0.0063 µg/bee (Thompson 1998) to 0.032 µg/bee (Harnish 2000b). This variability (i.e., about a factor of 5) is not uncommon in bioassays on the same species conducted at different times. The summaries (DERs) of the honeybee oral toxicity studies do not report the body weights of the

bees, which are generally somewhat variable, with typical body weights of worker bees ranging from about 81 to 151 mg (Winston 1987, p. 54). Taking a typical body weight as 100 mg (0.1 g or 0.0001 kg), the oral LD_{50}s of 0.0063 to 0.032 µg/bee would correspond to doses of about 0.063 to 0.32 mg/kg bw [0.0000063 mg to 0.000032 mg ÷ 0.0001 kg].

There are several insect bioassays involving injection exposure to dinotefuran. In two studies, LD_{50} values were comparable for the American cockroach after injections of dinotefuran: 0.035 mg/kg bw (Mori et al. 2002) and 0.057 mg/kg bw (Tan et al. 2007). Both studies, however, involved pre-treatment with piperonyl butoxide (PB), an inhibitor of mixed-function oxidases. The extent to which piperonyl butoxide enhanced the toxicity of dinotefuran in these studies cannot be determined directly. Kiriyama and Nishimura (2002) also assayed the response of the American cockroach to dinotefuran injections with and without piperonyl butoxide and observed that piperonyl butoxide increased the toxicity of dinotefuran by a factor of about 1.6 (i.e., LD_{50} of 47.3 mg/organism without PB and 28.7 mg/organism with PB). Applying a factor of 1.6 to the LD_{50} values reported by Mori et al. (2002) and Tan et al. (2007) leads to estimated LD_{50} values ranging from about 0.056 to 0.091 mg/kg bw for exposure to dinotefuran alone, very similar to the range of estimated oral LD_{50} values for the honeybee—i.e., from 0.063 to 0.32 mg/kg bw.

Notably, the cockroach toxicity study conducted by Kiriyama and Nishimura (2002) is not consistent with the studies conducted by Mori et al. (2002) and Tan et al. (2007). As indicated in Appendix 4, Kiriyama and Nishimura (2002, Table 2, p. 671) report the toxicity of dinotefuran with no synergists as the log[1/MLD] with a value of 8.36 mol. The designation of *mol* is not defined in the publication but is assumed by conventional use to refer to *millimoles*. Rearranging to solve for the MLD, the toxicity value would be $e^{-8.36}$ millimoles or 0.000234 millimoles. Using a molecular weight of 202.2 g/mole or mg/millimole, this value would correspond to a dose of 0.047 milligrams/animal. These investigators do not report the body weight of the cockroaches. Using a body weight of about 380 mg or 0.380 g for the American cockroach (Mullins and Cochran 1974, Table 1, p. 561), the 0.047 mg dose would correspond to a dose of about 0.124 mg/g [0.047 mg dose ÷ 0.38 g bw ≈ 0.123684 mg/g] or about 124 mg/kg bw, which is much higher than the doses of 0.035-0.057 mg/kg calculated from the studies by Mori et al. (2002) and Tan et al. (2007).

The injection toxicity study in houseflies (Kiriyama et al. 2003) reports the toxicity value for dinotefuran with no synergists as a $Log(1/EC_{50}$ mol) of 4.29. Taking the same approach as described above, the toxicity value corresponds to a dose of about 0.61µg/fly. The study does not specify the body weights of the treated flies (adult female). Taking a body weight of about 40 mg for an adult female fly (*Musca domestica*) from the Zanuncio et al. (2005) study, the toxicity value of 0.61 µg/fly corresponds to a dose of about 15 mg/kg bw [0.61 µg/40 mg ≈ 0.015 µg/mg = 15 mg/kg]. This again is substantially higher than the injection LD_{50} values for cockroaches cited in the Mori et al. (2002) and Tan et al. (2007) studies.

The open literature for dinotefuran includes only one oral toxicity study for insects. Wang et al. (2005) report an LC_{50} of about 2.2 ppm for the Asian long-horned beetle, one of the target

species for dinotefuran, after dietary exposure to treated maple leaves. Since the study does not report the food consumption of the beetles, an LD_{50} value expressed in units of mg/kg bw cannot be estimated directly. As discussed in Section 4.2.2.3, herbivorous insects generally consume vegetation at a rate of about 0.5 to 2 of their body weight per day. According to these approximations, the LC_{50} of 2.2 ppm corresponds to LD_{50} doses of about 1.1-4.4 mg/kg bw. This approach, however, may overestimate the acute LD_{50}. As the beetles consumed the treated vegetation, it is plausible that the organisms ingested sufficient amounts of dinotefuran to cause intoxication, thereby decreasing the normal rate of food consumption.

Several glass plate bioassays are available regarding dinotefuran exposure in nontarget species—i.e., predaceous mites (Aldershof 2000a), parasitoid wasps (Aldershof 2000b), and predacious bugs (Aldershof 2000b). In each of these studies, exposure levels are expressed as functional application rates with resulting LC_{50} values of 0.000012 lb a.i./acre for wasps, 0.00007 lb a.i./acre for bugs, and 0.027 lb a.i./acre for mites. The lowest adverse effect level reported in these studies is 0.0000012 lb a.i./acre (i.e., decreased fecundity in bugs). These studies support a concern for contact toxicity of dinotefuran demonstrated in the honeybee contact toxicity studies (Hummel 2001). Clearly, the nature of exposure in the glass plate bioassays is not directly comparable to anticipated field exposures.

As summarized in Table 15, several of the published insect studies involve the comparative toxicity of dinotefuran and imidacloprid. Table 15 provides the toxicity value for dinotefuran followed by the matched toxicity value for imidacloprid. The fourth column of the table provides the ratio of the toxicity values for dinotefuran to imidacloprid based on the toxicity values in the previous two columns. Thus, under the assumption that the toxicities are identical on a mass basis, the expected ratio would be 1. A molar ratio of less than 1 suggests that dinotefuran is more toxic than imidacloprid, and a ratio of greater than 1 suggests that imidacloprid is more toxic than dinotefuran.

The fifth column of Table 15 provides the molar ratio (i.e., the ratios corrected for differences in molecular weight). For example, the study by Kiriyama and Nishimura (2002) indicates that dinotefuran and imidacloprid are about equitoxic on a mass basis (i.e., the ratios of the toxicity values are approximately 1). The molecular weight of imidacloprid, however, is greater than that of dinotefuran by a factor of about 1.26. In other words, at equal mass doses of the two insecticides, the number of dinotefuran molecules will be greater than the number of imidacloprid molecules by about 25%. Thus, on a molar basis, dinotefuran is less toxic than imidacloprid and the molar ratio in Table 15 is greater than 1.

The relative toxicities are expressed on both a mass and molar basis, and because the Forest Service assesses application rates on a mass basis, the mass ratios may be more relevant and intuitive. Nevertheless, QSAR studies assess relative toxicity on a molar basis, and the molar ratios provided in Table 15 reflect the discussions of relative potency in the publications cited in Table 15.

As with the comparison of honeybee toxicity values, most studies suggest that dinotefuran is less toxic than imidacloprid or that the relative toxicities are about the same. As noted by Wang et al. (2005), the difference in toxicity is greater at the LD_{90}, in which dinotefuran is less toxic than imidacloprid by a factor of about 3 on a mass basis and 4 on a molar basis.

Two other studies (Prabhaker et al. 2005; Tan et al. 2007) indicate an opposite pattern in which dinotefuran is more toxic than imidacloprid—i.e., the ratios in Table 15 are less than 1. Tan et al. (2007) report a modest difference in toxicity, about a mass factor of 3.2 based on LD_{50} values. The comparative data for the whitefly reported by Prabhaker et al. (2005), however, exhibit a much greater difference. Based on LC_{50} values, dinotefuran is more toxic than imidacloprid by factors of about 135 at 24 hours and greater than 3000 at 48 hours. The Prabhaker et al. (2005) study is not comparable to the other studies in that the toxicity values are based on the concentrations of the two chemicals used to treat the leaves. The actual concentrations in the leaves were not determined. Thus, it is difficult to tell whether the differences reported by Prabhaker et al. (2005) are due to inherent differences in toxicity, a higher rate of dinotefuran uptake into the leaves, or a combination of these two factors.

4.1.2.4.3. Other Terrestrial Invertebrates

The available information on dinotefuran does not include toxicity studies on earthworms or other soil invertebrates.

4.1.2.5. Terrestrial Plants (Macrophytes)

Since dinotefuran is an insecticide, it is not surprising that there is limited information about its toxicity to terrestrial plants. The limit tests submitted to the EPA were conducted at the maximum application rate of 0.54 lb a.i./acre for seedling emergence (Porch et al. 2001a) and vegetative vigor (Porch et al. 2001b). No adverse effects were observed in either of the tests, each of which involved the exposure of six species of monocots and four species of dicots.

4.1.2.6. Terrestrial Microorganisms

The data on dinotefuran do not include toxicity studies on terrestrial microorganisms. In general these types of study are not required for pesticide registration.

4.1.3. Aquatic Organisms

4.1.3.1. Fish

Very few dinotefuran toxicity studies were conducted on fish. Moreover, the studies that were conducted are all very simple, each involving exposure to only one test concentration. These studies, summarized in Appendix 5, include three acute assays in freshwater fish (Peither 1999; Peither 2000a,b), an acute assay in a saltwater fish (Blankinship 2001b), and an egg-and-fry study in trout (Peither 2001).

The acute toxicity studies in fresh water fish were reviewed by the EPA and classified as *Core*, indicating that the tests were conducted and reported according to required guidelines. The acute

study in saltwater fish is classified as *Supplemental*, because the fish used in the study weighed less than the weights required by EPA guidelines. This deficiency is not critical.

The egg-and-fry study, however, is classified by the EPA as *Invalid* with respect to analytical chemistry: the EPA guidelines require accurate measurement of the chemical in water during the 94-day bioassay as well as reasonably consistent measurements of test concentration during the course of the bioassay. In the egg and fry study (Peither 2001), the nominal test concentration was 10 mg a.i./L. The measured concentrations ranged from 12.9 mg/L on Day 0 to 6.36 mg a.i./L on Day 76, and the generally low recoveries of the test chemical could not be explained. The reason for the fluctuations in the test concentrations is not apparent. The DER for this study specifies the use of a continuous-flow diluter which was monitored twice daily. The specifics of the preparation and storage of the test solution, however, are described in detail.

In addition to concerns with analytical chemistry, the EPA considered the egg-and-fry assay to be *invalid* because it tested only one nominal concentration, which apparently had no adverse effect on mortality or development. Studies classified as *Invalid* are not considered in U.S. EPA risk assessments. U.S. EPA/OPP (2004f) indicates that the bioassay should be repeated; however, the registrant has no plans to repeat this study unless an aquatic registration is requested from U.S. EPA (Horton 2009).

All of the acute toxicity studies for fish were conducted at a single test concentration of about 100 mg/L, with specific concentrations ranging from 99.1 to 109 mg/L. The results of the studies consistently show that exposure to dinotefuran did not cause mortality or other signs of toxicity in any of the test species. Similarly, dinotefuran had no adverse effects on any of the endpoints observed in the egg and fry study: fertilization success, hatching success, time to hatch, time to swim up, post-hatch survival, terminal length, wet weights, or dry weights.

As discussed in Section 3.2.3.4.6 (Concentrations in Water Used for Risk Assessment) and summarized in Table 9, the concentrations of 10-100 mg/L are substantially above the upper bounds of the expected peak concentrations of dinotefuran in water (i.e., 0.16-0.31 mg/L) and even further above the upper bounds of expected longer-term concentrations (i.e., 0.049-0.096 mg/L).

While the available studies on dinotefuran are limited, they consistently fail to provide a basis for asserting that dinotefuran is likely to pose a hazard to fish, even at concentrations that are far in excess of expected environmental concentrations.

4.1.3.2. Amphibians

As indicated in Section 4.1.2.3, the database maintained by Pauli et al. (2000) on reptiles and amphibians does not include toxicity data for dinotefuran. Furthermore, no other sources of such data were identified in the dinotefuran literature. Generally, in the absence of toxicity data concerning amphibian exposure to pesticides, the EPA assumes that fish may be useful surrogates for aquatic life-stages of amphibians (e.g., U.S. EPA/OPP 2004f, p. 66).

4.1.3.3. Aquatic Invertebrates

Like the toxicity data on fish, there are relatively few studies on the toxicity of dinotefuran to aquatic invertebrates. The available studies summarized in Appendix 6 include, freshwater acute bioassays of dinotefuran in *Daphnia magna* (Peither 2000a) and the DN metabolite of dinotefuran in *Daphnia magna* (Kelly et al. 2002), saltwater acute bioassays in mysid shrimp (Blankinship et al. 2001a) and oysters (Drottar et al. 2001), and a chronic bioassay in *Daphnia magna* (Peither 2000d). The EPA classifies each of these studies *Core*, meaning they meet all EPA requirements.

The acute toxicity study on dinotefuran in daphnids is similar to the acute toxicity studies in fish in that the daphnid study was conducted at a single concentration, 968.3 mg/L, at which adverse effects were not observed. The study with the DN metabolite of dinotefuran was conducted at two concentrations, 10 and 110.6 mg/L. A low incidence of immobility (10%) was observed at the higher concentration, and no effects were seen at the lower concentration.

The saltwater toxicity studies in mysids and oysters were all conducted at several concentrations. In the oyster study, the highest concentration tested, 141 mg/L, is a NOEC, indicating that adverse effects were not observed at any test concentration and that oysters are no more sensitive than daphnids to dinotefuran exposure.

The study in mysid shrimp, however, reports substantial and concentration-related mortality, and the LC_{50} with 95% confidence intervals is 0.79 (0.49-1.0) mg/L. Based on this study, U.S. EPA/OPP (2004f, p. 20) classifies dinotefuran as highly toxic to mysids. Because mysid shrimp are much more sensitive than daphnids to dinotefuran exposure, U.S. EPA/OPP (2004f, p. 18) also recommends that a life cycle toxicity study be conducted in mysid shrimp. The registrant, however, has no plans to initiate a life cycle study in mysid shrimp, unless an aquatic registration is requested from U.S. EPA (Horton 2009).

The difference in *daphnia*- and mysid-sensitivity to dinotefuran is striking but consistent with observed differences in sensitivity to other neonicotinoids. While *Daphnia magna* is often the most highly sensitive species of aquatic invertebrates to pesticide exposure, daphnids appear to be relatively tolerant to neonicotinoids, as noted in the Forest Service risk assessment on imidacloprid (SERA 2005a) and in the bioassays conducted by Beketov and Liess (2008) on thiacloprid, another neonicotinoid. As noted by Beketov and Liess (2008), the basis for the tolerance of *Daphnia magna* relative to other invertebrates is not clear.

The only available chronic toxicity study is the reproduction study in *Daphnia magna* by Peither (2000d). No effects were noted in this study at concentrations ranging from 6.25 to 95.3 mg/L. As noted above, mysid shrimp appear to be much more sensitive than daphnids to dinotefuran exposure. No longer-term toxicity studies are available on mysid shrimp exposed to dinotefuran. This limitation is discussed further in the dose-response assessment for aquatic invertebrates (Section 4.3.3.3).

4.1.3.4. Aquatic Plants

A freshwater species of aquatic algae (*Pseudokirchneriella subcapitata*) was used to assay the relative toxicities of dinotefuran (Seyfried 2000) and two metabolites of dinotefuran, MNG (Kelly and Ferguson 2002a) and DN (Kelly and Ferguson 2002b). Each of these studies was conducted at several concentrations. For dinotefuran, cell density was the most sensitive endpoint, with an NOEC of 25 mg/L and a corresponding LOEC of 50 mg/L. Neither MNG nor DN caused any signs of toxicity at the highest concentrations tested (i.e., about 100 mg/L).

To further determine the toxicity of dinotefuran to aquatic plants, Batcher (2002) conducted an algal study with the aquatic macrophytes, *Lemna gibba*, exposed to several concentrations of dinotefuran ranging from 11 to 110 mg/L. No effects were noted at any concentration over the 7-day exposure period.

4.2. EXPOSURE ASSESSMENT

4.2.1. Overview

As in the human health risk assessment, all exposure scenarios for nontarget species are detailed in the EXCEL workbooks that accompany this risk assessment:

Attachment 1a: Broadcast foliar, single application
Attachment 1b: Broadcast foliar, two applications
Attachment 2: Broadcast soil
Attachment 3: Bark Applications
Attachment 4: Soil Injection
Attachment 5: Tree Injection

The workbooks for broadcast foliar applications are based on the maximum broadcast foliar application rate of 0.2 lb a.i./acre. Attachment 1b is based on two broadcast foliar applications each at 0.2 lb a.i./acre with the minimum application interval of 14 days. All other workbooks are based on the maximum labeled application rate of 0.54 lb a.i./acre. The consequences of using lower application rates are discussed in the risk characterization.

The exposure scenarios that have become more or less standard in Forest Service risk assessments are not necessarily relevant to the specific application methods considered in the current risk assessment of dinotefuran, as discussed in the exposure assessment for human health effects (Section 3.2). Summaries of the exposure assessments considered in the current risk assessment are provided in Table 16 for mammals and birds and in Table 17 for aquatic organisms and terrestrial invertebrates. These tables are structurally similarly to Table 4, which summarizes the exposure scenarios considered in the human health risk assessment.

All of the exposure scenarios are relevant for assessing the effects of broadcast foliar applications with respect to birds and mammals. A similar set of exposure scenarios is used for broadcast granular applications, except that exposures associated with direct spray and spray drift are omitted. For other application methods, non-accidental exposure assessments omit scenarios for the consumption of contaminated vegetation by mammals and birds. Although these pathways of exposure cannot be ruled out, the treatment of trees by soil or tree injection as well as bark application are expected to cause very low, yet highly variable, levels of exposure for birds and mammals. Accordingly, the exposure scenario for dinotefuran contaminated vegetation is not considered quantitatively for soil injection, tree injection, or bark treatment.

The exposure scenarios for terrestrial invertebrates are considered quantitatively, given that the methods used to apply dinotefuran could result in foliar residues on treated trees that are hazardous to herbivorous insects. Relatively standard methods are used to estimate dinotefuran doses to herbivorous insects based on the concentration in treated vegetation as well as estimated rates of food consumption.

Exposure scenarios for honeybees are also considered for all application methods. Typically, in Forest Service risk assessments insecticides, risks to honeybees are assessed based on a direct spray scenario. Pathways for direct spray and spray drift are considered for broadcast applications of dinotefuran. Data that might be used to support an exposure assessment for other pathways, like nectar foraging are not available. Usually, the absence of such data precludes the development of an exposure assessment and the further development of a risk characterization. In the case of dinotefuran, however, the Forest Service expressed particular concern for potential risks to foraging honeybees. Moreover, the same concern is expressed in an ecological risk assessment of dinotefuran conducted by U.S. EPA.

To address concerns for the potential impact of dinotefuran to foraging honeybees, the current risk assessment uses data on other insecticides to estimate exposures to foraging honeybees. **The exposure estimates for honeybees are tenuous, and limitations on the use of the exposure assessments for foraging honeybees are discussed further in the risk characterization.**

4.2.2. Mammals and Birds

Mammals and birds might be exposed to any applied pesticide from direct spray, the ingestion of contaminated media (e.g., vegetation, prey species, or water), grooming activities, or indirect contact with contaminated vegetation. In the exposure assessments for the ecological risk assessment, estimates of oral exposure to mammals and birds are expressed in the same units as the available toxicity data. As in the human health risk assessment, these units are usually expressed as mg of agent per kg of body weight and abbreviated as mg/kg for terrestrial animals.

For dermal exposure of mammals and birds to an applied pesticide, the units of exposure 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.

Because of the relationship of body weight to surface area as well as to the consumption of food and water, small animals will generally receive a higher dose, in terms of mg/kg body weight, relative to large animals for a given type of exposure. Consequently, most general exposure scenarios for mammals and birds are based on a small mammal or a small bird. For small mammals, exposure assessments are conducted for direct spray (F01 and F02a), consumption of contaminated fruit (F03a, F04a, F04b), and contaminated water (F05, F06, F07). Generally, herbicide concentrations on grasses will be higher than concentrations on fruits and other types of vegetation (Fletcher et al. 1994). Although small mammals do not typically consume large amounts of grass over prolonged periods of time, small mammals, like the meadow vole (*Microtus pennsylvanicus*), may consume grasses as a substantial proportion of their diet at certain times of the year. Consequently, the acute consumption of contaminated grass by a small mammal is considered in this risk assessment (F03b). Large mammals may consume grasses over a long period of time, and these scenarios are included both for acute exposures (Worksheet

F10) and longer-term exposures (Worksheets F11a and F11b). Other exposure scenarios for mammals involve the consumption of contaminated insects by a small mammal (Worksheet F14a) and 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 (F16b), and the consumption of contaminated grasses by a large bird (F12, F13a, and F13b).

4.2.2.1. Direct Spray

The unintentional direct spray of wildlife during broadcast applications of a pesticide is a plausible exposure scenario 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 of pesticide absorbed depends on the application rate, the surface area of the organism, and the rate of absorption.

For this risk assessment, two direct spray or broadcast exposure assessments are conducted (Worksheets F01, F02). The first spray scenario (detailed in Worksheet F01) a 20 g mammal that is sprayed directly over one half of the body surface as the chemical is being applied. This exposure assessment assumes first-order dermal absorption. The second exposure assessment (detailed in Worksheet F02) assumes complete absorption over day 1 of exposure. This assessment is included in an effort to encompass the increased exposure due to grooming.

There are no exposure assessments for the direct spray of large mammals, principally because allometric relationships dictate that the amount of a compound to which large mammals will be exposed, based on body weight, as a result of direct spray is less than amount to which smaller mammals will be exposed, based on a body weight.

4.2.2.2. Dermal Contact with Contaminated Vegetation

As discussed in the human health risk assessment (Section 3.2.3.3), the only approach for estimating the potential significance of dermal contact with contaminated vegetation is to assume a relationship between the application rate and dislodgeable foliar residue. Unlike the human health risk assessment, in which transfer rates for humans are available, there are no transfer rates available for wildlife species. Wildlife species are more likely than humans to spend long periods of time in contact with contaminated vegetation. It is reasonable to assume that for prolonged exposures, equilibrium may be reached between pesticide levels on the skin, rates of dermal absorption, and pesticide levels on contaminated vegetation. Since, data regarding the kinetics of this process are not available, a quantitative assessment for this exposure scenario cannot be made in the ecological risk assessment.

4.2.2.3. Ingestion of Contaminated Vegetation or Prey

Dinotefuran may be used in broadcast applications; therefore, the consumption of contaminated vegetation is an obvious concern. Separate exposure assessments are developed for acute and chronic exposure scenarios involving a small mammal (Worksheets F03a, F03b, F04a and F04b),

a large mammal (Worksheets F10, F11a, and F11b), and large birds (Worksheets F12, F13a, and F13b). Similarly, the consumption of contaminated insects is modeled for a small bird (Worksheet 14a) and a small mammal (Worksheet 14b). As detailed in the exposure assessment for human health (Section 3.2.3.3), the empirical relationships based on those recommended by Fletcher et al. (1994) are used to estimate residues in contaminated insects (Worksheets F14a and F14b). For all exposure scenarios involving contaminated vegetation or insects, residues rates for broadcast foliar applications are higher than those for broadcast granular applications, as indicated in Table 10.

A similar set of scenarios is provided for the consumption of small mammals by either a predatory mammal (Worksheet 16a) or a predatory bird (Worksheet 16a). In addition to the consumption of contaminated vegetation, insects, and other terrestrial prey, exposure pathways for dinotefuran may be associated with ambient water and fish. Thus, a separate scenario is developed for the consumption of contaminated fish by a predatory bird involving acute (Worksheet F08) and chronic (Worksheet F09) exposure, as detailed in the cited worksheets.

4.2.2.4. Ingestion of Contaminated Water

The methods for estimating dinotefuran concentrations in water are identical to those used in the human health risk assessment (Section 3.2.3.4). The only major differences in the estimates of exposure involve the weight of the animal and the amount of water consumption. These differences are documented in the worksheets for the consumption of contaminated water (F05, F06, and F07).

Estimates of water consumption by nontarget mammals and birds are not available, as they are for humans. Thus, for the acute exposure scenario, the only factors affecting the estimation of the ingested dose are the field dilution rates (i.e., the chemical concentration in the spilled solution) and the amount of solution spilled. In the exposure scenario involving ponds or streams contaminated by runoff or percolation, the factors affecting the variability of exposure levels are the water contamination rates (Section 3.2.3.4.2) and the application rate.

4.2.3. Terrestrial Invertebrates

4.2.3.1. Direct Spray and Drift

For honeybees, estimated levels of exposure associated with broadcast applications of dinotefuran are detailed in Worksheet G02b. In all Forest Service risk assessments, honeybee exposure levels associated with broadcast applications are modeled as a simple physical process based on the application rate and surface area of the bee. The surface area of the honeybee (1.42 cm^2) is based on the algorithms suggested by Humphrey and Dykes (2008) for a bee with a body length of 1.44 cm. The broadcast application rate is taken as 0.2 lb a.i./acre, the maximum foliar broadcast application rate for dinotefuran. Because this scenario involves acute exposure which can only occur immediately after application, the level of exposure will be the same, regardless of single or multiple applications. Accordingly, only a single application is considered in Worksheet G02b.

The amount of dinotefuran deposited on a bee during or shortly after application depends on how close the bee is to the application site as well as foliar interception of the spray prior to deposition on the bee. Since aerial broadcast foliar applications are considered in this risk assessment (Section 2.3.2), the estimated proportions of the nominal application rate at various distances downwind given in G02b are based on Tier 1 aerial estimates from AgDrift Version 2.0.05 (Teske et al. 2002) for distances of 0 (direct spray) to 900 feet downwind of the treated site.

In addition to drift, foliar interception of applied dinotefuran is a concern in the exposure assessment for honeybees. The impact of foliar interception would vary depending on the nature of the canopy above the bee. For example, in studies investigating the deposition rate of diflubenzuron in various forest canopies, Wimmer et al. (1992) noted that deposition in the lower canopy, relative to the upper canopy, generally ranged from about 10% (90% foliar interception in the upper canopy) to 90% (10% foliar inception by the upper canopy). In Worksheet G02b, foliar interception rates of 0% (no interception), 50%, and 90% are used.

During broadcast applications of dinotefuran, terrestrial invertebrates other than bees will be subject to direct spray. As discussed in further detail in Section 4.3.2.3 (dose-response assessment for terrestrial invertebrates), the available toxicity data on terrestrial invertebrates do not support the derivation of separate toxicity values for different groups of terrestrial insects. Thus, the honeybee is used as a surrogate for other insect species, precluding the necessity of developing additional exposure scenarios for other insects.

The direct spray and spray drift scenarios are used only for broadcast foliar applications (Attachments 1a, 1b). As discussed in Section 3.2.3.6, Michael (1992) suggests that the amount of pesticide residues on treated vegetation after applications of granular formulations is about a factor of 0.04 less than the residues associated with broadcast liquid applications. Speculatively, the relationship will hold for deposition on insects. On the other hand, were the surface of a honeybee to efficiently intercept the aerially applied particulates from the granular formulation, the application of a 0.04 factor would underestimate risk. In the absence of any more applicable data, the hazards to insects from direct deposition of granular applications are not quantified; instead, they are discussed qualitatively in the risk characterization (Section 4.4).

4.2.3.2. Ingestion of Contaminated Vegetation or Prey

Various methods are used to estimate exposure levels to herbivorous insects, depending on the application method used. For foliar or granular broadcast applications, the methods are similar to those used in the human health risk assessment. For soil and tree injections as well as bark application, the exposure estimates are based on relatively sparse data with little supporting detail from field applications of imidacloprid. These estimates may be much less reliable than those made for broadcast applications; the uncertainty associated with these estimates is discussed further in the risk characterization.

4.2.3.2.1. Broadcast Foliar and Granular Applications

Like terrestrial mammals and birds, terrestrial invertebrates may be exposed to dinotefuran through the consumption of contaminated vegetation or contaminated prey. For broadcast foliar applications, estimates of residues on contaminated vegetation or prey are based on estimated residue rates (i.e., mg/kg residues per lb a.i. applied) from Fletcher et al. (1994), which is a reanalysis of residue rates derived by Hoerger and Kenaga (1972). These residue rates are the same ones used in Forest Service risk assessments and the ecological risk assessments conducted by the U.S. EPA/EFED (2001).

The original analysis by Hoerger and Kenaga (1972) as well as the reanalysis by Fletcher et al. (1994) give only central and upper bound estimates of residues rates. For the current analysis, lower limits on residue rates are calculated under the assumption that variability in the residue rates are distributed proportionately (i.e., the ratio of the central estimate to the upper limit will be the same as the ratio of the lower limit to the central estimate). The specific residue rates used to estimate plausible concentrations of dinotefuran in food items are summarized in Table 10. As discussed in Section 3.2.3.6, the residues rates provided in Fletcher et al. (1997) are used only for broadcast foliar applications.

For broadcast soil granular applications, the residue rates are adjusted downward by a factor of 25, based on the study by from Michael (1992). As discussed in Section 3.2.3.6, Michael (1992) noted that residues on vegetation after granular applications were only a factor of about 0.04 of residues after an equivalent application of a liquid formulation. This pattern is also noted but not addressed quantitatively by Hoerger and Kenaga (1972). There is some concern about the use of this factor for herbivorous insects, because broadcast applications of granular formulations of dinotefuran are essentially soil treatments with the expectation that dinotefuran will be taken up by the target plant, and concentrations in the plant tissue will increase. Thus, the use of the 0.04 adjustment factor could underestimate risk, as discussed further in the risk characterization (Section 4.4.2.3.2).

For broadcast foliar applications, the residue rates in Table 10 are used to estimate the concentration of dinotefuran in four groups of food items based on the maximum single application rate of 0.2 lb a.i./acre (Attachment 1a). Because a second broadcast application of dinotefuran may be made within 14-21 days of the first application, two applications are modeled with an application interval of 14 days—i.e., the worst case scenario (Attachment 1b). As detailed in Section 3.2.3.7, foliar half-lives are taken from the studies by Hattermann (2002a,b) with a central estimate of 6 days and a lower 10% confidence bound of 0.36 and an upper 90% confidence limit of 12 days. For broadcast granular applications, only a single application at the maximum application rate of 0.54 lb a.i./acre is used (Attachment 2).

An estimate of food consumption is necessary to estimate a dose level for a foraging herbivorous insect. Insect food consumption varies greatly, depending on the caloric requirements in a given life stage or activity of the insect and the caloric value of the food to be consumed. The derivation of consumption values for specific species, life stages, activities, and food items is

beyond the scope of the current analysis. Nevertheless, general food consumption values, based on estimated food consumption per unit body weight, are available.

Reichle et al. (1973) studied the food consumption patterns of insect herbivores in a forest canopy and estimated that insect herbivores may consume vegetation at a rate of about 0.6 of their body weight per day (Reichle et al. 1973, pp. 1082 to 1083). Higher values (i.e., 1.28-2.22 in terms of fresh weight) are provided by Waldbauer (1968) for the consumption of various types of vegetation by the tobacco hornworm (Waldbauer 1968, Table II, p. 247). The current risk assessment uses food consumption factors of 1.3 (0.6 to 2.2) kg food /kg bw. The lower bound of 0.6 is taken from Reichle et al. (1973), and the central estimate and upper bound are taken from the range of values provided by Waldbauer (1968).

Notably, the estimated doses in Worksheets G07a-d are likely to overestimate the actual amount of dinotefuran that an insect might ingest, based on the toxicity of dinotefuran. As discussed further in Section 4.4.2.3, the dose estimates in these worksheets lead to extremely high hazard quotients (i.e., the ratio of the estimated dose to the acute NOEC). The acute NOEC is based on the dose of 0.0013 µg/bee cited in Thompson (1998); however, the LD_{50} is only 0.0063 µg/bee, which is about 5 times greater than the acute NOEC. Thus, as the insect consumed the contaminated vegetation, it would likely become intoxicated (sicken), resulting in a decreased rate of food consumption. A decrease in food consumption during a dietary bioassay is an extremely common occurrence in mammalian toxicity studies, and this pattern of exposure is noted in a study involving dietary exposure of insects to imidacloprid (Cappaert et al. 2007). The overestimation of dose, however, has a minimal impact on the risk characterization, as discussed further in Section 4.4.2.3.

Details concerning estimated exposure levels for the consumption of contaminated vegetation by herbivorous insects are provided in Worksheets G07a, G07b, G07c, and G07d. These levels pertain to the four food items included in the standard residue rates provided by Fletcher et al. (1994). The use of specific rates, which differ for foliar and soil broadcast applications, is documented in Table 10. The exposure estimates are included only in the EXCEL workbooks for foliar broadcast applications (Attachments 1a and 1b) and granular broadcast applications (Attachment 2).

4.2.3.2.2. Tree Injection

Data are not available regarding the concentration of dinotefuran in leaves, nectar, or pollen after tree injection applications of dinotefuran. Usually, the absence of such data for a specific application method precludes the development of an exposure assessment and further development of a risk characterization. In other words, if exposure cannot be determined, the assessment of risk cannot be determined quantitatively.

With substantial reservation, the current risk assessment estimates exposure levels to dinotefuran applied by tree injection, based on analogy to imidacloprid. This approach is taken for two reasons: First, although broadcast foliar applications are relatively simple operations, the Forest Service generally does not use this type of application method because of the numerous

nontarget species that would be subject to exposure. Thus, the Forest Service is considering the use of tree injection to limit exposures to nontarget species. In order, then, to make this risk assessment more relevant to the application methods likely to be used in Forest Service programs involving dinotefuran, some attempt to assess exposures associated with tree injection seems justified. Second, the use of data on imidacloprid may be justified, based on the physical and chemical properties of dinotefuran and imidacloprid. As documented in SERA (2005a), imidacloprid has a pK_a of 11.2, a K_{ow} of 3.7 ($\log_{10}$ Kow = 0.56), and a water solubility of 610 mg/L. As summarized in Table 1 of this current Forest Service risk assessment, dinotefuran has a pK_a of 12.6, a K_{ow} of 0.28 ($\log_{10}$ Kow = -0.55), and a water solubility of 39,830 mg/L.

A classification scheme developed by Bromilow et al. (1990) relating the pK_a and K_{ow} of pesticides to translocation in phloem and xylem is illustrated in Figure 2. This figure includes an illustration the pK_a and K_{ow} values for dinotefuran, imidacloprid, and dimethoate. The dimethoate data—$\log_{10}$ Kow = 0.704, pKa = 2.0—are taken from Tomlin (2004). This compound is discussed further in the exposure assessment for honeybees foraging for nectar (Section 4.2.3.3).

Based on the classification system developed by Bromilow et al. (1990), it is plausible that the translocation of dinotefuran in phloem and xylem will be similar to, although perhaps more rapid than, the translocation of imidacloprid. This supposition is consistent with suggestions made during the preparation of this risk assessment on the properties of dinotefuran relative to imidacloprid (e.g., Cowles 2009a). In other words, peak residue rates for dinotefuran in vegetation after tree injection may be higher than those for imidacloprid, and the peak concentrations could occur more quickly and decrease more rapidly. Only marginal experimental data are available at this time to assess these suppositions quantitatively. The mean foliar half life for dinotefuran is about 6 days, and the comparable value for imidacloprid is about 10 days (SERA 2005a).

To characterize foliar residues of imidacloprid associated with tree injection applications, Lewis and Molongoski (2006) applied 0.16 g a.i. per centimeter DBH (diameter at breast height) or about 0.4 g per inch DBH imidacloprid by trunk injection to London plane trees averaging 18.6 inches DBH and Norway maple trees averaging 15.4 inches DBH. Figure 3 illustrates the foliar residues monitored in leaves, which generally range from 30 to 250 ppm (ignoring the single 450 ppm outlier) with a typical residue of about 100 ppm. The residues in maple appear to be somewhat higher than those in London plane, however, species-specific differences in residue rates are not considered quantitatively in exposure assessment, and the data from Lewis and Molongoski (2006) are used to develop an exposure assessment that is likely to reflect worst-case exposures (i.e., the MEI approach as discussed in Section 3.2.3.1.1). Nonetheless, the variability of species-specific residue rates and formulation differences can be substantial (Harrell 2006; Tatter et al. 1998), as discussed further in the risk characterization (Section 4.4.2.3.3).

Normalization of residues for g a.i. injected/inch DBH would yield residue rates of about 250 (75 to 625) ppm per g a.i./inch DBH. For example, the central estimate of the residue, 100 ppm, is

divided by 0.4 g per inch DBH, the application rate reported by Lewis and Molongoski (2006), to arrive at a residue rate of 250 ppm per g/inch DBH. Similar calculations are made for the range of foliar residues monitored in leaves, 30-250 ppm, to arrive at the range for the residue rates—i.e., 75-625 ppm per g a.i./inch DBH.

Note that no further normalization is conducted. In other words, the residues rates are not normalized for the total amount applied to the tree. This approach is taken under the assumption that the application rate in units of grams per inch DBH is intended to lead to uniform residue rates in vegetation for trees of different sizes.

Note also that the residue rates based on imidacloprid are not adjusted for dinotefuran. As discussed above, it seems plausible and perhaps likely that residue rates for dinotefuran will be higher than those for imidacloprid. Thus, the exposures estimated in this risk assessment may underestimate exposures to dinotefuran. As discussed further in Section 4.4.2.3 (Risk Characterization for Terrestrial Invertebrates), this potential underestimation of exposure levels has a minimal impact on the qualitative risk characterization, because the hazard quotients are substantially above the level of concern.

The normalized residue rates are used in Worksheet G07 of the EXCEL workbook for tree injection (Attachment 5) to estimate concentrations of dinotefuran in contaminated vegetation by multiplying the residue rates by the application rate. As discussed in Section 2 (Program Description), since tree injection is not a currently labeled use for dinotefuran, there is no *labeled application rate*. Cowles (2009a) suggests that the application rate for tree injection will be about one-tenth the maximum rate for soil injection. As summarized in Table 2, the application rate for soil injection ranges from 0.6 to 2.4 g a.i. per inch DBH. Thus, the application rate considered for tree injection is taken as 0.24 g a.i. per inch DBH. This application rate of 0.24 g a.i. per inch DBH is used in Worksheet G07 of Attachment 5. All other aspects of the calculations in Worksheet G07 of Attachment 5 are identical to calculations in the worksheets for broadcast foliar and granular applications (Section 4.2.3.2.1).

4.2.3.2.3. Soil Injection and Bark Applications

The data on dinotefuran do not include information about leaf residue in trees treated by soil injection or bark application. As discussed in the previous section, the absence of such data usually precludes the development of an exposure assessment or risk characterization for the specific application method. The Forest Service rationale for considering the use of soil injection and bark applications of dinotefuran, instead of broadcast foliar applications, is identical to the rationale for considering the use of tree injection: to limit exposures of nontarget species. Accordingly, this assessment of dinotefuran attempts to characterize exposure for soil injection and bark applications; however, the resulting exposure estimates must be regarded as crude approximations, at best.

Unlike the case with tree injection, there are no detailed studies concerning residue rates for imidacloprid after soil injection or bark application. In other words, concentrations of

imidacloprid in leaves cannot be associated with a specific application rate by soil injection or bark application

Lewis and Molongoski (2006) state the following:

> *Experience in sampling thousands of trees has shown that typical residue values from sap extractions of treated trees three months post-injection range from 20 to 200 ppb, while values from leaf extractions of trunk and soil injected trees typically range from 50 to 200 ppm and 15 to 50 ppm, respectively.*
>
> Lewis and Molongoski 2006, p. 115

Note that Lewis and Molongoski (2006) do not specifically address residues in leaves after bark applications. For the current risk assessment, it is assumed that residues in leaves after effective bark applications will be approximately equal to residues in leaves after effective soil injections. Note also, that this assumption is not supported by specific experimental data; however, as noted in Table 2, the application rates for soil injection and bark application are identical, leading to the assumption that equivalent treatment rates by bark application and soil injection will result in comparable residues in leaves.

As noted in a preliminary review of the current risk assessment, the assumption of equivalent residues for bark application and soil injection is not intuitive: … *the structure of tree bark differs greatly among tree species. For example, the bark on mature eastern hemlock (Tsuga canadensis) trees is thick and deeply furrowed, while the bark on mature white ash (Fraxinus americanus) is not as thick and ridged in a diamond pattern* (Hartung 2009). It is not clear at this time whether different carriers and/or different application techniques might be used for bark applications to different kinds of trees to accommodate different structures of tree bark.

As discussed in the previous section, residue rates for tree injection are taken as 250 (75-625) ppm per g a.i./inch DBH. Based on the quotation cited above, it appears that soil injection residues would be about 3-4 times less than those associated with tree injection. Using an adjustment factor of 3.5, the residue rate for soil injection would be about 70 (21-188) ppm per g a.i./inch DBH.

The application rates for soil injection of imidacloprid, however, are in the range of about 12 g a.i. per 8-16 inches DBH or about 0.75-1.5 g a.i./inch DBH (SERA 2005, Table 2-2, Marathon 60). These rates are about 2-4 times higher than the 0.4 g a.i./inch DBH injection data cited by Lewis and Molongoski (2006). Using a central value of 3 for differences in application rate, the residue rate for soil injection would be further adjusted to about 23 (7-62) ppm per g a.i./inch DBH—i.e., (70 (21-188) ppm per g a.i./inch DBH) ÷ 3. As with tree injection, no further adjustment in the residue rate is made for the possibly higher peak levels of dinotefuran that might be expected relative to imidacloprid.

The residue rates 23 (7-62) ppm per g a.i./inch DBH are used in Worksheet G07 to estimate concentrations of dinotefuran on vegetation after soil injection (Attachment 4). As noted above, these rates are used to characterize residues in leaves after bark applications (Attachment 3) simply because the application rates for soil injection and bark application are identical (Table 2). The exposure assessments in Worksheet G07 are based on the maximum application rate for soil injection (Attachment 4) and bark application (Attachment 3)—i.e., 2.4 g a.i./inch DBH. Other aspects of the exposure assessments given in Worksheet G07 are identical to the methods described in Section 4.2.3.2.1 for broadcast foliar applications.

4.2.3.3. Exposure to Contaminated Nectar

The data on dinotefuran do not include information about concentrations in nectar or pollen after any application method. Again, the absence of such data would usually preclude development of an exposure assessment and further development of a risk characterization of honeybees foraging on treated plants. The EPA also expressed concern about uncertainties associated with attempts to characterize honeybee exposure to pesticides, in a recent EPA risk assessment on dinotefuran:

> *EFED does not conduct a risk analysis for terrestrial invertebrates like the other nontarget organisms (fish, birds, small-mammals, etc.), however, the Agency is concerned about protecting nontarget terrestrial invertebrates. EFED does not usually assess risk to terrestrial invertebrates using RQs. A screening level RQ assessment method for estimating the risk to bees is not available because EFED has not developed an exposure design for bees.*
>
> – U.S. EPA/OPP 2006b, p. 4.

Notwithstanding the logic and appropriateness of reservations expressed by the EPA, the current Forest Service risk assessment of dinotefuran develops a preliminary and conservative exposure assessment on honeybees foraging for nectar. This approach is prompted by concerns raised by the Tier 1 analysis for imidacloprid conducted by the Forest Service (Appleton 2008) as well as a conceptually similar analysis of the potential impact of imidacloprid on honeybees developed for the French Ministry of Agriculture (Alix and Vergnet 2007; Halm et al. 2006; Rortais et al. 2005).

The analyses conducted for the French Ministry of Agriculture develop imidacloprid exposure assessments for several subgroups of honeybees (i.e., nectar foragers, pollen foragers, larvae,

brood attending bees, and winter bees). The current risk assessment of dinotefuran is limited only to nectar foragers because this is the subgroup estimated to be exposed to the highest doses of dinotefuran (Rortais et al. 2005, p. 73, Table 1). Analogous to the approach taken in the human health risk assessment (Section 3.2.3.1.1), a nectar forager is taken as the Most Exposed Individual (MEI).

The basic algorithm for estimating the daily dose (D) to the foraging bee, based on the nutritional requirements of the bee is:

$$D_{mg/kg\ BW} = C_{Nec\,mg/L} \times Am_{Nec_L} \div BW_{kg}$$

where:

C = Concentration of dinotefuran in nectar in units of mg/L
Am = Amount of nectar in liters consumed by a foraging bee per day based on the nutritional requirements of the bee.
BW = Body weight of the bee in kilograms.

The amount of nectar a bee needs to consume is calculated from the nutritional requirements of the bee. Nutritional requirements for bees are generally expressed in the literature as the amount of sugar per unit time. Rortais et al. (2005) express the sugar requirement of bee during flight as 8-12 mg/hour, which is reasonably close to the value of 11.5 mg/hour cited by Winston (1987). The current risk assessment uses a sugar requirement for flight of 10 (8 to 12) mg/hour.

The number of hours/day that a bee might spend foraging is likely to be highly variable. Rortais et al. (2005) use a range from 4 to 10.7 hours/day. This range is used in the current exposure assessment with a central estimate of 6.5 hours/day, the approximate geometric mean of the lower and upper bounds from Rortais et al. (2005).

Thus, the amount(s) of sugar ($Am_{SugarFl}$) required by a bee to support flight activities during foraging is calculated as the product of the sugar requirements per hour during flight and the number of hours/day that the bee spends in flight:

$$Am_{Sugar\ FL} = Rate_{mg/h} \times Fight_{h/day}$$
$$Am_{Sugar\ FL} = 10\ (8\ to\ 12)_{mg/h} \times 6.5\ (4\ to\ 10.7)_{h/day} \quad .$$

Using the above equation, the amount(s) of sugar required per day to support flight activities is calculated as 65.5 (32 to 128.4) mg/day.

Rortais et al. (2005) base their exposure assessment only on sugar requirements during flight. In the current Forest Service risk assessment, the estimated nutritional requirement also includes time at rest, using the value of 0.7 mg/hour from Winston (1987, p. 61). From the same equation depicted above, the sugar requirement(s) for hours other than those engaged in flight is calculated as:

$$Am_{Sugar\ Oth} = 7_{mg/h} \times 24_{h/day} - 6.5\ (4\ to\ 10.7)_{h/day}$$

which is equivalent to 12.25 (14 to 9.31) mg/day.

Thus, the total sugar requirement(s) per day for a foraging honeybee is calculated as:

$$Am_{Sugar\ Total} = Am_{Sugar\ Flt} + Am_{Sugar\ Oth}$$
$$Am_{Sugar\ Total} = 65\ (32\ to\ 128.4)_{mg/day} + 12.25\ (14\ to\ 9.31)_{mg/day}$$

which is equivalent to 77.25 (46 to 137.71) mg/day. Compared with the method used by Rortais et al. (2005), the inclusion of metabolic requirements during non-flight hours increases the sugar demand by about 20%.

The sugar content of nectar also varies among plants and locations. Rortais et al. (2005) uses a value of 0.4—i.e., nectar consists of 40% w/w nutritional sugars. This single value is also used in the current risk assessment. So, when the sugar requirement(s) is divided by 0.4 (mg sugar/mg nectar), the estimated amount of nectar required per day is about 193 (115 to 344) mg/day. In the worksheets for this exposure scenario, these values are converted to units of kg nectar per day by dividing mg/day by 1,000,000 mg/kg.

Although the nectar requirements of a foraging bee are relatively well documented and simple to estimate using the general method of Rortais et al. (2005), dinotefuran concentrations in nectar are much less certain.

Based on the statement from Lewis and Molongoski (2006, p. 115), quoted in Section 4.2.3.2.3, Appleton (2008) assumed that the concentration of imidacloprid in the sap of treated trees ranged from 20 to 200 ppb. Cowles (2009a) suggests that compared with imidacloprid, dinotefuran may be more readily transported from sap to nectar. As noted in Section 4.2.3.2.2, the lipophilicity and acidity of dinotefuran suggest that it may be more readily transported in xylem and phloem compared to imidacloprid, which may be limited to translocation in xylem.

The estimated 20-200 ppb of imidacloprid in sap is not associated with a specific application rate. Moreover, there is relatively little information regarding pesticide concentrations in nectar that can be associated with a specific application rate for methods considered in the current risk assessment on dinotefuran.

Waller et al. (1984) reports dimethoate concentrations in flowering lemons were up to 1400 ppb following broadcast foliar applications of 1.12 kg a.i./ha (1 lb a.i./acre) in several lemon orchards. Dimethoate was detected in nectar from all except one orchard (n=16) (Waller et al. 1984, p. 72, Table 3). As would be expected, concentrations of dimethoate declined over time and were below the limit of detection by day 20 after treatment. Over the first 4 days, however, no systematic decrease in dimethoate concentrations in nectar is apparent. The average of the

mean values across all orchards at which dimethoate was detected over this period is 142 ppb with a 95% confidence interval of 54-230 ppb. Because the dimethoate concentrations in nectar are all based on an application rate of 1 lb a.i./acre (foliar broadcast), these concentrations may be perceived as normalized rates—i.e., plausible concentrations of dimethoate in nectar per lb a.i. applied per acre.

Just as using imidacloprid data as a surrogate for dinotefuran involves uncertainty, the extent to which peak dimethoate concentrations can be used as reasonable surrogates for dinotefuran concentrations is not clear. As illustrated in Figure 2, dinotefuran and dimethoate are both likely to be mobile in phloem and xylem; however, the pK_a for dimethoate is much lower than the corresponding pK_a for dinotefuran.

As noted by Satchivi et al. (2001, Figure 3, p. 81), the translocation of hydrophilic compounds with high pKa values (i.e., similar to dinotefuran) is likely to be somewhat greater than the translocation of compounds with pKa values of about 2 (i.e., similar to dimethoate). Based on water solubility, dimethoate— water solubility of 23.3 g/L (Tomlin 2004)—and dinotefuran—water solubility of 39.9 g/L (Table 1)—are clearly hydrophilic.

The available data suggest that using dimethoate is no more tenuous than using imidacloprid as a surrogate for dinotefuran. Hence, the data from Waller et al. (1984) are used to derive peak residue rates—i.e., 140 (54 to 230) ppb per lb a.i. applied per acre—of dinotefuran in nectar, after broadcast foliar applications. Like water contamination rates, nectar residue rates are expressed in units of ppm the EXCEL workbooks—i.e., 0.14 (0.054 to 0.23) ppm. In Attachments 1a and 1b, these residue rates are used in Worksheet G09 with the application rate of 0.2 lb a.i./acre to estimate exposure for foraging honeybees.

The residue rates for nectar derived from Waller et al. (1984) are used only for broadcast foliar applications. For all other application methods, the available data are not sufficient to develop residue rates. Consequently, the dinotefuran concentration in nectar for these other applications—i.e., 60 ppb with a range of 20-200 ppb—is based on the range of concentrations reported by Lewis and Molongoski (2006). The central estimate of 60 ppb is the approximate geometric mean of the 20 to 200 ppb range. Thus, the underlying assumption is that equally effective applications of dinotefuran by methods other than broadcast foliar application could yield similar dinotefuran residues in honey. In Worksheet G09 of Attachments 2 through 5, residues concentrations in nectar—i.e., 60 (20 to 200) ppb—have been converted to units of ppm—i.e., 0.06 (0.02 to 0.2) ppm, and because these concentrations are not residue rates, they are not linked to the application rates used in the EXCEL workbooks.

The exposure assessments in the EXCEL workbooks are based on honey and not nectar consumption which is inconsequential, since the basis of the exposure assessment is the energy requirement of the bee and not the source of the toxicant. As discussed by Rortais et al. (2005, p. 73, column 2,

> *As we do not know the bees' differential consumption of nectar and honey, we related their sugar consumption depending on whether they consume nectar or honey. With the example of sunflower, when a honeybee requires 1 mg of sugar, it will have to consume either2.5 mg of fresh sunflower nectar or 1.25 mg of sunflower honey.*
>
> – Rortais et al. 2005, p. 73

In other words, the amount of dinotefuran consumed by the bee could be the same whether the exposure is based on nectar consumption or honey consumption.

The basis of the exposures assessments in the current risk assessment and in Rortais et al. (2005) is the sugar demand of the honeybee; accordingly, the equivalence of nectar and honey exposures hold only if the amount of the pesticide per unit of sugar in nectar and honey are constant. Because there is more sugar in honey than in nectar, it would seem to follow that the pesticide concentration in honey would be greater than the pesticide concentration in nectar. Nonetheless, the opposite trend has been observed in at least some instances discussed in the available literature. Waller et al. (1984) note that although dimethoate was not detected in hive honey, dimethoate residues at concentrations of up to 1.4 ppm were detected in nectar. Similarly, Barker et al. (1980) report honey-to-nectar ratios of about 0.44 to 0.8 after a field application of dimethoate to alfalfa. A similar pattern was observed in a study involving seed treatment of canola with clothianidin, another neonicotinoid, in which the honey-to-nectar ratio was about 0.4 (Cutler and Scott-Dupree 2007). If the dinotefuran concentrations in honey were generally less than the concentrations in nectar, in terms of equivalent amounts of sugar, the exposure assessments based on nectar consumption could overestimate pesticide exposure from honey residue.

The above discussion is not intended to imply any sense of precision in the exposure assessment for plausible concentrations of dinotefuran in nectar; no such information is available. It does appear, however, that the two independent sources of information—i.e., the residues reported by Lewis and Molongoski (2006) and the residue rates derived from Waller et al. (1984)lead to reasonably similar estimates of dinotefuran concentrations in nectar.

No monitoring data are available on dinotefuran in nectar. The USDA assayed 186 samples of commercial honey as part of the Pesticide Data Program for calendar year 2007. No dinotefuran was found in honey at a limit of detection of 30 ppb (USDA/STP 2008, Appendix D). While the limit of detection would be sufficient to identify dinotefuran in honey over the central to upper bound estimates of potential exposure—i.e., 60 ppb to 200 ppb—the failure to detect dinotefuran in the commercial samples of honey assayed by the USDA does not impact the exposure assessment for bees because there is no indication in the USDA report that the honey samples assayed in the Pesticide Data Program were associated with field applications of dinotefuran.

4.2.3.4. Contact with Contaminated Surfaces

Toxicity studies involving insect exposure to dinotefuran from contact with contaminated surfaces are discussed in Section 4.3.2.3.3. Insects are likely to come into contact with

dinotefuran on surfaces after broadcast foliar, soil, and bark applications; however, data and methods to quantify this type of exposure in terms of mg/kg bw doses are not available. Consequently, the potential risks of exposure from contact with dinotefuran contaminated surfaces are discussed qualitatively in Section 4.4.2.3 (Risk Characterization for Terrestrial Invertebrates).

4.2.3.5. Contact with Contaminated Soil

Terrestrial invertebrates are certain to be exposed to dinotefuran in soil as a result of soil broadcast, drench, or injection. Moreover, the levels of exposure from contact with contaminated soil are likely to be substantial. Dinotefuran concentrations in soil can be modeled using GLEAMS. In addition, soil concentrations of imidacloprid monitored by Cowles (2009b) can be used to assess the reliability of the estimated soil concentrations of dinotefuran. Nevertheless, as indicated in Section 4.1.2.3.3, toxicity data involving the exposure of earthworms or other soil dwelling invertebrates to dinotefuran are not available. Consequently, a formal exposure assessment is not developed, but the obvious risks to soil dwelling insects are considered further in Section 4.4.2.3 (Risk Characterization for Terrestrial Invertebrates).

4.2.4. Terrestrial Plants

A relatively standard set of exposure assessments for terrestrial plants is developed in Forest Service risk assessments involving direct deposition or spray drift, off-site transport of the pesticide by runoff, and pesticide loss from the treated site by wind erosion of soil. As discussed in Section 4.1.2.5, the assertion that dinotefuran is not likely to damage terrestrial plants is self-evident from the registered uses of dinotefuran, which focus on plant protection (Section 2). Nonetheless, Porch et al. (2001b) provide an adequate basis for a minimal dose-response relationship for plants. Hence, the standard exposure scenarios for terrestrial plants are considered in this risk assessment. As with other groups of organisms, the specific scenarios considered vary according to the actual application methods, as specified in Table 17.

4.2.5. Aquatic Organisms

An assessment of the effects of dinotefuran on aquatic organisms is based on estimated water concentrations identical to those used in the human health risk assessment. These values are summarized in Table 9 and discussed in Section 3.2.3.4.6.

4.3. DOSE-RESPONSE ASSESSMENT

4.3.1. Overview

Table 18 summarizes the toxicity values used in this risk assessment. The derivation of each of these values is discussed in the following subsections. Available toxicity data support separate dose-response assessments in eight classes of organisms: terrestrial mammals, birds, terrestrial invertebrates, terrestrial plants, fish, aquatic invertebrates, aquatic algae, and aquatic macrophytes. Different units of exposure may be used for different groups of organisms, depending on the nature of exposure and the way in which the toxicity data are expressed. When possible, a range of toxicity values, based on the most sensitive and most tolerant species within a given group of organisms, is provided.

As would be expected for an insecticide, the most sensitive group of terrestrial organisms appears to be insects. Separate toxicity values are derived for acute oral exposure (0.014 mg/kg bw) and acute contact exposure (0.034 mg/kg bw). No chronic toxicity data are available. Data that exist for other species are often difficult to compare to data on the honeybee. The whitefly *Bemisia tabaci* appears to be a highly sensitive species but quantitative comparisons to honeybees are confounded by differences in exposure protocols. In any event, there are likely to be insect species that are at least as sensitive or perhaps even more sensitive than honeybees to exposures to dinotefuran.

Other terrestrial organisms are much less sensitive than insects to dinotefuran. For terrestrial mammals, the dose-response assessment for dinotefuran is based on the same data as the human health risk assessment. For acute exposures, the dose-response assessment is based on the acute gavage NOAEL of 125 mg/kg bw. For chronic exposures, the chronic dietary LOAEL of 20 mg/kg/day is adjusted to 2 mg/kg bw/day to approximate the NOAEL. In terms of acute toxicity, birds appear to be less sensitive than mammals to dinotefuran with an acute NOAEL of about 1000 mg/kg/day from a 5-day dietary study and a longer-term NOAEL of 325 mg/kg/day from a dietary reproduction study. A set of standard toxicity studies indicates that at the maximum application rate of 0.54 lb a.i./acre, dinotefuran is not likely to cause adverse effects in terrestrial plants.

Only a few bioassays are available on the acute toxicity of dinotefuran to aquatic organisms. Nonetheless, the available studies suggest that most aquatic organisms are relatively tolerant to dinotefuran with acute NOEC values of 25 mg/L for algae, about 100 mg/L for fish and macrophytes, and about 1000 mg/L for tolerant species of invertebrates. A bioassay in mysid shrimp, however, yields a much lower NOEC of 0.49 mg/L with a corresponding LC_{50} of 0.79 mg/L, indicating a very steep dose-response curve. The sensitivity of saltwater mysid shrimp to dinotefuran, relative to other aquatic invertebrates, is similar to patterns of species sensitivity observed with exposure to other neonicotinoids. Although most mysid shrimp are a saltwater species, they are used in this risk assessment as a surrogate for sensitive species of freshwater invertebrates.

The chronic toxicity of dinotefuran to aquatic organisms is assayed in a standard reproduction study in daphnids and an egg-and-fry study in fish, which the EPA classified as *Invalid* – i.e., a study that should not be used for risk assessment. The NOEC values for chronic exposure in both studies— i.e., 10 mg/L in fish and 100 mg/L in daphnids—indicate that dinotefuran is not very toxic to aquatic organisms, which is consistent with the results of acute toxicity studies. Since the dose-response assessment for aquatic species is severely limited by the lack of a chronic exposure study in mysid shrimp, the relative potency method is used to approximate a chronic NOEC of 0.051 mg/L dinotefuran from imidacloprid toxicity data. Concern that this toxicity value may not be sufficiently protective is discussed further in the risk characterization.

4.3.2. Toxicity to Terrestrial Organisms

4.3.2.1. Mammals

As summarized in Table 11 and discussed in the dose-response assessment for the human health risk assessment (Section 3.3), U.S. EPA/OPP uses the acute NOAEL of 125 mg a.i./kg/day (with a corresponding acute LOAEL of 300 mg a.i./kg/day based on neurotoxicity) from a gavage study in rabbits to derive an acute RfD of 1.25 mg/kg bw (Section 3.3.2) and a chronic dietary LOAEL of 20 mg a.i./kg/day for decreased thymus weight in dogs, as the basis of the chronic RfD (Section 3.3.3).

In the current risk assessment, the acute NOAEL of 125 mg/kg bw is used to assess mammalian wildlife exposure to dinotefuran. For longer-term toxicity, the LOAEL of 20 mg a.i./kg/day is divided by 10, resulting in an approximated longer-term NOAEL of 2 mg/kg bw/day. This approach is analogous to using an extra uncertainty factor of 10, which the EPA does to derive the chronic RfD (U.S. EPA/OPP 2004e).

To assess acute oral exposure to dinotefuran, U.S. EPA/OPP (2006b) uses the acute LD_{50} of 2804 mg/kg bw from the Glaza (1997a) study. As discussed in SERA (2007a), the EPA typically bases the risk characterization for mammals on an acute LD_{50} and interprets the resulting HQ values with variable levels of concern (LOC) ranging from 0.5 for acute toxicity to 0.1 for acute endangered species. The dose associated with the most conservative LOC of 0.1 would be about 280 mg/kg bw. In Forest Service risk assessments, the LOC is always 1. Thus, the approach in the current Forest Service risk assessment of using the acute toxicity value of 125 mg/kg bw is reasonably consistent with and only modestly more conservative than the approach taken by EPA to assess acute effects from oral exposure.

For chronic effects, U.S. EPA/OPP (2006b) uses the NOAEL of 3000 ppm from the 2-generation reproduction study by Sakurai (2002). As summarized in Appendix 2, this dietary NOAEL corresponds to a dose of 241 mg/kg bw/day. In this instance, the longer-term toxicity value of 2 mg/kg bw/day used in the current risk assessment is much lower than the longer-term toxicity value used by the EPA. This discrepancy reflects differences in the EPA and Forest Service methodologies. The EPA tends to base ecological risk assessments on reproductive endpoints; whereas, the Forest Service prefers to base both human health and ecological risk assessments of pesticides on the most sensitive endpoint in a particular group of organisms.

Notably, using the chronic toxicity value of 2 mg/kg bw/day is not necessarily the most conservative approach. As discussed in the dose-response assessment for human health (Section 3.3.3) and the hazard identification for mammalian wildlife (Section 4.1.2.1), the chronic feeding study in mice (Weiler 2000a) noted a LOAEL of 3 mg/kg bw/day in males, based on decreased spleen weight and the LOAEL of 4 mg/kg bw/day in females, based on increased ovarian weights. The most conservative approach would be to adjust the 3 mg/kg bw/day LOAEL to an approximate NOAEL of 0.3 mg/kg bw/day. This approach is not taken for two reasons. First, U.S. EPA/OPP (2004e) reviewed this study in some detail and determined that it was not appropriate for the derivation of an RfD. As discussed in Section 3.3.3, this determination seems reasonable. Second, as discussed in Section 4.1.2.1 and summarized in Table 12, subchronic or developmental studies in mice, rats, rabbits, and dogs are not consistent with the determination that mice are remarkably more sensitive than other species to dinotefuran. Thus, the weight-of-evidence supports using the higher estimated NOAEL of 2 mg/kg bw/day from the chronic feeding study in dogs (Weiler 1999b).

4.3.2.2. Birds

As summarized in Appendix 3 and discussed in Section 4.1.2.2, there are only five studies regarding the toxicity of dinotefuran to birds: three acute studies and two reproduction studies. What is more, the interpretation of these studies is not complicated. U.S. EPA/OPP (2006b) uses the reproductive NOAEC of 2150 ppm in bobwhite quail (Mitchell et al. 2002a) to characterize longer-term risks in birds. The current Forest Service risk assessment uses the same study and the same endpoint. Forest Service risk assessments, however, base the HQ value on the estimated exposure in units of mg/kg bw/day. Thus, the toxicity value given in Table 18 and used in Section 4.4 for risk characterization is the dose of 324 mg/kg bw/day from the 2150 ppm exposure group in the Mitchell et al. (2002a) study.

For acute exposures, the current risk assessment uses the NOAEL of 997.9 mg/kg bw from the 4732 ppm exposure group in the 5-day dietary study in mallards (Burri 2000c). The dose is taken as 997.9 mg/kg bw simply because it is reported as such in the DER for this study. All three acute toxicity studies (Burri 2000a,b,c) report essentially the same NOAEL (i.e., about 1000-1300 mg/kg bw). Given the very low risk quotients for birds (Section 4.4), these minor differences in the reported NOAELs are of no consequence.

4.3.2.3. Terrestrial Invertebrates

Two general types of exposure scenarios are considered quantitatively for terrestrial invertebrates: ingestion and direct contact through spray or drift (Section 4.2.2). Because dinotefuran appears to be somewhat more toxic by oral exposure than by direct contact (Section 4.1.2.3), different toxicity values are used to characterize the two types of exposures. The EPA typically uses LD_{50} and LC_{50} values as endpoints for dose-response assessments in ecological risk assessments; whereas, the Forest Service prefers to use no-effect levels, like the NOEC. For dinotefuran, NOEC values are reported in honeybee toxicity studies submitted to the EPA to support the registration of dinotefuran.

4.3.2.3.1. Oral Toxicity Value

The lowest oral NOEC reported in a honeybee toxicity study is 0.0013 µg/bee (Thompson 1998). This study involves exposure to a 20% SG formulation of dinotefuran. This NOEC is based on sublethal effects—i.e., stumbling or knockdown. The NOEC for mortality reported in the same study is 0.0061 µg/bee. The EPA bases the designation of the NOEC for mortality on the Kruskal Wallis test, followed by Dunn's multiple comparison. As noted in Appendix 4, bee mortality at this dose was 13/30 at both 24 and 48 hours, and mortality in the control group was 6/30. Using the Fisher Exact test, the response at a dose of 0.0061 µg/bee is significant, albeit only marginally (p=0.0473). Other reported oral NOEC values for sublethal effects in the honeybee are 0.003 µg/bee (TGAI in Harnish 200a) and 0.005 µg/bee (25% SG formulation in Harnish 2000b), factors of about 2.3 and 3.8 above the lowest NOEC.

The lowest oral NOEC (i.e., 0.0013µg/bee) is used to characterize risk quantitatively, and the uncertainties associated with the higher NOEC values are discussed further in Section 4.4.2.3.4 (risk characterization for foraging honeybees). The oral exposures for terrestrial invertebrates are based on doses expressed in units of mg/kg bw. Forest Service risk assessments generally use a bee body weight of 93 mg (0.000093 kg) for the honeybee (USDA/APHIS 1993). Using this body weight, the oral NOEC of 0.0013 µg/bee is equivalent to 0.0000013 mg/bee or 0.014 mg/kg bw [0.0000013 mg/bee ÷ 0.000093 kg /bee].

Dinotefuran NOEC values for other insects are not reported in the open literature (Appendix 4). As discussed in Section 4.1.2.3.1.1, a number of studies report LD_{50} or LC_{50} values for injection exposures (Kiriyama et al. 2003; Mori et al. 2002; Tan et al. 2007). One oral LC_{50} value reported in the open literature is not comparable to the honeybee studies because of uncertainties associated with estimating doses in units of mg/kg bw (Wang et al. 2005). As also noted in Section 4.1.2.3.1.1, two injection studies regarding effects in the American cockroach suggest that the LD_{50} for dinotefuran in the cockroach is comparable to the oral LD_{50} values in the honeybee. Two other injection studies suggest that the cockroach (Kiriyama and Nishimura 2002) and the housefly (Kiriyama et al. 2003), are substantially more tolerant than the bee to dinotefuran. In the absence of any additional information to better define oral toxicity values in terrestrial invertebrates, the honeybee NOEC of 0.014 mg/kg bw is used as a toxicity value for other species of terrestrial insects.

4.3.2.3.2. Contact Toxicity Value (for Direct Spray)

Honeybee contact exposure bioassays (i.e., the deposition of the compound directly onto the surface of the bee with a micropipette) are required for pesticide registration. As detailed in Appendix 4 and discussed in Section 4.1.2.3.1.1, honeybee toxicity studies consistently indicate that LD_{50} values for oral exposure are somewhat lower than LD_{50} values for contact exposure, by factors ranging from about 1.9 (Harnish 2000b) to 3.8 (Thompson 1998). Although the differences are within the range of variability for oral LD_{50} determinations (i.e., 0.0063-0.032 µg/bee, or a factor of 5) the consistent differences between the oral and contact LD_{50} values seem to justify using a separate toxicity value for contact exposures (i.e., exposure from direct spray or spray drift).

As discussed, the preferred methodology in Forest Service risk assessments is to use an NOEC rather than an LD_{50} for risk characterization. Moreover, when possible, the NOEC should be based on a sublethal, rather than a lethal, effect. All of the available honeybee contact bioassays report sublethal NOEC values based on ataxia/stumbling: 0.0063 µg/bee (Harnish 20001), 0.0125 µg/bee (Harnish 2000b), 0.0032 µg/bee (Thompson 1998). The range of reported NOEC values for contact exposure is a factor of about 3.9, which is similar to the range of NOEC values reported in the oral toxicity studies. The lowest NOEC of 0.0032 µg/bee cited in the Thompson (1998) study is used as the toxicity value for contact exposures. Like the oral NOEC, the contact NOEC of 0.0032 µg/bee or 0.0000032 mg/bee is divided by a bee body weight of 93 mg (0.000093 kg) for the honeybee (USDA/APHIS 1993) to calculate the NOEC of 0.034 mg/kg bw. The NOEC of 0.034 mg/kg bw for contact exposure is a factor of about 2.4 greater than the NOEC of 0.014 mg/kg bw for oral exposure.

4.3.2.3.3. Contact with Contaminated Vegetation

In addition to direct spray and oral exposure, broadcast applications of dinotefuran result in insect exposure to pesticide residues on vegetation and other surfaces. As discussed in Section 4.2.3.4, methods for estimating pesticide doses for insects in contact with contaminated vegetation or other contaminated surfaces are not available—i.e., dose estimates in units of mg/kg bw—for this type of exposure have not been developed. Nonetheless, dinotefuran residues on contaminated surfaces can be estimated, based on the highest labeled application rate for broadcast foliar applications (i.e., 0.2 lb a.i./acre). The suitability of the available toxicity data for estimating the consequences of exposure to contaminated surfaces is limited, nonetheless.

The most relevant study for estimating the consequences of insect exposure to contaminated surfaces is the residue bioassay by Hummel (2001). As discussed in Section 4.1.2.3.1.1, this study involved treating alfalfa plots with dinotefuran at an application rate of about 0.13 lb a.i./acre. Bees were exposed to the contaminated vegetation harvested from 3 to 48 hours after treatment. Honeybee mortality was significantly greater among bees exposed to treated vegetation, compared with bees exposed to control vegetation, for harvest intervals of up to 24 hours after application; however, mortality in bees exposed to contaminated vegetation harvested 48 hours after treatment was not significantly different from mortality in bees exposed to untreated vegetation.

4.3.2.4. Terrestrial Plants (Macrophytes)

A formal dose-response assessment for terrestrial macrophytes is only marginally relevant because of the low toxicity of dinotefuran to terrestrial plants. Nonetheless, the NOEC of 0.54 lb a.i./acre from the study by Porch et al. (2001b) can be used to derive hazard quotients for terrestrial plants. As discussed further in Section 4.4 (Risk Characterization), these hazard quotients are far below a level of concern.

4.3.2.5. Terrestrial Microorganisms

Because toxicity data regarding the effects of dinotefuran on terrestrial microorganisms are not available, it is not possible to develop a dose-response assessment for this group of organisms. This lack of pertinent data is discussed further in the risk characterization (Section 4.4).

4.3.3. Aquatic Organisms

4.3.3.1. Fish

Very little information is available regarding the toxicity of dinotefuran to fish. U.S. EPA/OPP (2006b) elected not to select toxicity values for fish. As noted in Section 4.1.3.1., the one chronic study in fish (Peither 2001) is classified as invalid.

As discussed in Section 1, the current risk assessment attempts to characterize risks whenever possible, in an effort to determine whether the use of this new insecticide is advantageous over the use of similar insecticides in terms of risks to nontarget organisms. The lack of a chronic toxicity study in fish, classified by the EPA as acceptable, is a serious limitation. Because additional toxicity studies involving chronic exposure of fish to dinotefuran are planned at this time, the chronic NOEC of 10 mg/L is used, albeit with reservation, in the risk characterization for fish (Section 4.4.3.1).

For peak exposures, the results of three acute toxicity studies, all classified as *Core* by U.S. EPA, are essentially same—i.e., no mortality or signs of toxicity were observed in fish exposed to 100 mg/L dinotefuran over a 96-hour period. For assessing risks posed by acute exposures, the lowest reported NOEC of 99.1 mg/L (Peither 2000c) is used. As documented in Appendix 5, adverse effect concentrations for dinotefuran have not been determined. Thus, the NOEC for fish is poorly defined in that the true NOEC is probably higher, and perhaps much higher, than 100 mg/L.

Both the acute and chronic NOEC values are treated as NOEC values for tolerant species. Forest Service risk assessments generally attempt to identify different toxicity values for both tolerant and sensitive species of fish and other aquatic organisms. For dinotefuran, however, toxicity values for sensitive species cannot be derived.

4.3.3.2. Amphibians

Due to the lack of toxicity data on aquatic stage amphibians (Section 4.1.3.2), a dose-response assessment cannot be made for this group of organisms.

4.3.3.3. Aquatic Invertebrates

As with fish, relatively few studies are available on the toxicity of dinotefuran to aquatic invertebrates. Nonetheless, the available studies are all classified as *Core* by U.S. EPA.

U.S. EPA/OPP (2004f, 2006b) uses the acute LC_{50} of 0.79 mg/L in mysid shrimp (Blankinship et al. 2001a) and the chronic NOEC of 95.3 mg/L in *Daphnia magna* (Peither 2000d) to characterize risks to aquatic invertebrates. While these are the most sensitive acute and chronic

endpoints based on the available data, it does not seem sensible to use an acute toxicity value that is lower than the chronic toxicity value.

In the current Forest Service risk assessment, the acute toxicity study in mysid shrimp (Blankinship et al. 2001a) is used to designate a toxicity value for sensitive species. The acute toxicity value used is the NOEC for sublethal effects of 0.49 mg/L, rather than the LC_{50} of 0.79 mg/L. Notably, the NOEC is not substantially lower than the LC_{50}. The proximity of the NOEC to the LC_{50} suggests a very steep dose-response relationship; hence, any excursion above the NOEC could be associated with adverse effects. This concern is discussed further in risk characterization (Section 4.4.3.3).

For tolerant species, the NOEC for sublethal effects in *Daphnia* magna—i.e., 968.3 mg/L from the study by Peither (2000a)—is used as the acute toxicity value.

The chronic NOEC of 100 mg/L in *Daphnia magna* (Peither 2000d) is used for the risk characterization of tolerant species for longer-term exposures. As with some of the toxicity values for fish, a chronic LOEC for daphnids has not been defined and the true chronic NOEC for daphnids may be higher than 100 mg/L. This NOEC is not used for sensitive species because the concentration of 100 mg/L is a more than a 100 times greater than the LC_{50} in mysid shrimp.

Due to the lack of a chronic toxicity study in mysid shrimp, , the relative potency method (SERA 2007a, Section 4.3.4) is used to approximate a chronic NOEC for sensitive species. The LC_{50} of dinotefuran was not determined in *Daphnia magna* because of the very low toxicity of dinotefuran to this species (i.e., the highest concentration tested was an NOEC). Thus, to estimate a chronic NOEC for mysid shrimp, the relative potency is based on the ratio of the acute NOEC values—i.e., 0.49 mg/L ÷ 968.3 mg/L ≈ 0.00051. In other words, dinotefuran appears to be more acutely toxic to mysids than to daphnids by a factor of about 1960. Based on this relative potency, the chronic NOEC for mysids is estimated as: [100 mg/L × 0.00051 = 0.051 mg/L].

In the absence of direct experimental data regarding the chronic toxicity of dinotefuran to aquatic invertebrates other than daphnids, the adequacy of the estimated NOEC of 0.051 mg/L for mysids cannot be assessed directly. For imidacloprid, chronic NOEC values are available for mysids and daphnids. As discussed in SERA (2005a, Section 4.3.3.3), the chronic NOEC values for imidacloprid in mysids and daphnids are 0.000163 and 1.8 mg/L, respectively. Thus, for imidacloprid, the relative potency is about 0.000091 [0.000163 mg/L ÷ 1.8 mg/L]—i.e., chronic exposure to imidacloprid appears to be more toxic to mysids than to daphnids by a factor of about 11,000. Thus, by analogy to imidacloprid, there is concern that the relative potency method used to derive the chronic toxicity value for mysids may not be sufficiently conservative. This concern is discussed further in risk characterization (Section 4.4.3.3).

4.3.3.4. Aquatic Plants

As with terrestrial plants, there is little basis for asserting that dinotefuran is likely to pose a hazard to aquatic plants. Acute NOEC values are available for algae—25 mg/L (Seyfried

2000)—and macrophytes—10 mg/L (Batscher 2002). These NOEC values are used for the risk characterization, with the conservative assumption that these values apply to tolerant species.

Due to the extremely limited amount of toxicity data on aquatic plants, no dose-response assessment or subsequent risk characterization is proposed for sensitive species of aquatic plants.

4.4. RISK CHARACTERIZATION

4.4.1. Overview

4.4.1.1. Risk Summary

The dinotefuran toxicity data and exposure estimates support quantitative risk characterizations in mammals, birds, terrestrial insects, terrestrial plants, fish, aquatic invertebrates, and aquatic plants. Risk characterizations for terrestrial invertebrates other than insects, reptiles, and amphibians are not possible because of the lack of toxicity data.

Risks to nontarget species appear to be minimal, except for terrestrial insects, which appear to be at substantial risk. Dinotefuran foliar sprays are likely to kill insects that are sprayed directly, while drift associated with foliar sprays may also involve risk to insects, depending on their distance from the application site and the extent of foliar interception. Herbivorous insects appear to be at greatest risk, with HQ values ranging from about 60 to greater than 7000.

The risk to foraging honeybees is less certain, and data to support a risk analysis are scant. For certain types of dinotefuran applications (e.g., tree injections to wind-pollinated trees), exposure may be minimal for foraging bees. A worst-case assessment results in risks ranging from marginal (HQs from 0.95 to 1.8) to substantial (HQs from 12 to 53), depending on the application method. A less conservative analysis consistent with an extremely brief summary of an incomplete field study indicates that risks to foraging bees could range from insubstantial to marginal (HQs from 0.2 to 2). Without additional data to support a less speculative assessment, (i.e., one that relies less heavily on the use of surrogate chemicals), the risk characterization for the potential effects of dinotefuran on honeybees cannot be further refined.

4.4.1.2. Terrestrial Insects

The nature of the risk characterizations for terrestrial insects is fundamentally different from the risk characterization for all other groups of organisms. The risk characterization for terrestrial insects is, in some respects, a tautology: If an effective insecticide like dinotefuran is applied at effective rates and in an effective manner, insects will be killed. Nevertheless, the risk characterization for terrestrial insects is complicated and in many ways compromised due to the limited amount of available data on dinotefuran, which necessitates using available data on a surrogate pesticide, chiefly imidacloprid. The risk characterization for all other groups of organisms is simple: Under worst-case exposure assumptions and from a very conservative approach to the dose-response assessment, there is no basis for asserting plausible risks to nontarget species, other than terrestrial insects.

The impact of foliar broadcast applications on insects is not difficult to characterize. For both sensitive and tolerant species of terrestrial insects, the hazard quotient for direct spray of a honeybee with dinotefuran is greater than 500. The direct spray of a bee with dinotefuran would lead to mortality. The actual impact of foliar applications of dinotefuran on an insect or group of insects is variable, depending on the distance downwind from the application site and the extent of foliar interception. In the case of substantial (90%) foliar interception, the HQ values based

on Tier 1 drift modeling are below the level of concern at distances of about 500 feet downwind from the application site.

While foliar interception would reduce risks associated with direct spray, foliar interception would be associated with residues of dinotefuran on or in vegetation. Based on standard methods used to estimate pesticide concentrations on vegetation after broadcast applications as well as reasonably well-documented estimates of the amount of vegetation that an herbivorous insect would consume, the risks associated with the consumption of contaminated vegetation are greater than those associated with direct spray. For broadcast foliar applications, the HQ values range from about 30 to greater than 10,000. For broadcast soil applications, the HQ values range from 3 to greater than 800. By definition, broadcast application methods will involve a high likelihood of exposure over a relatively broad area.

For all other application methods (i.e., bark application, soil injection, and tree injection) the exposure assessment is much less certain, and the estimated levels of exposure could be much lower depending on the species of the treated tree, the time of treatment, and the specific conditions of the treatment. Nonetheless, the HQ values for herbivorous insects associated with these other application methods range from about 700 to greater than 20,000. While the exposure assessments may in some cases substantially overestimate exposure, risks to herbivorous insects, based on available information, are substantial. Unlike broadcast applications, the more focused application methods would be used only on certain species of trees; thus, their impact would be more limited in scope.

The potential for adverse effects in honeybees foraging for nectar is far less certain than the potential for adverse effects in terrestrial herbivores. Using conservative Tier 1 screening assumptions (i.e., the upper bound of exposure and the lowest reported oral NOEC in honeybees), the upper bound of the HQ values range from 12 (foliar broadcast, one application) to 53 (all non-broadcast applications). Risk quotients of up to 53 would likely result in substantial bee mortality. These HQ values, however, are not applicable to more focused applications of dinotefuran to certain species of trees (i.e., trees that are not pollinated by bees). The risk characterization is far less severe taking into consideration the variability in plausible levels of exposure, the variability in NOECs reported for bees, and the results from the summary of a field study on honeybees. Considering these factors, honeybee exposure to dinotefuran, were it to occur, would be in the range of or only slightly greater than plausible NOEC values. In the absence of additional data on dinotefuran to permit a more detailed assessment, the risk characterization for the potential effects of dinotefuran on honeybees cannot be further refined.

4.4.1.3. Other Organisms

Unlike the risk characterization for terrestrial insects, the risk characterization for other groups of terrestrial organisms is quite simple and is accompanied by few reservations. The toxicity data on mammals are relatively complete, and most HQ values are below the level of concern. The only exception is the upper bound HQ of 1.3 for the longer-term consumption of contaminated vegetation by a large mammal after two foliar broadcast applications at the maximum application rate. While the toxicity data on birds are less complete, the studies required by EPA for

pesticide registration are available and have been classified by the EPA as acceptable. Birds appear to be less sensitive than mammals, and the HQ values for birds are below a level of concern by factors of 50 to greater than 300,000. Dinotefuran toxicity studies in terrestrial plants failed to identify any adverse effects at the maximum applications rate.

The risk characterization for aquatic organisms is generally similar to that for non-insect terrestrial organisms; however, is accompanied by greater reservations. Based on the available information, applications of dinotefuran are not likely to cause adverse effects in aquatic organisms. For fish, tolerant species of aquatic invertebrates, and aquatic plants, all HQ values are substantially below the level of concern. The HQ values for sensitive species of aquatic invertebrates are based on toxicity studies in mysids, which are generally sensitive to neonicotinoids. Based on the mysid data, non-accidental exposures are below a level of concern by factors of 5-50 for acute exposures and 14-140 for longer-term exposures. The lack of toxicity data on any species of aquatic insect is a major reservation in the relatively benign risk characterization for aquatic invertebrates. Confidence in the risk characterization for aquatic invertebrates would be greatly enhanced if toxicity studies as well as field studies were available on the effects of dinotefuran on aquatic insects.

4.4.2. Terrestrial Organisms

4.4.2.1. Mammals

The HQ values for mammals and birds are given in Worksheets G02 of the attachments that accompany this risk assessment. To facilitate a discussion of these HQ values, copies of these G02 worksheets are compiled in Appendix 11 of this risk assessment.

The only hazard quotient that exceeds the level of concern is the upper bound of the HQ (1.3) for the longer-term consumption of vegetation by a large mammal after two broadcast foliar applications of dinotefuran at the maximum application rate of 0.2 lb a.i./acre. As noted previously in this risk assessment, broadcast foliar applications are considered in this risk assessment; however, they are not likely to be used in Forest Service programs. For all other application methods and other exposure scenarios, there is no basis for asserting that adverse effects are plausible in large or small mammals.

As noted in the Forest Service risk assessment on imidacloprid (SERA, 2005a), a possible concern involves porcupines (*Erethizon dorsatum*) which preferentially consume the inner bark, small twigs and buds of eastern hemlock trees. When dinotefuran is used in a similar fashion to control the hemlock wooly adelgid by any of the contemplated control methods, it will enter the sap of the hemlock tree and result in unintended exposures for the porcupine. Assuming that the porcupine consumes 20% of its bodyweight in materials derived from hemlock, and that hemlock contains 2 mg/kg dinotefuran after a standard soil drench exposure (Cowles, 2009c), then the resulting exposure is estimated to be 0.4 mg/kg/day. Based on the chronic toxicity value of 2 mg/kg/day (Table 18), the resulting HQ would be 0.2 [0.4 ÷ 2], below the level of concern by a factor of 5.

4.4.2.2. Birds

Birds appear to be somewhat less sensitive than mammals to dinotefuran. Given the apparently low risks to mammals, the risk characterization for birds is essentially identical to the risk characterization for mammals: There is no basis for asserting that birds are likely to be at risk at the maximum application rate for dinotefuran for any of the application methods considered in this risk assessment. As noted in the previous section, the specific HQ values for birds are given in Appendix 11 of this risk assessment.

The upper bound HQ values for birds range from 0.000003 (the consumption of contaminated water by a small bird after bark applications) to 0.02 (the consumption of contaminated insects by a small bird after broadcast foliar applications). These HQ values are below the level of concern by factors from 50 to greater than 300,000.

The risk characterization for birds, like the one for mammals, is consistent with the risk characterization in U.S. EPA/OPP (2006b); furthermore, and there are no substantial reservations associated with this risk characterization. Notably, however, the dinotefuran toxicity database for birds is more limited than one for mammals and does not include field studies. This is the case for almost all new pesticides. Again, given the very low HQ values for birds based on the conservative methods used in the current risk assessment, reservations concerning the limited information on potential effects in birds are noteworthy but not substantial.

4.4.2.3. Terrestrial Invertebrates

4.4.2.3.1. Direct Spray

The hazard quotients for the honeybee, based on direct spray or spray drift after aerial broadcast applications of dinotefuran at the maximum labeled rates of 0.2 lb a.i./acre, are presented in the bottom section of Worksheet G02b in Attachments 1a and 1b and in Table 19 of the current risk assessment.

As discussed in Section 4.2.2.1, the exposure estimates are based on the Tier 1 aerial application drift estimates from AgDrift at downwind distances of 0 (direct spray) to 900 feet and on estimates of foliar interception from Wimmer et al. (1992). The toxicity value used to calculate the HQ values is the NOEC of 0.034 mg/kg bw from the contact toxicity study by Thompson (1998).

The hazard quotients are reasonably simple to interpret. Without substantial foliar interception, aerial broadcast foliar applications of dinotefuran would lead to exposure levels substantially higher than the NOEC. In the study used to derive the NOEC (Thompson 1998), the reported LD_{50} value for contact exposure is 0.024 µg/bee, a factor of 7.5 above the NOEC [0.024 µg/bee ÷ NOEC 0.0032 µg/bee]. Thus, HQ values of 7.5 would correspond to the reported LD_{50}. Based on this relationship, substantial bee mortality is anticipated at distances of up to 500 feet (HQ=10) in the absence of foliar interception, 300 feet with 50% foliar interception (HQ=8), and 50 feet with 90% foliar interception (HQ=9).

This risk characterization for potential honeybee exposure is consistent with the risk assessment for imidacloprid (SERA 2005a) in which the direct spray scenario for the honeybee with no foliar interception leads to an HQ of 5000. As discussed in Section 4.1.2.4.1, imidacloprid is somewhat more toxic than dinotefuran to honeybees. The higher HQ for imidacloprid is also associated with a higher application rate (i.e., 0.4 lb a.i./acre for imidacloprid vs. 2 lb a.i./acre for dinotefuran).

Despite the variability in the reported toxicity values for honeybees (i.e., a factor of about 5), the magnitude of the HQ clearly indicates that direct spray or spray drift is likely be hazardous to the honeybee and could result in substantial mortality.

The U.S. EPA requires the following warning and limitation on applications of imidacloprid:

> *Do not apply this product or allow it to drift to blooming crops or weeds if bees are visiting the treatment area.*

While this limitation applied to dinotefuran would limit the exposure of bees to direct spray or spray drift, the extent to which other insect species would be at risk to direct spray or drift of dinotefuran is less certain. Limited data are available to assess the toxicity of dinotefuran to other insects. Based on comparisons that can be made (Section 4.1.2.3.2), the toxicity of dinotefuran appears to be similar for cockroaches and honeybees.

Comparisons of relative toxicity with other species are less certain. The available glass surface contact toxicity studies in predaceous mites (Aldershof 2000a), parasitoid wasps (Aldershof 2000b), and predacious bugs (Aldershof 2000b) suggest that these species may be extremely sensitive to dinotefuran, by comparison to the honeybee contact bioassay with alfalfa residues (Hummel 2001). The nature of glass surface contact bioassays and contact bioassays with contaminated vegetation, however, are very different, and it is not clear a direct comparison is justified. Nonetheless, the LOEC values in the glass surface contact studies range from 0.0000012 lb a.i./acre (*Orius laevigatus* from Aldershof 2000c) to 0.013 lb a.i./acre (*Typhlodromus pyri* from Aldershof 2000a). These are factors of about 10 to over 110,000 below the application rate of 0.134 lb a.i./acre in the alfalfa residue study using honeybees (Hummel 2001). While glass surface toxicity studies may lead to greater exposure levels than vegetation contact studies do, the glass surface bioassays suggest that some mites, wasps, and predacious bugs may be at least as sensitive as the honeybee to dinotefuran.

Conversely, the oral toxicity study in the Asian long-horned beetle by Wang et al (2005) and injection studies investigating toxicity to cockroaches and houseflies (Kiriyama and Nishmura 2002; Kiriyama et al. 2003) suggest that some target species may be less sensitive than the honeybee to dinotefuran. As discussed in Section 4.1.2.3.2, the estimated oral LD_{50} for the Asian long-horned beetle is 1.1-4.4 mg/kg bw, about 3-13 times greater than the highest reported oral LD_{50} in the honeybee—i.e., 0.34 mg/kg bw from the study by Harnish (2000b). If some target species are less sensitive than the honeybee to dinotefuran, it may be reasonable to assume that some nontarget species will also be less sensitive. Since it is estimated that some insects

may be about 13 times less sensitive than honeybees to dinotefuran, the risk characterization for tolerant species of insects would be less severe than the one for honeybees. Nonetheless, the basic conclusions would remain the same. If insects are directly sprayed with dinotefuran at an application rate of 0.2 lb a.i./acre, insect mortality is to be expected.

The hazard quotients in Table 19 are for the maximum foliar broadcast application rate of 0.2 lb a.i./acre, and are linearly related to the application rate. Taking the HQ of about 500 for the direct spray of a sensitive species, an HQ of 1 would be associated with an application rate of 0.0004 lb a.i./acre for a sensitive species [0.2 lb a.i./acre ÷ 500] and an application rate of about 0.005 lb a.i./acre for tolerant species [13 × 0.2 lb a.i./acre ÷ 500 = 0.0052 lb a.i./acre]. These application rates associated with an HQ of 1 are far below effective foliar broadcast application rates for dinotefuran. Thus, effective foliar broadcast applications of dinotefuran would be associated with mortality in insects exposed to direct spray applications. The actual impact on an insect or group of insects would vary, depending on the distance downwind from the application site and the extent of foliar interception of the pesticide.

4.4.2.3.2. Contaminated Vegetation or Prey, Aerial Application

Table 20 summarizes the hazard quotients for insects exposed to dinotefuran from the consumption of contaminated vegetation or prey after aerial applications and also includes hazard quotients for herbivorous insects a risk of exposure from other application methods (discussed in Section 4.4.2.3.3). In addition, Table 20 summarizes the HQ values for foraging honeybees (discussed in Section 4.4.2.3.4). The hazard quotients presented in Table 20 are all rounded to the nearest digit. Some of the very high hazard quotients in the worksheets imply a level of precision that is not reasonable. The use of digit rounding for the HQ is simply a convention and is not intended to imply a level of precision or accuracy beyond two significant figures.

The hazard quotients given in Table 20 are taken from the EXCEL workbooks that accompany this risk assessment. The hazard quotients for aerial broadcast foliar applications are based on application rates of 0.2 lb a.i./acre using either a single application (Attachment 1a) or two applications with a 14-day application interval (Attachment 1b). Aerial broadcast granular/soil applications are based on a single application at a rate of 0.54 lb a.i./acre (Attachment 2). Standard residue rates from Fletcher et al. (1997) are used for foliar applications, and lower residue rates based on the data from Michael (1992) are used for granular applications. Details about the calculations of the hazard quotients are provided in Worksheets G07a through G07d. A summary of the hazard quotients for all of the four food types are given in Worksheet G08b.

Across the range of food items, the hazard quotients substantially exceed the level of concern (i.e., an HQ equal to 1). The HQ values are based on the oral NOEC of 0.014 mg/kg bw for sublethal effects from the honeybee toxicity study by Thompson (1998). In this study, the oral LD_{50} is 0.0076 µg/bee or about 0.082 mg/kg bw. Thus, a hazard quotient of about 6 would correspond to exposure at the LD_{50} level, and substantial mortality would be expected at HQ values of about 6 and higher. This relationship is similar to the relationship of the LD_{50} to the NOEC for contact toxicity—i.e., a factor of about 7.5, as discussed in Section 4.1.2.4.1.1.

As with the hazard quotients for direct spray and spray drift, the qualitative interpretation of the hazard quotients for aerial application is relatively simple. For all food types, the lower bounds of the hazard quotients associated with broadcast foliar applications substantially exceed the LD_{50}. For foliar broadcast applications, the lower bounds of the HQ values range from 27 to greater than 250. These HQs are associated with exposure levels that exceed the LD_{50} by factors of about 5 to greater than 40. Thus, the *best case* exposure scenarios suggest that the aerial foliar broadcast applications of dinotefuran would cause substantial mortality in insects feeding on treated vegetation.

The HQ values for soil broadcast applications (i.e., the broadcast of the granular formulation) are substantially lower than those for foliar broadcast application because of the 0.04 residue adjustment, based on the study by Michael (1992). As noted in Section 4.2.3.2.1, the use of the 0.04 adjustment factor could underestimate risks, because this factor adjusts for initial differences in residues on vegetation but does not consider the subsequent uptake of dinotefuran by treated plants. This potential underestimate of risk does not have a substantial impact on the risk characterization for terrestrial herbivores. As indicated in Table 20, the lower bounds of HQ values for broadcast granular applications range from 3 for contaminated fruit to 28 for short grass. The lower bound hazard quotient of 3 for fruit corresponds to about one-half of the LD_{50}, the trigger level of concern for acute risk using the U.S. EPA/OPP classification system. Thus, even at the lower bound doses, mortality is anticipated for some species.

Like the HQ values discussed in Section 4.4.2.3.1, the HQ values in Table 20 are based on honeybee toxicity data, and there is uncertainty in the estimated sensitivity of inspect species to dinotefuran. At the central and upper limits of the HQ values, however, uncertainties in variability of species sensitivities to dinotefuran do not remarkably impact the risk characterization. If aerial foliar broadcast applications of dinotefuran are made, mortality and perhaps substantial mortality is anticipated for at least some and perhaps many groups of terrestrial insects that consume treated vegetation or other insects. Soil broadcast applications may pose a lesser risk, at least initially, but the qualitative assessment of mortality in terrestrial insects is not substantially different from that associated with broadcast foliar applications.

An additional uncertainty in the HQ values in Table 20 involves the rather general estimates of food consumption—i.e., 1.3 (0.6-2.2) kg food/kg bw per day. As discussed in Section 4.2.2.2.1, the lower bound of 0.6 is taken from Reichle et al. (1973), and the central estimate and upper bound are taken from the range of values given by Waldbauer (1968). Confidence in the resulting hazard quotients would be enhanced if more detailed and species-specific estimates based on specific food items and/or caloric requirements were used.

Nonetheless, the estimates of food consumption for herbivorous insects from Reichle et al. (1973) and Waldbauer (1968) are reasonably well-documented. In addition, the resulting hazard quotients for insects summarized in Table 20 are sufficiently high that even substantial changes in food consumption rates would have no substantial impact on the risk characterization. For example, the central estimates of the hazard quotients are based on a food consumption rate of

1.3 kg food/kg bw per day. The lowest estimate of the lower bound of the hazard quotients for foliar broadcast applications is 60 (fruit). Thus, to reach an HQ of 1 (the level of concern) would require a food consumption rate of about 0.02 kg food/kg bw [1.3 kg food/kg bw per day ÷ 60 ≈ 0.0216], which is implausibly low for any organism.

A final uncertainty in the hazard quotients derived for herbivorous insects involves using the standard residue rates from Fletcher et al. (1997) rather than deriving rates based on the dinotefuran residue study by Hummel (2003b). As discussed in Section 3.2.3.6, the study by Hummel (2003b) suggests that the standard residue rates from Fletcher et al. (1994) may overestimate dinotefuran residues by factors of about 2 for mean residues and 6 for upper bound residues (Section 3.2.3.6). The use of a 2-fold lower residue rate for the central estimates of the HQ values would bring the lowest central estimate of HQ—i.e., the HQ 14 for broadcast granular applications onto fruit—to 7. The use of a 6-fold lower residue rate on the upper bound HQ values would bring the lowest upper bound HQ—i.e., the HQ of 51 for broadcast granular applications onto fruit—to about 8. Thus, while the use of the residue rates from Hummel (2003b) would lower the HQ values, they would remain above the level of concern.

While there are several uncertainties in the risk characterization for herbivorous insects, in terms of the magnitude of exposure, the likelihood of exposure is obviously high. By definition, any effective aerial broadcast application of dinotefuran will involve treating vegetation over a relatively wide area, resulting in the exposure of herbivorous insects.

4.4.2.3.3. Contaminated Vegetation or Prey, Other Application Methods

Uncertainties in the hazard quotients associated with tree injection, bark application, and soil injection are much greater than those associated with aerial broadcast foliar applications. As discussed in detail in Section 2.2.2.2, data are not available on leaf residues associated with these application methods. While this is also the case for aerial applications, a large body of literature suggests that aerial and other broadcast methods of application lead to initial pesticide residues on vegetation that can be estimated reasonably well (i.e., Hoerger and Kenaga 1972; Fletcher et al. 1994). This type of information is not available for tree injection, bark application, and soil injection. Thus, the entire risk characterization for these application methods rests on analogy to imidacloprid. Cowles (2009c) is currently developing data on foliar residues of dinotefuran in hemlock. This information, and any data that becomes available on dinotefuran, should be considered in subsequent risk assessments. In the absence of such data, the following risk characterization is heavily qualified.

As summarized in Table 20, the hazard quotients associated with tree injection, bark application, and soil injection of dinotefuran are somewhat higher than those associated with aerial foliar broadcast applications. Consequently, the qualitative risk characterization for these application methods are essentially the same: The *best case* exposure scenarios—i.e., the lower bounds of the HQ values—suggest that the tree injection, bark application, or soil injection of dinotefuran may be associated with substantial mortality in insects (target or nontarget) feeding on contaminated vegetation.

As discussed in Section 4.2.2.2.2, the exposure assessment for tree injection is based on the Lewis and Molongoski (2006) study, which gives foliar residues in four London plane trees and four Norway maple trees after the injection of imidacloprid. Based on this study, residue rates for tree injection are estimated at 250 (75-625) ppm per g a.i./inch DBH.

The residue rates derived from the Lewis and Molongoski (2006) study appear to represent worst-case exposures and may not be representative of residue rates in other tree species. For example, Tatter et al. (1998) treated eastern hemlock by trunk injection with an imidacloprid formulation at a rate of 0.225 g a.i./inch DBH and noted peak leaf residues of 7.9 ppm. This rate corresponds to a rate of about 35 ppm per g a.i./inch DBH [7.9 ppm ÷ 0.225 g a.i./inch DBH ≈ 35.11 ppm per g a.i./inch DBH]. This rate is a factor of about 2 less than the lower bound from the Lewis and Molongoski (2006) study. Similarly, Kreutzweiser et al. (2008a) noted residues of about 11 ppm in maples after trunk injections of about 0.6 g a.i./inch DBH, corresponding to a residue rate of about 17 ppm per g a.i. per inch DBH. This rate is a factor of about 4 less than the lower bound of 75 ppm from the Lewis and Molongoski (2006) study. A more extreme deviation is illustrated in the study by Harrell (2006) in which green ash were injected with two formulations of imidacloprid at rates of about 0.125 g a.i./inch DBH (Pointer) and 0.055 g a.i./inch DBH (Merit). After 30 days, leaf concentrations of imidacloprid were only about 1 ppm for the trees treated with the Pointer formulation and 0.1 ppm for the trees treated with the Merit formulation. These rates correspond to residue rates of about 8 ppm per g a.i./inch DBH for the Pointer formulation and 1.8 per g a.i./inch DBH for the Merit formulation.

In terms of a practical impact on the interpretation of the risk characterization, it should be recognized that it is difficult to achieve efficient and uniform results with tree injections of pesticide and that some formulations may be more easily applied (i.e., injected) than others (Harrell 2006). Currently, there is no tree-injection formulation of dinotefuran. Thus, it seems appropriate to use the more conservative values (i.e., higher residue rates) from the Lewis and Molongoski (2006) study. Notably, using even the lowest residue rate from Harrell (2006) would lead to HQ values that exceed the level of concern. For example, the central estimate of the HQ for tree injection is 5571. Using the residue rate of 1.8 per g a.i./inch DBH for the Merit formulation from the Harrell (2006) study, would lead to an adjusted HQ of about 40 [5571 × 1.8 per g a.i./inch DBH ÷ 250 ppm per g a.i./inch DBH ≈ 40.1112].

Of equal importance, however, is the possibility that the residue rates based on imidacloprid may not be representative of residue rates for dinotefuran. Based on the general relationship of translocation in xylem to physiochemical properties noted by Bromilow et al. (1990), it seems plausible that dinotefuran residues will be greater than those for imidacloprid after equivalent tree injections. Thus, it is possible that the exposure assessment on which the hazard quotients for tree injection are based may underestimate risk.

The hazard quotients for bark application and soil injection are somewhat less than those for tree injection but are still substantially above the level of concern—i.e., HQ values of 5126 (720-23,383). As discussed in Section 4.2.2.2.2, these hazard quotients are based on a very brief and only semi-quantitative statement in the Lewis and Molongoski (2006) study. As with the above

discussion on hazard quotients for tree injection, however, the hazard quotients would remain above the level of concern even if the leaf residues were 2 ppm.

Unlike broadcast applications, however, any of the more localized application methods (i.e., bark treatment, soil injection, and tree injection) will lead to more localized exposures of herbivorous insects to dinotefuran. This is one of the major reasons that these more localized and focused application methods are used in Forest Service programs. Thus, while the HQ values for these more localized application methods are higher than those for broadcast applications, the more localized application methods could have less of an impact on herbivorous insects. In addition, these more localized application methods will only be used to treat specific types of trees. Consequently, the greatest impact would be to populations of herbivorous insects that feed on the treated trees. Exposures and consequently risks to other groups of herbivorous insects would likely be much lower.

4.4.2.3.4. Contaminated Nectar

As with risks to herbivorous insects, the risk characterization for honeybees exposed to dinotefuran is based almost entirely on exposure assessments that use information on other pesticides, specifically imidacloprid and dimethoate, to estimate honeybee exposure to dinotefuran. In a typical risk assessment, this would preclude the development of any risk characterization. The risk characterization for honeybees foraging for nectar is given in an attempt to generally address concerns associated with the potential impact of neonicotinoids on honeybees.

The HQ values for honeybees presented in this section are based on the assumption that an exposure to dinotefuran occurs. For broadcast applications of dinotefuran, this is a reasonable assumption. For other application methods to certain species of trees, the probability of significant honeybee exposure to dinotefuran is far less certain. The major planned uses of dinotefuran by the Forest Service are for the control of pest species on hemlocks (hemlock wooly adelgid) and on ash trees (emerald ash borer). The potential exposure of bees is greatly reduced in bark application or tree injections of these species of trees because these trees are wind pollinated.

As summarized in Table 20, the HQ values for honeybees generally exceed the level of concern but are substantially below the HQ values associated with other exposure scenarios (i.e., direct spray and the consumption of contaminated vegetation by herbivorous insects). These lower HQ values make the risk characterization more difficult to interpret because the generally conservative assumptions (i.e., selecting the most sensitive endpoint and focusing on the most exposed individual) may in some ways distort the characterization of risk.

For broadcast foliar applications, the HQ values are 4 (0.95-12) for one application and 5 (0.95-17) for two applications. These values are based on dimethoate exposure data from Waller et al. (1984), and, as with most other exposure assessments, the HQ values are based on residue rates. For all other application methods, the exposure assessments are based on the general observation from Lewis and Molongoski (2006) that imidacloprid residues in sap are likely to range from 20

to 200 ppb, and the central estimate in this risk assessment is taken as 60 ppb. Thus, only a single set of HQ values are given, 9 (1.8-53), which are used for the risk characterization of all application methods other than broadcast foliar. Because these HQ values are not based on residue rates, the HQ values are not dependant on the application rate. The underlying assumption is that equally effective applications of dinotefuran by these other application methods will result in dinotefuran residues of 20-200 ppb in nectar.

As with all other risk characterizations for terrestrial insects, there are several uncertainties associated with the risk characterization for bees foraging for nectar on vegetation treated with dinotefuran. Uncertainties associated with the exposure assessment are detailed in Section 4.2.2.3. No information is available at this time regarding dinotefuran concentrations in nectar after any application method.

Based on the consumption of nectar from sunflowers after seed treatment with imidacloprid, Halm et al. (2006, Figure 1A, p. 2452) estimated risk quotients for nectar-foraging honeybees ranging from about 10 to 30, based on variations in the proportion of nectar that might be contaminated. While the current Forest Service risk assessment does not quantitatively address this type of variability, the HQ values will be linearly related to the proportion of nectar that is contaminated. In other words, the hazard quotients of 9 (1.8-53) are based on contamination of 100% of the nectar sources. If only 50% of the nectar sources were contaminated, the hazard quotients would decrease by a factor of 2. The hazard quotient of 30 reported by Halm (2006) corresponds to 100% contamination and is consistent with the hazard quotients for dinotefuran given in this risk assessment.

As with hazard quotients for the consumption of contaminated vegetation (Section 4.4.2.3.3), the HQ values for the collection or consumption of contaminated nectar are based on the oral NOEC of 0.014 mg/kg bw for sublethal effects (Thompson 1998) in which the corresponding LD_{50} value is about 6 times greater—i.e., an LD_{50} of 0.082 mg/kg bw. As also discussed in Section 4.4.2.3.3 and summarized in Table 13, other NOEC values for dinotefuran are higher than the NOEC reported by Thompson (1998). The highest reported sublethal oral NOEC for the honeybee is 0.005 µg/bee (Harnish 2000b). Using the bee body weight of 0.000093 kg, the NOEC of 0.005 µg/bee corresponds to a dose of about 0.054 mg/kg bw [0.005 µg/bee ÷ 0.000093 kg = 53.8 µg/kg bw = 0.053763 mg/kg bw], which is a factor of about 3.9 greater than the lowest NOEC of 0.014 mg/kg bw.

Because of the much lower risk quotients for foraging honeybees, relative to exposure scenarios for herbivorous insects, the variability in the toxicity data and the uncertainties in the exposure assessment require that the risk characterization be far more nuanced than that for other exposure scenarios. Based on worst-case assumptions, the upper bound risk quotients of 12-53 suggest the likelihood of adverse effects in honeybees. Based on a *best-case* exposure assessment—i.e., the lower bounds of the hazard quotients—the HQ values of 0.95-1.8 suggest only marginal concern for adverse effects in honeybees. Were the assumption made that field populations of honeybees might be better represented by the higher NOEC values for honeybees, the lower bound of the

HQ values could be decreased by a factor of about 3.9 resulting in lower bound HQs of about 0.2-0.5.

The central estimate of the HQ values for broadcast foliar application is 4. This HQ is associated with an exposure below the most sensitive LD_{50} value but above the most sensitive NOEC. In other words, mortality would be plausible but might not be pronounced. Using the upper bound of the available NOEC values, the adjusted HQ would be about 1—at, but not substantially above, the level of concern.

The field study by Landis (2009) may be used to evaluate the various HQ values that can be derived for bees. As discussed in Section 4.1.2.3.1.2, a field study was conducted involving the broadcast foliar application of dinotefuran to cotton at application rates up to 0.134 lb a.i./acre (Landis 2009). Landis International submitted an interim report for this study to the U.S. EPA and provided a 1-page summary of the report for use in the current Forest Service risk assessment. No adverse effects in bees are reported in the abstract of the interim report.

Working with an interim report is not desirable, particularly because it does not include information on the analyses of dinotefuran in honey, nectar, pollen, or other media. Given the uncertainties in the use of imidacloprid data emphasized throughout this risk assessment, the residue data that will be included in the final Landis report will be most useful in subsequent assessments of dinotefuran.

As stated above, working with an abstract of any report is less desirable than working with the full report. Nonetheless, the abstract from Landis (2009) is the only available source of information regarding the impact of dinotefuran on honeybees under field conditions. Given the uncertainties in the risk characterization based on the HQ method; some attempt to interpret the available information on this field study is clearly justified.

A preliminary and very limited analysis of the field study is given in Attachment 6. This attachment is an EXCEL workbook containing two worksheets that are similar to the G09 worksheet for foraging bees, which is included in Attachments 1b (i.e., two broadcast foliar applications with a 14-day application interval). The first worksheet, designated WS01, is identical to the G09 worksheet in Attachment 1b, except that the application rate is set to 0.134 lb a.i./acre, the application rate specified in the Landis (2009) abstract. The second worksheet, WS02, is identical to WS01, except that the toxicity value for the honeybee is based on the highest reported NOEC rather than the lowest reported NOEC. As discussed above, this higher NOEC is used to consider the possibility that the field population of honeybees used in the Landis (2009) study might be better represented by a less sensitive, rather than more sensitive, population of bees.

Based on the most sensitive toxicity values in WS01, the expected HQ values from the Landis field study are 3 (0.6-12). Based on the central and upper bound of these HQ values, some adverse effects in bees would be expected. Based on the lower bound of 0.6, no adverse effects would be expected. The lower bound of the HQ would reflect the lower bound of the exposure

assessment. Using the less sensitive toxicity values in WS02, the expected HQ values are 0.9 (0.2-3). Thus, assuming that the bee population used in the field study was modestly tolerant to dinotefuran—i.e., an NOEC of about 3.9 times greater than the most sensitive NOEC—the lack of effects reported in the Landis (2009) abstract would be expected.

A final complication in the interpretation of the HQ values for dinotefuran involves the available toxicity endpoints. As discussed in Section 4.3.2.3.1, the NOEC values used in the current risk assessment reflect the Forest Service preference for using NOEC rather than LD_{50} values. In addition, two types of NOECs are presented in the DERs for the bee studies—i.e., NOEC values for mortality and NOEC values for sublethal effects. Again following the general approach used in all Forest Service risk assessments, only the NOEC values for sublethal effects are used in this risk assessment.

While the sublethal NOEC values are the most sensitive endpoints available for dinotefuran, they are all based on acute, rather than chronic, exposures. Bee behavior is complex (e.g., Winston 1987), and it is reasonable to be concerned with effects on normal behavior that might not be noted in a routine acute toxicity study. This premise is essentially the same as that used by U.S. EPA to require specialized neurotoxicity assays in mammals (Section 3.1.6). These types of studies are not required in honeybees.

That concern for subchronic or chronic sublethal effects is somewhat reduced by the summary of the field study by Landis (2009). The abstract of this study indicates that effects on foraging were monitored for up to 22 days, effects on hive frame mass for up to 78 days, and effects on the number of capped broods for up to 198 days. Because a full copy of this interim study has not been made available for the current Forest Service risk assessment and because a review of this study is not available from the EPA, confidence in the use of this information is diminished.

The potential quantitative significance of chronic sublethal effects relative to acute sublethal effects can also be illustrated in the risk assessment of imidacloprid by Halm et al. (2006). The various toxicity values used in the imidacloprid risk assessment are specified in the dose-response assessment of risk assessment of imidacloprid (i.e., Halm et al. 2006, p. 2451, Table 2),. The NOEC for gross behavioral effects (knockdown) is expressed as 0.94 ng/bee. The LOEC for feeding dysfunction from longer-term field simulation studies is expressed as 0.075 ng/bee, which is about 13 lower than the acute NOEC for knockdown. No NOEC for feeding dysfunction is noted in the risk assessment (Halm et al. 2006). Whether this observation is applicable to dinotefuran is unknown.

The risk characterization for bees exposed to dinotefuran raises concern, both quantitatively and qualitatively, for potential adverse effects in honeybees. The qualitative risk characterization, however, is far less severe than the risk characterization for imidacloprid provided by Halm et al. (2006). Because much of the focus in the current Forest Service risk assessment involves considerations of the use of dinotefuran rather than imidacloprid, the risk characterization by Halm et al. (2006) is relevant.

In the qualitative risk characterization offered by Halm et al. (2006) for the consumption of nectar by foraging bees exposed to imidacloprid, the term *PEC/PNEC* is used. This term corresponds to the hazard quotient used in the current Forest Service risk assessment. The qualitative assessment by Halm et al. (2006) is as follows:

> *The PEC/PNEC derived from the calculation of honey bees' exposure to which appropriate assessment factors were applied show that the risk posed by imidacloprid is alarming for all categories of honey bees. ... These estimates are in agreement with observations made in regions of extensive sunflower and maize cultures, which report a decrease in honey production since the launching of imidacloprid on sunflower plants in 1994 (32), and several behavioral dysfunctions, foragers disappearances, and great honey bee mortalities in summer, during the blossoming of maize and sunflower plants, and after winter, when all sunflower and maize pollens have been consumed by colonies.*
>
> – Halm et al. 2006, p. 2451

This *alarming* risk characterization is justified by the HQ analysis by Halm et al. (2006), but does not consider the available field studies on imidacloprid. Notably, an imidacloprid concentration of 1.9 µg/kg in nectar is used in the risk assessment by Halm et al. (2006, p. 2450, under *Results*), which fails to address the chronic study by Schmuck et al. (2001) in which no effects on bee colonies were noted at concentrations of up 20 µg/kg, the study by Colin et al. (2004) in which effects on feeding behavior were noted in two of three hives at 6 µg/g, and the study by Faucon et al. (2005) in which no effects were noted at concentrations of up 5 µg/kg.

As noted in the Forest Service risk assessment for imidacloprid,

> *The repeated observation that imidacloprid-exposed insect populations rebound after initially observed increased mortality or reduced fecundity (Hewa-Kapuge et al. 2002; Kunkel et al. 2001; James 1997; Grafton-Cardwell and Gu 2003) deserves additional consideration. It calls into question the validity of using the results of short-term laboratory studies (LD_{50} studies, for example) to determine whether or not the use of imidacloprid under field conditions causes adverse effects on populations.*
>
> — SERA 2005a, Section 4.1.2.3.

In other words, risk characterizations based solely on the HQ approach are useful screening tools. A risk characterization, however, should consider all available and relevant data from field and field simulation studies, as these types of studies may afford a sounder basis for risk characterization.

For dinotefuran, the HQ values for honeybees could be interpreted as *alarming* if only the upper bound exposure estimates are considered with the results of the lowest available sublethal

NOEC. Risk quotients of up to 53 would be expected to result in substantial bee mortality. Considering the variability in plausible levels of exposure, the variability in reported NOEC values, and the one scant summary of a dinotefuran field study, the risk characterization is far less severe and suggests that the exposure of honeybees to dinotefuran would be in the range of or only slightly above plausible NOEC values. Until additional data are available on dinotefuran to permit a more detailed assessment and one that relies less heavily on surrogate chemicals, the risk characterization for the potential effects of dinotefuran on honeybees cannot be further refined.

4.4.2.3.5. Contaminated Surfaces

A quantitative risk characterization is not developed for contact exposure of insects to dinotefuran contaminated surfaces. As discussed in Section 4.3.2.3.3, available contact-exposure studies investigate the effects of honeybee contact with contaminated vegetation and the contact of other insect species with contaminated glass surfaces. These studies clearly indicate that contact exposure to surfaces contaminated by dinotefuran can cause sublethal adverse effects and even mortality; however, the nature of the exposures is not directly comparable to anticipated field exposures. For example, decreased fecundity in *Orius laevigatus* is reported in glass surface exposures to dinotefuran, and the NOEC for this endpoint is a surface application rate of is 0.0000012 lb a.i./acre (Aldershof 2000c). While a hazard quotient could be developed using the broadcast foliar application rate of 0.2 lb a.i./acre, this would have little relevance to assessing the contribution of risks from contact with dinotefuran on surfaces like bark, leaves, or rocks. While contact with a surface contaminated with dinotefuran may augment risks associated with other routes of exposure (e.g., direct spray or the consumption of vegetation) the hazard quotients associated with these other routes of exposure are very high. It seems unlikely that the quantitative consideration of exposures associated with contaminated surfaces would have an impact on the overall risk characterization.

4.4.2.3.6. Contaminated Soil

Notwithstanding available means of estimating soil concentrations of dinotefuran, a risk characterization for soil invertebrates is not developed, due to the lack of available toxicity data. As detailed in the Forest Service risk assessment on imidacloprid (SERA 2005a), earthworm toxicity data are available for imidacloprid. Like dinotefuran, imidacloprid may also be applied by soil injection or soil drench. The risk characterization for imidacloprid suggests that transient adverse effects in earthworm populations are plausible. This may or may not be the case with dinotefuran. Toxicity studies involving the exposure of earthworms or other soil dwelling invertebrates to dinotefuran are needed to assess risk. As the open literature on dinotefuran develops, such studies will probably be conducted. Given available toxicity data in insects, soil applications of dinotefuran would probably be associated with adverse effects in ants and burrowing soil insects.

4.4.2.3.7. Duration of Potential Adverse Effects

A final consideration in the risk characterization for dinotefuran involves the duration over which treated vegetation might be toxic to foraging insects. Because the hazard quotient is directly related to the concentration on vegetation, the hazard quotient ($\boldsymbol{HQ_t}$) at any time ($\boldsymbol{t}$) after

application can be calculated from the hazard quotient immediately after application (***HQ₀***) and the first-order dissipation rate (***k*** in units of days^{-1}) on vegetation:

$$HQ_t = HQ_0 \times e^{-k\,t}$$

The above equation can be simply rearranged to solve for ***t***:

$$t = -\frac{\ln(HQ_t \div HQ_0)}{k}$$

In order to calculate the time required for HQ_t to reach 1 (the level of concern), the above equation can be further simplified to:

$$t = -\frac{\ln(1 \div HQ_0)}{k}$$

Notably, all of the HQ values given in Table 20 are based on residue rates immediately after application—i.e., these can be viewed as ***HQ₀*** values. As discussed in Section 4.2.2.2.1, the foliar half lives of dinotefuran are about 6 (0.36-12) days, based on the dinotefuran studies conducted by Hattermann (2002a,b). These half lives (t_{50} values) correspond to dissipation/degradation coefficients (*k*) of about 0.12 (0.058-1.9) days^{-1}—i.e., $k = \ln(2)/t_{50}$.

Any of the above dissipation/degradation coefficients for dinotefuran could be used with the HQ values in Table 20 to calculate the time required for the HQ values to reach 1. For example, the central estimate of the HQ for broadleaf vegetation is about 836. Taking the central estimate of the dissipation/degradation coefficient, 0.12 days^{-1}, the time to an HQ of 1 is about 56 days [$-\ln(1/836) \div 0.12$ days$^{-1} \approx 56.072$ days].

Based on the residue contact bioassay of dinotefuran toxicity to bees (Hummel 2001), the EPA states that: *dinotefuran applied at a 0.15 lb ai/A will remain toxic to bees for more than 38 hours* (U.S. EPA/OPP 2006b, p. 4). Within the context of the Hummel (2001) study, this statement is correct for honeybees. In the Hummel (2001) study, however, the honeybees were exposed only to residues on leaves. As noted in the DER for this study:

> *The majority of bees in the control (85%) were observed congregating near the top of the test chamber with approximately 15% observed crawling on the foliage* [8-hour residues].

In other words, at least some groups of bees tended to avoid contact with the vegetation and may have been able to do so. In addition, the honeybees were exposed only to contaminated leaves. While some bees may cut leaves, and honeybees may cut through parts of flowers to get to nectar, honeybees will not consume the leaves. The honeybees in the study by Hummel (2001) had *ad libitum* access to a 50% sucrose solution as a food source. Finally, it seems plausible that the dinotefuran was absorbed into plant tissue relatively rapidly, thus decreasing the residue

available for contact with the bees. Because of these factors, it is likely that risks associated with direct contact of dinotefuran contaminated vegetation will diminish rapidly.

These observations from the vegetation residue contact toxicity study by Hummel (2001) do not impact the assessment of risk to herbivorous insects—insects for which the primary route of exposure to dinotefuran involves the consumption of contaminated vegetation. For these insects, it seems likely that dinotefuran residues in vegetation could remain toxic for several months after aerial foliar broadcast applications. While this slow rate of dissipation enhances the efficacy of dinotefuran, it also increases potential risks to nontarget phytophagous insects.

The above discussion of dissipation from vegetation applies only to aerial foliar broadcast applications of dinotefuran. For this type of application, the use of foliar half life data to estimate the duration of potential adverse effects seems reasonable. For other application methods (e.g., soil injection, tree injection, soil broadcast, and bark application) the kinetics involved in the uptake of dinotefuran and subsequent translocation to and dissipation from leaves are more complex than those associated with foliar broadcast application; moreover, these kinetics are not well characterized. It seems plausible that the duration of toxicity to nontarget insects from any effective application of dinotefuran may be substantial; however, the duration of toxicity after applications other than foliar broadcast cannot be quantified at this time.

4.4.2.4. Terrestrial Plants

Hazard quotients for terrestrial plants are given in the EXCEL workbooks that accompany this risk assessment—i.e., Worksheets G04 (runoff), G05 (drift), and G06 (erosion of contaminated soil by wind). The highest HQ value is 0.4 (i.e., the direct foliar spray of a plant at an application rate of 0.2 lb a.i./acre). This HQ value, however, is based on a free-standing NOAEL in plants. In other words, the toxicity studies in plants are limited to a single exposure at the maximum labeled application rate of 0.54 lb a.i./acre. Thus, if foliar broadcast applications of 0.54 lb a.i./acre were allowed, the HQ would be 1.

Typically, an HQ of 1 would be associated with an exposure that *reaches but does not exceed the level of concern*. This would not be the case for dinotefuran or any HQ that is based on a free standing NOEC. Because the LOEC has not been defined, there is no indication that exposures above the NOEC are likely to cause an adverse effect.

4.4.3. Aquatic Organisms

4.4.3.1. Fish

The risk characterization for fish and other aquatic organisms is summarized in Worksheets G03 of the EXCEL workbooks that accompany this risk assessment—i.e., Attachments 1a,b through 5. Copies of these GO3 worksheets are compiled in Appendix 12 of this risk assessment to facilitate a discussion of the HQ values for fish and other aquatic organisms.

While there are concerns with the quality of the chronic toxicity value for fish as well as the limited number of bioassays on fish (Section 4.3.3.1), there is no basis for asserting that fish are

likely to be adversely affected by dinotefuran at the maximum application rate used in any of the application methods considered in this risk assessment. The highest HQ values are 0.6 for the accidental spill (soil injection), 0.01 for expected peak concentrations (broadcast foliar), and 0.0004 for expected longer-term concentrations (broadcast soil and soil injection).

The accidental spill scenario is extremely severe and arbitrary. As with the use of this scenario in the human health risk assessment, the accidental spill scenario is included in all Forest Service risk assessments simply to indicate the possible consequences of a serious accident.

The highest upper bound HQ values for expected concentrations are below the level of concern by factors of 100 for peak exposures and 2500 for longer-term exposures. As discussed in Section 4.3.3.1, the study that provides the chronic toxicity value for fish is classified by the EPA as *invalid*. Typically, an invalid study is not and should not be used in a risk assessment. As detailed further in Section 4.1.3.1, however, the reason for the EPA classification is the uncertainties associated with the actual test concentrations and the failure of the study to define an adverse effect level. Given that peak environmental exposure estimates are a factor of 2500 below the nominal test concentration, the uncertainties in the precise test concentration and the uncertainties concerning the lack of an adverse effect level do not seem sufficient to justify disregarding the chronic fish study and declining to provide a risk characterization for fish.

Failing to provide a risk characterization for longer-term effects in fish would leave a misleading sense of uncertainty that plausible levels of longer-term exposure might pose a hazard. For fish, the uncertainties seem minimal. Notwithstanding this assertion, the toxicity data on fish are meager. While no plausible hazards to fish can be identified based on the available data, confidence in this risk characterization would be enhanced if better data were available on a larger number of fish species. While worth articulating, this limitation applies to virtually all new pesticides and is not specific to dinotefuran.

4.4.3.3. Aquatic Invertebrates

As with the risk characterization for fish, the detailed HQ values for aquatic invertebrates are detailed in Appendix 12 of this risk assessment as well as in the G03 worksheets of Attachments 1a,b through 5. Also as with fish, the non-accidental exposure scenarios are below the level of concern. Unlike the case with fish, however, separate toxicity values are derived for tolerant and sensitive species of aquatic invertebrates, and the toxicity values for sensitive species (based on mysids) are substantially below the toxicity values for tolerant species (based on daphnids).

Notwithstanding the sensitivity of mysids to dinotefuran, upper bounds of the HQ values associated with the non-accidental exposure scenarios for sensitive species of aquatic invertebrates are all below the level of concern. For acute exposures, the HQ values range from 0.02 (bark applications) to 0.2 (broadcast granular and soil injection), below the level of concern by factors from 5 to 50. For longer-term exposures, the HQ values range from 0.007 (bark application) to 0.07 (soil injection), below the level of concern by factors from about 14 to 140.

As discussed in the dose-response assessment for aquatic invertebrates (Section 4.3.3.3), the longer-term NOEC for sensitive species of aquatic invertebrates is estimated using the relative potency method based on the acute NOEC values in mysids and daphnids, which indicates that mysids may be more sensitive than daphnids to dinotefuran by a factor of about 1960. For imidacloprid, however, chronic studies in both daphnids and mysids are available and indicate that mysids are more sensitive than daphnids to imidacloprid by a factor of about 11,000. Based on the imidacloprid data, a case could be made to reduce the chronic toxicity value for dinotefuran in sensitive species by a factor of about 6 [11,000 ÷ 1,960 ≈ 5.6]. While data on imidacloprid is used extensively in the current risk assessment on dinotefuran, it is only used in the absence of data on dinotefuran. Because the acute toxicity data on dinotefuran are sufficient for the application of the relative potency method, the more conservative approach based on imidacloprid is not used. Given that the chronic HQ values for sensitive species of aquatic invertebrates are below the level of concern by factors from 14 to 140, the use of the more conservative approach based on imidacloprid would not alter the conclusion that longer-term exposures to dinotefuran are below the level of concern for sensitive species of aquatic invertebrates.

For sensitive species of aquatic invertebrates, accidental spill scenarios approach a level of concern for foliar broadcast applications (HQ=0.7) and exceed the level of concern for all other application methods. The higher HQ values associated with granular broadcast, bark application, and soil injection are all due to the assumptions concerning the amount of material that is spilled and/or the concentration of the dinotefuran in the field solution. As noted in Section 4.3.3.3, the NOEC value for mysids is very close to the LC_{50} value for mysids. Thus, the high HQ values—i.e., upper bounds from 42 to 125—for granular broadcast, bark application, and soil injection suggest that the spill of a large amount of dinotefuran into a relatively small pond could be associated with substantial mortality in sensitive species of aquatic invertebrates.

The lack of toxicity data on any species of aquatic insect is a major reservation in the relatively benign risk characterization for aquatic invertebrates. While mysids are extremely sensitive to dinotefuran and other neonicotinoids, confidence in the risk characterization for aquatic invertebrates would be greatly enhanced if toxicity studies as well as field studies were available on the effects of dinotefuran on aquatic insects. Concern for aquatic insects is enhanced by the well-documented effects of imidacloprid on aquatic insects. As noted in the Forest Service risk assessment on imidacloprid (SERA 2005a), midges appear to be nearly as sensitive as mysid shrimp to imidacloprid. As noted more recently by Kreutzweiser et al. (2008a,b), stonefly and crane fly larvae also appear to be sensitive to imidacloprid.

4.4.3.4. Aquatic Plants

The risk characterization for aquatic plants is similar to that of terrestrial plants—i.e., all HQ values are below the level of concern. Also as with terrestrial plants, the NOEC for aquatic macrophytes is free standing—i.e., the NOEC is 100 mg/L, and no LOEC has been identified. For algae, the NOEC is somewhat lower, 25 mg/L, and the LOEC is 50 mg/L. These values are based on only a single study in *Lemna* (aquatic macrophyte) and a single study in *Pseudokirchneriella* (alga).

For non-accidental exposures, the upper bounds of HQ values range from 0.0001 (longer term exposures for macrophytes after bark applications) to 0.005 (algae based on expected peak concentrations associated with granular broadcast applications). These HQ values are below the level of concern by factors from 200 to 10,000.

The only reservation with this risk characterization for aquatic plants is that the toxicity values are based on only a single species of alga and a single species of aquatic macrophyte. While this reservation is acknowledged, it is not serious. As noted in Section 4.1.2.5, the studies by Porch et al. (2001a,b) involved tests with 10 species of terrestrial plants with no adverse effects on seedling emergence or vegetative vigor. The studies on terrestrial plants do not completely alleviate concern for the potential existence of sensitive species of aquatic plants. Nonetheless, the available studies in aquatic plants combined with the studies in terrestrial plants and information on the mechanism of action of dinotefuran do not provide a basis for serious concern for the potential effect of dinotefuran on algae or aquatic macrophytes.

5. REFERENCES

NOTE: The initial entry for each reference in braces {} simply specifies how the reference will be cited in the text. The final entry for each reference in brackets [] indicates the source for identifying the reference.

SET00	**Preliminary publications identified prior to formal literature search.**
SET01	**Initial TOXLINE Screen.**
SET02	**Tree search of Set 01.**
IMID	**References included in the imidacloprid risk assessment.**
Std-	**Standard references used in most Forest Service risk assessments.**
FOIA01	**The initial Freedom of Information Act (FOIA) request to the U.S. EPA.**
MRID01	**The initial request to Landis for DERs of studies submitted to the U.S. EPA/OPP in support of the registration of dinotefuran.**
MRID02	**The supplemental request to Landis for DERs of studies submitted to the U.S. EPA/OPP in support of the registration of dinotefuran.**
Landis	**Other studies and documents provided by Landis International.**
Com01	**Comments from reviewers on preliminary program description.**
Bees	**Supplemental references relating to honeybees or other nontarget invertebrates.**
Sundry	**Reports/publications/other information obtained from review comments and personal communications.**

Note: Some files contain DERs on the peer review CD contain more than one MRID. These are noted in the following reference list in blue Courier font.

{Abou-Donia et al. 2008} Abou-Donia MB; Goldstein LB; Bullman S; Tu T; Khan WA; Dechkovskaia AM; Abdel-Rahman AA. 2008. Imidacloprid Induces Neurobehavioral Deficits and Increases Expression of Glial Fibrillary Acidic Protein in the Motor Cortex and Hippocampus in Offspring Rats Following in Utero Exposure. J Toxicol Environ Health A. 71(2):119-30. [Set 01 - Neonic01]

{AgBio 2008} AgBio. 2008. Technical Data Sheet on Pentra-Bark. Available at: http://www.agbio-inc.com/page4/page23/page17/page17.html. [Internet]

{Aldershof 2000a} Aldershof S. 2000a. A Laboratory Dose-Response Study to Evaluate the Effects of MTI-446 20% SG on Survival and Reproduction of the Predaceous Mite *Typhlodromus pyri* Scheuten (Acari:Phytoseiidae): Lab Project Number: RCC011TPL: 756268. Unpublished study prepared by MITOX Stichting Bevordering Duurzame Plaagbestrijding. 27 p. MRID No. 45640120. [MRID01]

{Aldershof 2000b} Aldershof S. 2000b. A Laboratory Dose-Response Study to Evaluate the Effects of MTI-446 20% SG on Survival and Reproduction of the Parasitoid Wasp *Aphidius rhopalosiphi* (DeStephani-Perez) (Hymenoptera: Braconidae): Lab Project Number: RCC012ARL: 756270. Unpublished study prepared by MITOX Stichting Bevordering Duurzame Plaagbestrijding. 24 p. MRID No. 45640121. [MRID01]

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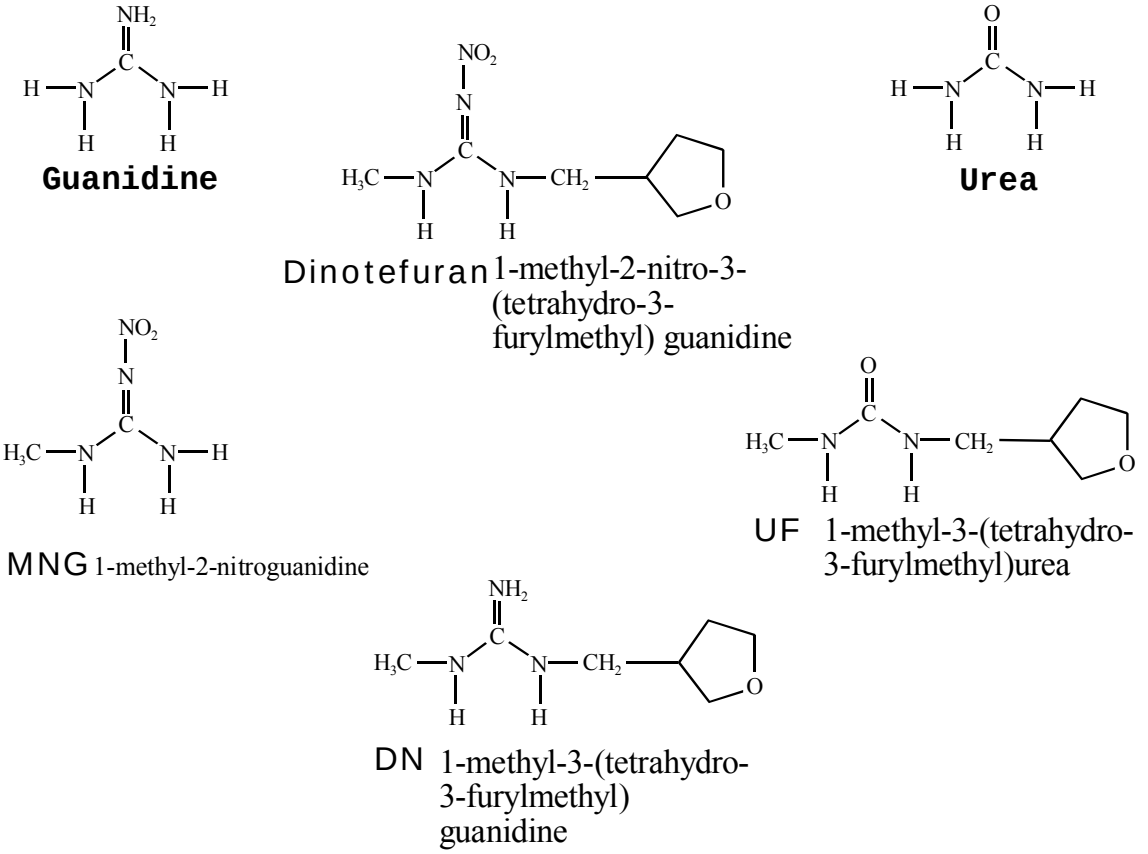


Figure 1: Chemical Structure of Dinotefuran and Selected Metabolites

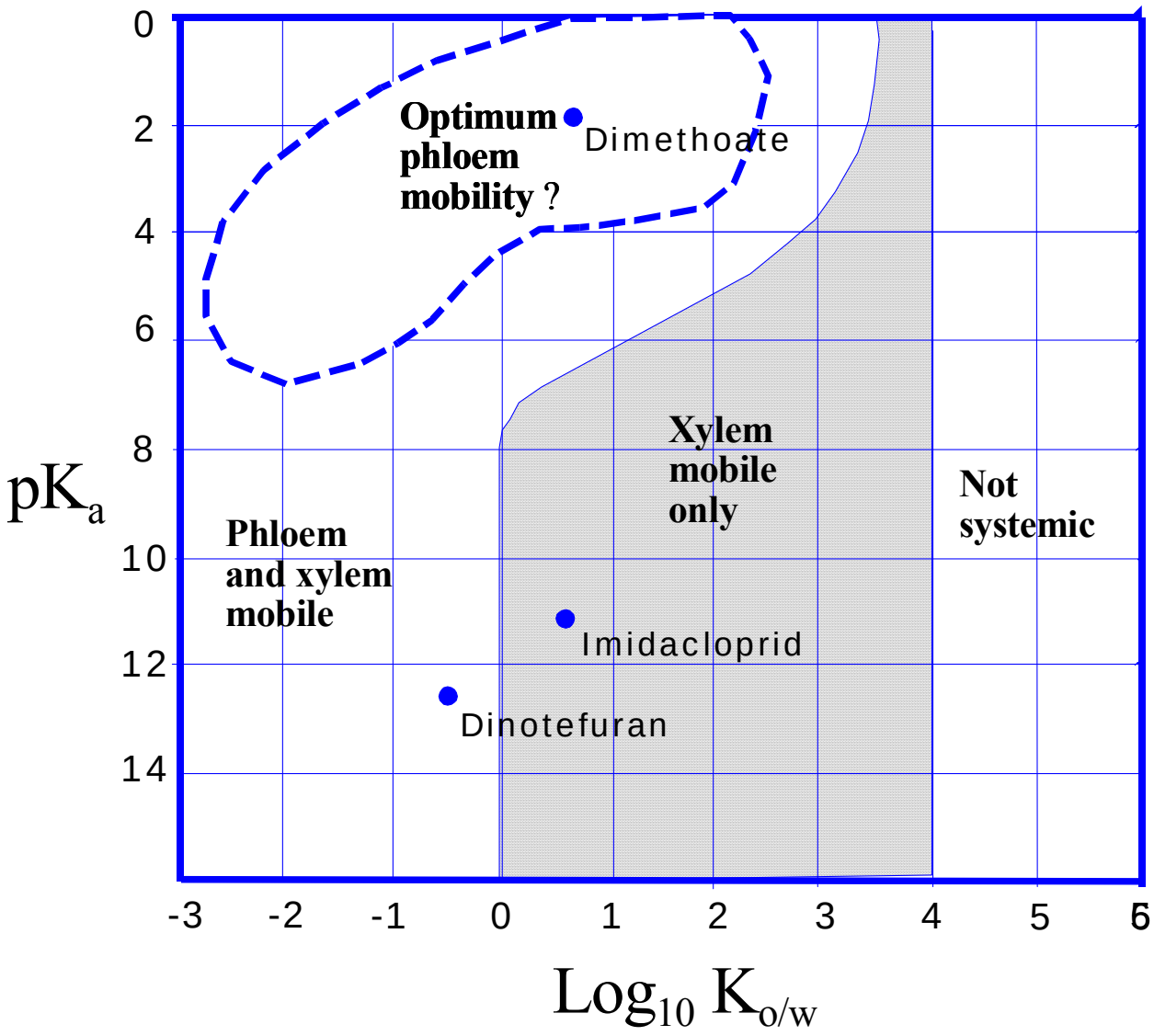


Figure 2: Physiochemical properties for weak acids for translocation

(Figure 2 is redrawn from Bromilow et al. 1990, Figure 5, p. 313 and modified to illustrate the data on dinotefuran, imidacloprid, and dimethoate)

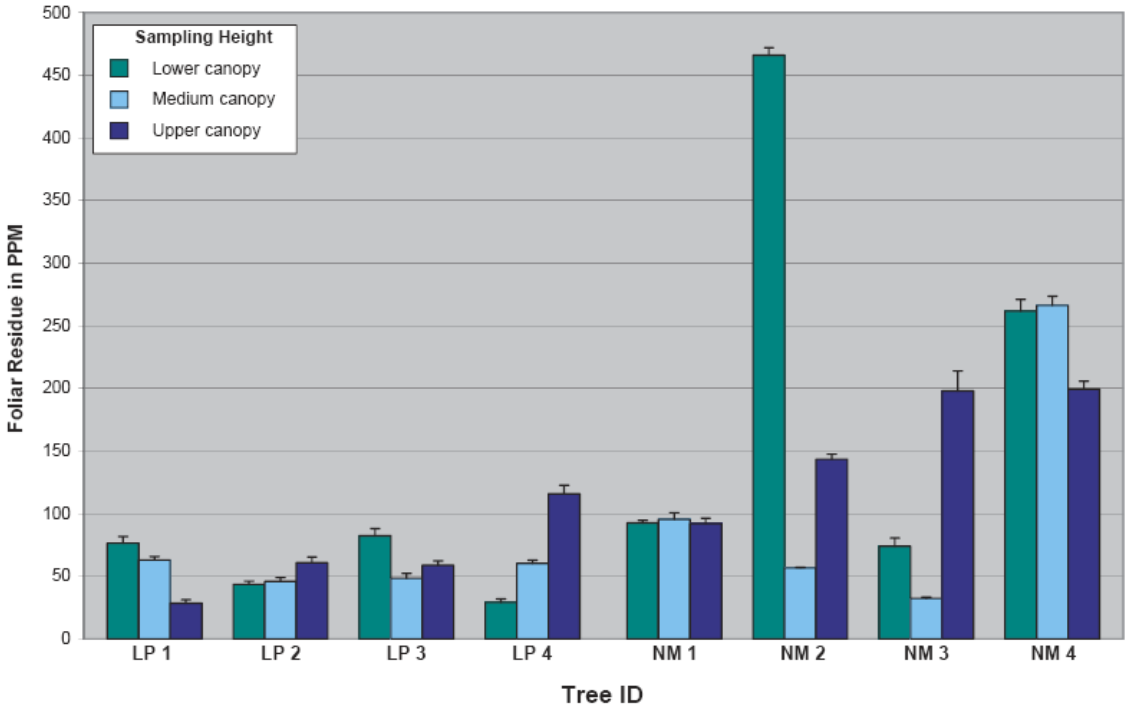


Figure 3: Imidacloprid concentrations in leaves after tree injection

The above figure is Figure 1 in Lewis and Molongoski (2006)

Table 1: Physical and chemical properties of Dinotefuan

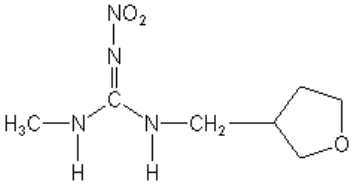
Property	Value [a]	Reference
Nomenclature		
Common Name	Dinotefuran	Tomlin 2004
IUPAC Name	(RS)-1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine	Tomlin 2004
CAS Name	N-methyl-N'-nitro-N"-[(tetrahydro-3-furanyl)methyl]guanidine	Tomlin 2004
Development Code	MTI-446 (Mitsui)[b]	Tomlin 2004
CAS number	165252-70-0	Tomlin 2004
Structure		
Air, photolysis	0.067 days (12/12 hour cycle)	van der Gaauw 2000
Bioconcentration	3.162 (QSAR)	Meylan and Howard 2007
Bulk density	1.4 g/mL	Landis 2002a
Density	1.33	Tomlin 2004
Foliar half-lives [all based on DFR]	Ornamentals: 1.77 days (GA), 7.86 days (PA), 37.7 days (CA)	Hattermann 2002a
	Turf: 1.36 days (CA), 0.76 days (PA), 1.51 days (GA).	Hattermann 2002b
	Leafy vegetables: 1.6 days (CA), 0.7 days (FL) and 0.7 days (PA)	Hummel 2002a
Henry's law constant	3.29 x 10^{-14} atm-m3/mole (QSAR) 1.35 x 10^{-12} unitless (QSAR)	Howard and Meylan 2007
	8.63 x 10^{-14} atm-m3/mole	U.S. EPA/OPP 2004a
Kd	0.60 clay loam; 0.38 loam; 1.12 clay; 0.38 loamy sand	Ishii 2000c
	0.119 loamy sand; 0.215 silt loam; 1.009 loam; 0.714 sandy loam; 1.221 clay loam	Volkel 2001b
K_{oc}	63.62	Howard and Meylan 2007
	6 to 45	U.S. EPA/OPP 2004a
	23.3 clay loam; 31.4 loam; 33.6 clay; 25.3 loamy sand	Ishii 2000c
	66 loamy sand; 178 silt loam; 397 loam; 213 sandy loam; and 299 clay loam.	Volkel 2001b
log K_{ow}	-0.644 (pH 7) [Kow = 0.23]	Tomlin 2004
	-0.549 (at 25°C) [Kow = 0.283]	Landis 2002a; U.S. EPA/OPP 2004a
	-0.64 [Kow = 0.23]	Tomizawa and Casida 2005
	-0.19 (QSAR)	Meylan and Howard 2007
Melting point	94.5-101.5 °C	Tomlin 2004

Table 1: Physical and chemical properties of Dinotefuan

Property	Value [a]	Reference
	107.5°C	Landis 2002a; U.S. EPA/OPP 2004a
Molecular formula	$C_7H_{14}N_4O_3$	Tomlin 2004
Molecular weight (g/mole)	202.2	Tomlin 2004
pKa	12.6	Landis 2002a
Sediment-Water halftimes	337.5 days (QSAR)	Howard and Meylan 2007
SMILES Notation	`CNC(=N[N+](=O)[O-])NCC1CCOC1`	Tomlin 2004
Soil field dissipation halftimes	65.4 days (CA); 19.4 days (GA); 55.9 days (NY)	Hummel 2003a
Soil halftimes (aerobic)	Mean: 81.5 days Upper 90th percentile: 138.4 days	U.S. EPA/OPP 2004a
	Several soil types: 17 to 89 days	Lentz 2001a
	Loamy sand: 63 to 100 days	Lentz 2001b
Soil photolysis	Insubstantial 46.2 days [irradiated] 37.3 days [dark control]	Shah and Hatzenbeler 2001
U.S. EPA Docket Number	NONE	
Vapor pressure	<1.7 x 10^{-6} Pa at 25°C <1.27 x 10^{-8} mm Hg	U.S. EPA/OPP 2004a
Water halftime (NOS)	37.5 days (QSAR)	Howard and Meylan 2007
Water halftime, river	Water: 73.2 days Sediment (aerobic): 108.5 days Composite: 79.3 days	Volkel 2000
Water halftime, pond	Water: 52.6 days Sediment (aerobic): 131.2 days Composite: 76 days	Volkel 2000
Water/sediment halftime	Water: 51 days Sediment (anaerobic): 62 days Composite: 65 days	Volkl 2003
Water hydrolysis halftime	Stable at ambient temperature. Half-life of 165 days at pH 9 and 40° C.	Ishii 2000a
	pH 4: 7,702 hours [320 days] pH 7: 3,466 hours [144 days] pH 9: 1,155 hours [48 days]	Sydney 1998
Water, aerobic aquatic metabolism	80.8 days	U.S. EPA/OPP 2004a
Water photolysis halftime	1.8 days (12/12 hour cycle)	van der Gaauw 2002
	0.097 to 0.104 days (experimental)	Ishii 2000b
Water solubility (mg/L)	39,800 mg/L	Tomlin 2004
	39,830 mg/L	Landis 2002a; U.S. EPA/OPP 2004a
	54,300 mg/L	Tomizawa and Casida 2005
	61,400 mg/L (QSAR)	Meylan and Howard 2007

[a] See Table 4 in this risk assessment for properties of MNG. See Tables 13 and 14 in U.S. EPA/OPP (2004a) for environmental fate parameters for other metabolites of dinotefuran.

[b] Discovered by Mitsui Chemicals Inc. (www.mitsui.co.jp/) and registered in Japan in 2002 (Tomlin 2004)

Table 2: Commercial End-Use Formulations of Dinotefuran

Formulation/Producer/ Type of formulation [a]	Application Rates	Labeled Application Methods
Safari 2 G/ Valent/ Granules/2% a.i.	Cum. Max. Annual: 0.54 lb a.i./acre. 2 to 4 oz (avoirdupois) of formulation per inch DBH.	Broadcast soil, within 18 inches of trunk, optionally followed by irrigation.
Safari 20 SG/ Valent/ Granules/20% a.i.	Cum. Max. Annual: 0.54 lb a.i./acre. Single foliar application rates of 0.1 to 0.2 lb a.i./acre at a dilution of 0.05 to 0.1 lb a.i./100 gallons. Second application after 14 to 21 days.	Aerial or ground broadcast foliar or directed foliar. Soil drench or soil injection methods may also used.
	Cum. Max. Annual: 0.54 lb a.i./acre. 3 – 12 grams formulation (0.6 – 2.4 g a.i.) per inch DBH. Applied in volume of about 1 fl oz/inch DBH (about 29.6 mL/inch DBH)[b].	Soil injection
	Cum. Max. Annual: 0.54 lb a.i./acre. 3 – 12 grams formulation (0.6 – 2.4 g a.i.) per inch DBH. Applied as a solution at a rate of 2 to 3 fl oz per inch DBH.	Trunk spray/Bark application for HWA [See Sections 2.3.3 and 2.4.3 for details.]

[a] Both formulations are labeled for adelgids as well as flatheaded and roundheaded borers. All information taken from product labels unless otherwise specified.
[b] Information on application volumes from Chamberlain (2009).

Table 3: Inerts Contained in End-use Formulations of Dinotefuran Based on MSDSs

Formulation (% of formulation classified as inerts) [a]	Inerts: Name, CAS No.	Inert % by Weight
Safari 2G (98%)	Hydrated amorphous silica (7631-86-9)	<1%
	Wood or particle board flour (9004-34-6)	Unknown
	Other (NOS, proprietary) [b]	98%
Safari 20 SG (80%)	Particulates not otherwise classified (No CAS No.) [b]	80%

[a] Information from Material Safety Data Sheets.
[b] Cautionary Language on MSDS: *Some of these* (ingredients) *may be hazardous, but their identity is withheld because they are considered trade secrets*.

Table 4: Summary of Exposure Scenarios for the HHRA

Scenario	Person	Application Method: 1a and 1b Broadcast Foliar	2 Broadcast Soil	3 Bark	4 Soil Injection	5 Tree Injection	Worksheet
Workers							
General Exposure	Worker	■	■	■	■	■	C01
Accidental Exposures							
Contaminated gloves, 1 minute	Worker	■	■	■	■	■	C02a
Contaminated gloves, 1 hour	Worker	■	■	■	■	■	C02b
Spill, hands, 1 hour	Worker	■		■	■	■	C03a
Spill, lower legs, 1 hour	Worker	■		■	■	■	C03b
General Public							
Accidental Acute Exposures							
Direct Spray of Child, whole body	Child	■		■			D01a
Direct Spray of Woman, feet and lower legs	Female	■		■			D01b
Water consumption (spill)	Child	■	■	■	■		D05
Fish consumption (spill)	Male	■	■	■	■		D08a
Fish consumption (spill)	SP	■	■	■	■		D08b
Non-Accidental Acute Exposures							
Vegetation Contact, shorts and T-shirt	Female	■		■			D02
Contaminated Fruit	Female	■	■				D03a
Contaminated Vegetation	Female	■	■				D03b
Swimming, one hour	Female	■	■	■	■		D11
Water consumption	Child	■	■	■	■		D06
Fish consumption	Male	■	■	■	■		D09c
Fish consumption	SP	■	■	■	■		D09d
Chronic/Longer Term Exposures							
Contaminated Fruit	Female	■	■				D04a
Contaminated Vegetation	Female	■	■				D04b
Water consumption	Male	■	■	■	■		D07
Fish consumption	Male	■	■	■	■		D09a
Fish consumption	SP	■	■	■	■		D09b

SP: Subsistence Populations

Table 5: Summary of Modeled Concentrations in Surface Water

Scenario	Peak	Long-Term Average
MODELING FOR THIS RISK ASSESSMENT (1 lb a.i./acre)		
Direct Spray and Spray Drift		
Pond, Direct Spray (Section 3.2.3.4.2) [a]	112 ppb	N/A
Pond, drift at 25 feet (Section 3.2.3.4.2) [a]	25.0 ppm	N/A
Stream, Direct Spray (Section 3.2.3.4.2) [a]	91.4 ppb	N/A
Stream, drift at 25 feet (Section 3.2.3.4.2) [a]	20.4 ppb	N/A
Gleams-Driver		
Broadcast Foliar, Single Application		
Pond, Section 3.2.3.4.4	26 (0.0115 - 157) ppb	8.24 (0.003 - 49) ppb
Stream, Section 3.2.3.4.4	24.9 (0.0135 – 126) ppb	0.83 (0.00015 - 6.1) ppb
Broadcast Foliar, Two Applications at 14-day Interval		
Pond, Section 3.2.3.4.4	43.9 (0.05 - 314) ppb	12.7 (0.0004 - 96) ppb
Stream, Section 3.2.3.4.4	38.7 (0.05 - 134) ppb	1.57 (0.0004 - 10.9) ppb
Broadcast Ground, Single Application		
Pond, Section 3.2.3.4.4	34.7 (0.03 - 208) ppb	11 (0.0045 - 65) ppb
Stream, Section 3.2.3.4.4	35.8 (0.02 - 201) ppb	1.11 (0.00025 – 8) ppb
Soil Injection		
Pond, Section 3.2.3.4.4	28.8 (0.025 - 207) ppb	10.4 (0.0025 - 65) ppb
Stream, Section 3.2.3.4.4	16.6 (0.02 - 102) ppb	1.05 (0.00025 - 8.1) ppb
PRZM-EXAMS		
Pond, Section 3.2.3.4.4 [d]	5.29 (2.80 – 20.6) ppb	2.21 (0.06 – 9.84) ppb
Index Reservoir, Section [d] 3.2.3.4.4	10.1 (5.70 – 42.3) ppb	3.52 (0.12 – 16.9) ppb
Other Modeling		
U.S. EPA		
GENEEC [b]	53 to 96 ppb	N.S.
FIRST (Reservoir model) [c]	89.3 ppb	14.8 ppb
SCIGROW (Ground water) [c]	5.10 ppm	N/A

[a] Section 3.2.3.4.2 discusses expected concentrations in terms of the nominal application rate of 1 lb a.i./acre. The values for direct spray and drift are taken from Worksheet 10a (direct spray and drift as 25 feet for a pond) and Worksheet 10b (direct spray and drift as 25 feet for a stream) adjusted to WRC values based on the application rate of 0.75 lbs/acre.

[b] U.S. EPA/OPP 2006b, Table 1, pp. 3-4. Values adjusted to WCR values by dividing the modeled concentration by the maximum seasonal application rate used in the modeling.

[c] U.S. EPA/OPP 2004g, Table 1. Adjusted to WCR values by dividing by the modeled application rate of 0.54 lb a.i./acre.

[d] PRZM-EXAMS Express run with Oregon Christmas Tree scenario using values for loam soil. Values given as average (lower to upper) in 20 year simulation.

Table 6: General Site Conditions used in Gleams-Driver runs

Field Characteristics	Description		
Type of site	Mixed pine-hardwood		
Treated and total field areas	10 acres		
Field width	660 feet		
Slope	0.1		
Depth of root zone	60 inches		
Cover factor	0.15		
Type of clay	Mixed		
Surface cover	No surface depressions		
Pond Characteristics	**Description**		
Surface area	1 acre		
Drainage area:	10 acres		
Initial Depth	2 meters		
Minimum Depth	1 meter		
Maximum Depth	3 meters		
Sediment Depth	2 centimeters		
Stream Characteristics	**Description**		
Width	2 meters		
Flow Velocity	6900 meters/day		
Flow Rate	710,000 liters/day		
Soil Specific Factors [a]	**Clay**	**Loam**	**Sand**
Runoff potential	High	Moderate	Low
Surface type	Road	Woods	Meadow
Surface condition	Hard surface	Fair	Dirt

[a] Detailed input values for the soil types are given in SERA (2007b, Tables 2 and 3) .

Table 7: Chemical and site parameters used in GLEAMS modeling for dinotefuran

Parameter	Clay	Loam	Sand	Note/ Reference
Halftimes (days)				
Aquatic Sediment		131.2		Note 1
Foliar		11.6		Note 2
Soil		138.4		Note 3
Water		82.59		Note 4
Soil $K_{o/c}$, mL/g	33.6	31.4	21.3	Note 5
Sediment K_d, mL/g	1.12	0.38	0.714	Note 5
Water Solubility, mg/L		39,830		Note 6
Foliar wash-off fraction		0.5		Note 7
Fraction applied to foliage	Foliar: 0.5 0			Note 8
	Granular broadcast: 0.01			
	Soil Drench : 0.01			
	Soil injection: 0.01			
Depth of Soil Injection	Soil injection: 5 cm (2 inches)			Section 2.3.1.
	All others: 1 cm			
Irrigation after application	Soil Drench: 1.3 cm (0.5 inch)			Section 2.3.1.
	All Others: none			

Note 1 Based on the highest aerobic sediment half life reported by Volkel (2000). – i.e., 108.5 days for a small pond. [Consider increasing by a factor (3) for anaerobic sediment.]

Note 2 90% upper bound value from the half lives reported by Hattermann 2002a,b and Hummel 2002a. See Table 2 for listing.

Note 3 This is the 90th percentile for aerobic metabolism and is the value used by U.S. EPA/OPP 2004a.

Note 4 This is the composite values for aerobic aquatic metabolism and photolysis used by U.S. EPA/OPP (2004g, Table 3a, P. 95) in FIRST modeling. It is based on half time of 82.7 days (k=0.0083814654 days^{-1}) for aquatic metabolism and the assumption that dinotefuran is stable to photolysis – i.e., an assumed photolysis half life of 500 days corresponding to an effective field photolysis halftime of 62,000 days (k=0.000011179 days^{-1}).

Note 5 Values for clay and loam from Ishii 2000c. Value for sand taken as the lowest value, sandy loam, reported in Volkel 2001b. This latter value is used in all EPA modeling.

Note 6 Water solubility taken from Landis 2002a and this is the value used by U.S. EPA/OPP 2004a. Tomizawa and Casida report a somewhat higher value of 54,300 mg/L.

Note 7 No data available. As in the risk assessment on imidacloprid (SERA 2005), a default value of 0.5 is used.

Note 8 A value of 0.5 used for foliar as a default. For granular applications (broadcast or drench) and soil injection, foliar application will be negligible. See Section 2 for details.

Table 8: Precipitation, Temperature and Classifications for Standard Test Sites

Location	Precipitation	Temperature	Average Annual Rainfall (inches)	Average Annual Temperature (°F)
HI, Hilo	Wet	Warm	126.06	73.68
WA, Quillayute [1]	Wet	Temperate	95.01	49.14
NH, Mt. Washington	Wet	Cool	98.49	27.12
FL, Key West	Average	Warm	37.68	77.81
IL, Springfield	Average	Temperate	34.09	52.79
MI, Sault Ste. Marie	Average	Cool	32.94	40.07
AR, Yuma Test Station	Dry	Warm	3.83	73.58
CA, Bishop	Dry	Temperate	5.34	56.02
AK, Barrow	Dry	Cool	4.49	11.81

[1] Based on composite estimation in WEPP using a latitude of 47.94 N and a longitude of -124.54 W. See SERA (2006c) for details.

Table 9: Concentrations of dinotefuran in surface water used in this risk assessment

(see Section 3.2.3.4.6 for discussion)

		Water contamination rate in mg/L per lb/acre applied [a]	
Foliar Broadcast, one application		**Peak**	**Longer-term**
	Central	0.026	0.0082
	Lower	0.000012	0.0000003
	Upper	0.16	0.049
Foliar Broadcast, two applications		**Peak**	**Longer-term**
	Central	0.044	0.013
	Lower	0.00005	0.0000004
	Upper	0.31	0.096
Broadcast Ground, one application		**Peak**	**Longer-term**
	Central	0.036	0.010
	Lower	0.00002	0.0000003
	Upper	0.210	0.065
Soil Injection, one application		**Peak**	**Longer-term**
	Central	0.029	0.010
	Lower	0.000025	0.0000025
	Upper	0.20	0.065

[a] Water contamination rates – concentrations in units of mg a.i./L expected at an application rate of 1 lb a.i./acre. Units of mg a.i./L are used in the EXCEL workbook that accompanies this risk assessment.

Table 10: Estimated residues in food items per lb a.i. applied

Food Item	Concentration in Food Item (ppm per lb a.i./acre)		
	Central [a]	Lower [b]	Upper [a]
Broadcast Foliar Applications			
Short grass	85	30	240
Tall grass	36	12	110
Broadleaf/forage plants and small insects	45	15	135
Fruits, pods, seeds, and large insects	7	3.2	15
Broadcast Granular Applications [c]			
Short grass	3.4	1.2	9.6
Tall grass	1.44	0.48	4.4
Broadleaf/forage plants and small insects	1.8	0.6	5.4
Fruits, pods, seeds, and large insects	0.28	0.13	0.6

[a] From Fletcher et al. (1997) and U.S. EPA/EFED 2001, p. 44.
[b] Central values × (Central Value ÷ Upper Value).
[c] Based on estimates from Michael (1992). See Section 3.2.3.6 for discussion.

Table 11: Summary of toxicity values used in human health risk assessment

Duration	Derivation of RfD	Reference	Comment
Acute – single exposure			
NOAEL Dose	125 mg/kg bw/day	Sakurai 1998b MRID 45654208	EPA selected the dose of 300 mg/kg bw because this single dose was associated with signs of neurotoxicity on gestation day 6-7. The 125 mg/kg bw dose is the study LOAEL for decreased body weight. See Section 3.3.2 for discussion.
LOAEL Dose	300 mg/kg bw/day		
LOAEL Endpoint(s)	Neurotoxicity		
Species, sex	Rabbits, female		
Uncertainty Factor	100	U.S. EPA/OPP 2004e.	
RfD	1.25 mg/kg bw/day		
Chronic – lifetime exposure			
NOAEL Dose	N/A	Weiler 1999b MRID 45654209	The chronic study in mice (Weller 2000a) has a LOAEL of 3 mg/kg bw/day. This study was considered by U.S. EPA/OPP 2004e and judged inappropriate for risk assessment. See Section 3.3.3 for discussion.
LOAEL Dose	20 mg/kg bw/day		
Species, sex	Dogs, male		
LOAEL Endpoint(s)	Decreased thymus weights		
Uncertainty Factor	1000	U.S. EPA/OPP 2004e.	
RfD	0.02 mg/kg bw/day		
Occupational – 1 to 6 month exposure periods			
NOAEL Dose	22 mg/kg bw/day	Weiler 1999b MRID 45654209	The dietary exposure groups in this study was classified as a LOAEL (thymus weights) for male dogs and is used to derive the chronic RfD. Effects on thymus weights are *...not assumed to have occurred in the intermediate term time frame*. See Section 3.3.4 for discussion.
LOAEL Dose	111 mg/kg bw/day		
LOAEL Endpoint	Reduced body weight gain		
Species, sex	Dogs, female		
Uncertainty Factor/MOE	100	U.S. EPA/OPP 2004e	
Equivalent RfD	0.22 mg/kg bw/day		

Table 12: Summary of Subchronic and Chronic Toxicity Studies in Mammals					
Species, Sex	**Duration (Days)**	**Endpoint [a]**	**Dose (mg/kg bw/d)[b]**		**Reference**
			NOAEL	**LOEAL**	
Mice, M/F	28	BW gain ↓ [c]	901	4,612	Weiler 1997d
Mice, M/F	90	BW gain ↓	4,442	10,635	Weiler 1997c
Mice, M/F	546	Spleen, ovaries	—	3	Weller 2000a
Rats, M	1	Neurological	750	1500	Weiler 2001b
Rats, F	1	Neurological	325	750	Weiler 2001b
Rats, F	12	BW gain ↓	300	1000	Sakurai 2002
Rats, M/F	28	BW gain ↓	1,814	3,720	Weiler 1997b
Rats, M	90	Adrenals	34	336	Weiler 1997a
Rats, F	90	BW gain ↓, adrenals	384	1,871	Weiler 1997a
Rats, M/F	91	Neurological	33	327	Weiler 2001a
Rats, M/F	728	BW gain ↓, ovaries, kidney	99.7	991	Weller 2000b
Rabbit, F [d]	13	BW gain ↓	53	125	Skaurai 1998b
Dog, M	90	BW gain ↓	307	862	Weiler 1999a
Dog, F	90	BW gain ↓	—	58	Weiler 1999a
Dog, M	365	Thymus	—	20	Weiler 1999b
Dog, F	365	BW gain ↓, thymus	22	108	Weiler 1999b

[a] *BW* = body weight, *d* = days; *M* = males; *F* = females

[b] For dietary exposures in which no differences were noted between males and females in the NOAEL, doses for NOAELs and LOAELS are based on the lowest dose for either males or females.

[c] Decreased body weight gains variously accompanied by other related effects. Additional study details are given in Appendix 2.

[d] Single day NOAEL for neurotoxicity of 300 mg/kg bw. See Section 3.3.2 for discussion.

Table 13: Acute oral and contact toxicity studies in honeybees

Material	Analysis	LD_{50} µg/bee	NOEC µg/bee	Reference
Oral Toxicity				
TGAI	Study	0.023 (0.019-0.027)	0.003 (sublethal)	Harnish 2000a
	EPA	0.018 (0.0059-0.066)	0.023 (mortality)	
20% SG	Study	0.032 (0.025-0.041)	0.005 (sublethal)	Harnish 2000b
	EPA	0.032 (0.025-0.040)	0.0046 (mortality)	
20% SG	Study	0.0076 (0.004-0.12)	0.0013 (sublethal)	Thompson 1998
	EPA	0.0063 (0.001-7.7)	0.0061 (mortality)	
Contact Toxicity				
TGAI	Study	0.056 (0.044-0.072)	0.0063 (sublethal)	Harnish 2000a
	EPA	0.047 (0.039-0.057)	0.1 (mortality)	
20% SG	Study	0.065 (0.053-0.080)	0.0125 (sublethal)	Harnish 2000b
	EPA	0.061 (0.050-0.073)	0.01 (mortality)	
20% SG	Study	0.023 (0.014-0.046)	0.0032 (sublethal)	Thompson 1998
	EPA	0.024 (0.018-0.031)	0.08 (mortality)	

Table 14:Toxicity of dinotefuran to other insects

Organism	Exposure	Toxicity Value	Reference
American cockroach	Injection with PB [a]	LD_{50}: 0.035 mg/kg bw	Mori et al. 2002
	Injection with PB [a]	LD_{50}: 0.057 mg/kg bw	Tan et al. 2007
	Injection with PB [a]	MLD [b]: 0.0287 mg/animal	Kiriyama and Nishimura 2002
	Injection, no PB [a]	MLD [b]: 0.047 mg/animal	
Asian long-horned beetle	Oral (vegetation)	LC_{50}: 2.2 ppm	Wang et al. 2005
Housefly	Injection	LC_{50}: 0.61 µg/fly	Kiriyama et al. 2003
Typhlodromus pyri (mite)	Contact (glass)	LC_{50}=30,100 mg/ha	Aldershof 2000a
Aphidius rhopalosiphi (wasp)	Contact (glass)	LC_{50}=77 mg/ha	Aldershof 2000b
Orius laevigatus (bug)	Contact (glass)	LC_{50}=77 mg/ha	Aldershof 2000c

[a] PB = piperonyl butoxide ; [b] minimum lethal dose (n=3)

Table 15: Comparative toxicity of dinotefuran and imidacloprid in insects

Organism	Dinotefuran	Imidacloprid	Ratio (D/I) [a]	Molar Ratio (D/I) [a]	Reference/Endpoint
American cockroach (inj) [b]					Kiriyama and Nishimura 2002 / Minimum lethal dose
No synergists	0.047 mg	0.046 mg	1.0	1.3	
With PB	0.029 mg	0.028 mg	1.0	1.3	
With NIA	0.013 mg	0.016 mg	0.81	1.0	
American cockroach (inj)	0.057 mg/kg	0.18 mg/kg	0.31	0.4	Tan et al. 2007 /LD_{50}
Asian long-horned beetle					Wang et al. 2005 / LC_{50}
Dietary 72-h LC_{50}	2.2 ppm	1.9 ppm	1.2	1.5	
Dietary 72-h LC_{90}	22.7 ppm	7.1 ppm	3.2	4.0	
Housefly (inj) [b]					Kiriyama et al. 2003 / LC_{50}
No synergists	0.61 µg/fly	0.51 µg/fly	1.19	1.5	
With PB	0.58 µg/fly	0.46 µg/fly	1.3	1.6	
With NIA	0.31 µg/fly	0.24 µg/fly	1.3	1.6	
With PB and NIA	0.29 µg/fly	0.15 µg/fly	2.0	2.4	
Whitefly					
Dietary 24-h LC_{50}	3.72 µg/ml	498 µg/ml	0.0074	0.0094	Prabhaker et al. 2005
Dietary 24-h LC_{90}	99 µg/ml	1102 µg/ml	0.090	0.11	
Dietary 48-h LC_{50}	0.098 µg/ml	293 µg/ml	0.00033	0.0042	
Dietary 48-h LC_{90}	4.56	843 µg/ml	0.0054	0.0068	

[a] Molar ratio is the mass ratio divided by the ratio of the MW of imidacloprid (255.7) to the MW of dinotefuran (202.2).
[b] inj=injection; PB=piperonyl butoxide (oxidative inhibitor); NIA= propargyl propyl benzenephosphonate (inhibitor of hydrolytic metabolism)

Table 16: Exposure Scenarios for Mammals and Birds

		Application Method					
	Attachment No.	**1a & 1b**	**2**	**3**	**4**	**5**	**Worksheet**
Scenario	**Receptor**	**Broadcast Foliar**	**Broadcast Soil**	**Bark**	**Soil Injection**	**Tree Injection**	
	Fish-eating bird	■	■	■	■		F09b
Accidental Acute Exposures							
Direct Spray							
1st-order absorp.	Small mammal	■		■			F01
100% absorption	Small mammal	■		■			F02
Contaminated Water							
Spill	Small Mammal	■	■	■	■		F05a
Spill	Small Bird	■	■	■	■		F05b
Contaminated Fish							
Spill	Fish-eating bird	■	■	■	■		F08
Non-Accidental Acute Exposures							
Contaminated Vegetation							
Fruit	Small Mammal	■	■				F03a
Grass	Small Mammal	■	■				F03b
Grass	Large Mammal	■	■				F10
Grass	Large Bird	■	■				F12
Contaminated Water							
	Small Mammal	■	■	■	■		F06a
	Small Bird	■	■	■	■		F06b
Contaminated Insects							
	Small Mammal	■	■				F14a
	Small Bird	■	■				F14b
Consumption of small mammal (after direct spray)							
	Carnivorous mammal	■	■				F16a
	Carnivorous bird	■	■				F16b
Contaminated Fish							
	Fish-eating bird	■	■	■	■		F09a
Chronic/Longer Term Exposures							
Contaminated Vegetation							
On-site	Small Mammal	■	■				F04a
Off-Site		■	■				F04b
On-Site	Large Mammal	■	■				F11a
Off-Site		■	■				F11b
On-Site	Large Bird	■	■				F13a
Off-Site		■	■				F13b
Contaminated Water							
	Small Mammal	■	■	■	■		F07a
	Small Bird	■	■	■	■		F07b
Contaminated Fish							

Table 17: Scenarios for Aquatics as well as Terrestrial Plants and Invertebrates

Attachment No. / Scenario	Application Method: 1a & 1b Broadcast Foliar	2 Broadcast Soil	3 Bark	4 Soil Injection	5 Tree Injection	Work-sheet
Aquatics						
Accidental	■	■	■	■		G03
Acute	■	■	■	■		G03
Chronic	■	■	■	■		G03
Terrestrial Plants						
Runoff	■	■	■	■		G04
Drift	■					G05
Soil Erosion by Wind	■	■				G06
Herbivorous Insects						
Treated Tree			■	■	■	G07
Fruit	■	■				G07a
Broadleaves	■	■				G07b
Short Grass	■	■				G07c
Tall Grass	■	■				G07d
Honeybees						
Direct spray	■					G02b
Spray drift	■					G02b
Nectar Consumption	■	■	■	■	■	G09

Table 18:Summary of toxicity values used in ecological risk assessment

Group/Duration Organism		Endpoint	Toxicity Value (a.i.)	Reference
Terrestrial Animals				
Acute				
Non-canine Mammals		NOAEL	125 mg/kg bw	Section 4.3.2.1.
Canine Mammals		NOAEL	125 mg/kg bw	Section 4.3.2.1.
Birds		NOAEL	997.9 mg/kg bw	Section 4.3.2.2
Honey Bee		Oral NOEC	0.014 mg/kg bw	Section 4.3.2.3.1
Honey Bee		Contact NOEC	0.034 mg/kg bw	Section 4.3.2.3.2
Longer-term				
Small Mammal		Estimated Chronic NOAEL	2 mg/kg bw/day	Section 4.3.2.1
Large Mammal		Estimated Chronic NOAEL	2 mg/kg bw/day	Section 4.3.2.1
Bird		Repro. NOAEL	325 mg/kg bw/day	Section 4.3.2.2.
Terrestrial Plants				
Soil Exposure		NOEC	0.5352 lb a.i./acre	Section 4.3.2.4
Foliar Exposure		NOEC	0.5352 lb a.i./acre	Section 4.3.2.4
Aquatic Animals				
Acute				
Amphibians	Sensitive	N/A	N/A	
	Tolerant	N/A	N/A	
Fish	Sensitive	NOEC	N/A	Section 4.3.3.1.1.
	Tolerant	NOEC	99.1 mg/L	Section 4.3.3.1.1.
Invertebrates	Sensitive	NOEC	0.49 mg/L	Section 4.3.3.3.1.
	Tolerant	NOEC	968.3 mg/L	Section 4.3.3.3.1.
Longer-term				
Amphibians	Sensitive	N/A	N/A	
	Tolerant	N/A	N/A	
Fish	Sensitive	N/A	N/A	Section 4.3.3.1.2
	Tolerant	NOEC (**Invalid**)[a]	10 mg/L	Section 4.3.3.1.2
Invertebrates	Sensitive	Estimated NOEC	0.051 mg/L	Section 4.3.3.3.2
	Tolerant	NOEC	95.3 mg/L	Section 4.3.3.3.2
Aquatic Plants				
Algae	Sensitive	N/A	N/A	Section 4.3.3.4.2
	Tolerant	NOEC	25	Section 4.3.3.4.2
Macrophytes	Sensitive	N/A	N/A	Section 4.3.3.4.1
	Tolerant	NOEC	100 mg/L	Section 4.3.3.4.1

[a] See text for discussion.

Table 19: Hazard Quotients for Honeybees (spray and drift)After Foliar Broadcast

Distances Downwind	Foliar Interception		
	None	50%	90%
Direct Spray 0	**503**	**252**	**50**
25	**112**	**56**	**11**
50	**86**	**43**	**9**
100	**49**	**25**	**5**
300	**16**	**8**	**1.6**
500	**10**	**5**	0.97
900	**6**	**3**	0.6

Table 20: Hazard Quotients for Insects (other than direct spray)

Application Method / Food Item	Hazard Quotient		
	Central	Lower	Upper
Herbivorous Insect			
Aerial Broadcast Foliar – One Application [a]			
Fruits, pods, and seeds	130	27	471
Broadleaf/forage plants	836	129	4,243
Short grass	1,579	257	7,543
Tall grass	669	103	3,457
Aerial Broadcast Foliar – Two Applications [a]			
Fruits, pods, and seeds	156	27	676
Broadleaf/forage plants	1,002	129	6,081
Short grass	1,892	257	10,810
Tall grass	801	103	4,955
Aerial Broadcast Granular			
Fruits, pods, and seeds	14	3	51
Broadleaf/forage plants	90	14	458
Short grass	170	28	815
Tall grass	72	11	373
Bark Treatment and Soil Injection			
Leaves of treated tree	5,126	720	23,383
Tree Injection			
Leaves of treated tree	5,571	771	23,571
Honeybee Foraging for Nectar			
Aerial Broadcast Foliar – 0.2 lb/acre, 1 application	4	0.95	12
Aerial Broadcast Foliar – 0.2 lb/acre, 2 applications	5	0.95	17
All other application methods [b]	9	1.8	53

[a] The identical lower bounds for one and two aerial applications are not typographic errors but are due to the lower bound of the foliar half-time – i.e., 0.36 $days^{-1}$.

[b] Residue rates for application methods other than broadcast foliar are not derived. The HQ values for all other application methods are based on the assumption that effective applications of dinotefuran would lead to residues levels in nectar of 60 ppb with a range of 20 ppb to 200 ppb. See Section 4.2.3.3 for discussion.

Appendix 1: Acute toxicity to Experimental Mammals

Species	Exposure	Response	Reference
ORAL			
Gavage			
Rats, albino, Crl:CD(SD)BR; 8-14 weeks; weight: males 259-299 g, females 233-281g; 5/sex/group	TGAI (purity 99.1%). Single gavage dose of 1000, 2000, 3000, 4000 or 5000 mg/kg.	Males: LD_{50} 2804 (1947-4037) mg/kg bw Females: LC_{50} 2000 (1354-2954) mg/kg bw MTI-446 classified as Toxicity Category III.	Glaza 1997a MRID 45639823 Acceptable
Rats, Sprague-Dawley, 7 weeks; weight: males 230-245 g, females 151-177 g; 5/sex/group	**20% SG formulation**: 0 or 2000 mg/kg bw by gavage.	No mortality or signs of toxicity. MTI-446 **20% SG** classified as Toxicity Category III.	Oda 2001a, MRID 45639109, Acceptable
Mice, young adult albinos; 4-8 weeks; weight: males 23.7-29.6 g, females 23.0-28.6 g; 5/sex/group	TGAI.(purity 99.1%). Single gavage dose of 1000, 2000, or 3000 mg/kg.	Males: LD_{50} 2450 (1801-3331) mg/kg bw Females: LD_{50} 2275 (1537-3369) MTI-446 classified as Toxicity Category III.	Glaza 1997b MRID 45639824 Acceptable
NOTE: MRID 45639824 appears to be based on a cut and paste of Glaze 1997a in rats, MRID 45639823. The toxicity values reported, however, are different from those in the rat study.			
DERMAL TOXICITY			
Rats, albino, Crl:CD(SD)BR, 8-16 weeks; weight: males 254-274 g, females 264-290 g; 5/sex	TGAI (purity 99.1%): 2000 mg/kg bw limit test.	No mortality. *Dermal irritation: slight to moderate erythema and/or slight edema; all signs of irritation cleared by day 10 of observation* MTI-446 classified as Toxicity Category III.	Glaza 1997c MRID 45639901 Acceptable
Rats, Sprague-Dawley, 7 weeks; weight: males 253-272 g, females 184-200 g; 5/sex	**20% SG formulation**: 0 or 2000 mg/kg bw.	No mortality or signs of toxicity. MTI-446 **20% SG** classified as Toxicity Category III.	Oda 2001b, MRID 45639110, Acceptable
PRIMARY SKIN IRRITATION			
Rabbits, Hra: (NZW)SPF strain, 14-18 weeks; weight: males 2260-2599 g, female 2602 g; 5 males and 1 female	TGIA (purity 99.1%) 0.5 g in 0.3 mL distilled water for 4 hours.	Very slight (grade 1) erythema in 3/6 rabbits at 4 hours after exposure; at 24 hours after exposure, 1/6 rabbits continued to exhibit very slight erythema; all signs of dermal irritation disappeared by 48 hours after exposure. Category IV: erythema, resolving within 48 hours.	Glaza 1998b, MRID 45639904, Acceptable

Appendix 1: Acute toxicity to Experimental Mammals *(continued)*

Species	Exposure	Response	Reference
Rabbits, Japanese, females, 18 weeks; weight: 3.14-3.57 g [Surely this is a typo in the DER and the body weights should be in units of kg an not g.]	**20% SG formulation** (purity 23.0%): 0.5 g in 0.5 mL water for 4 hours.	Erythema with slight edema in 2/3 rabbits at 72 hours. No effects by Day 8. MTI-446 **20% SG** classified as Toxicity Category III based on presence of well-defined erythema (grade 2) with slight edema (grade 1) in 2/3 rabbits at 72 hours, resolving within 8 days.	Ukon 2002b MRID 45639113 Acceptable
DERMAL SENSITIZATION			
Guinea pig, Cd: (HA)BR, male albino, 4-8 weeks; weight: 372-500 g, 20 for definitive study test group; 20 for definitive study control group.	TGAI (purity 99.1%): Concentrations of 1%, 5%,10% or 15%.	No sensitization or other dermal effects.	Glaza 1997d MRID 45639905 Acceptable
Guinea pig, female Hartley strain albinos, 6 weeks; weight: 305-381 g; animals for irritation screening, 20 test group animals, and 10 naïve control animals.	**20% SG formulation** (23.0% purity): Concentration of 50% for induction and 25% for challenge.	No sensitization or other dermal effects; ***slight body weight loss (5/20 test animals and 2/10 naïve control animals) not considered related to test substance.***	Ukon 2002c MRID 45639114 Acceptable
INHALATION			
Rats, Crl:WI(GLx/ BRL/Han)BR, 12 weeks; weight: males 321-378 g, females 188-2107 g; 5/sex/dose group	TGAI (92.9% purity): nose only exposures to 4.09 mg/L for 4 hours	No mortality and no effects on body weight. No signs of toxicity. MTI-446 classified as Toxicity Category IV for acute inhalation, based on lack of mortality.	Shepherd 1999 MRID 45639902 Acceptable

Appendix 1: Acute toxicity to Experimental Mammals *(continued)*

Species	Exposure	Response	Reference
Rats, HanBrl:WIST(SPF) strain; males 8 weeks old, females 10 weeks old; weight: males 238.9-252.2 g, females 194.0-212.8 g; 5/sex	**20% SG formulation** (23.9% purity): nose only exposures to 2.94 mg/L for 4 hours	No mortality. Transient decrease in body weight gain in 1/5 males and 1/5 females. Decreased body weight in 1 female. Not clearly substance related. MTI-446 **20% SG** classified as Toxicity Category IV for acute inhalation, based on lack of mortality.	Decker 2002 MRID 45639111 Acceptable
EYE IRRITATION			
Rabbits, albino, Hra: (NZW)SPF, 6 males and 3 females; 14-18 weeks; weight: males 2334-2694 g, females 2437-2685 g.	TGAI (purity 99.1%): 0.1 g right eye. Left eye control. With and without washing	Unwashed group: corneal opacity resolving in 14 days (Category II). Washed group: minor eye irritation.	Glaza 1998a MRID 45639903, Acceptable
Rabbits, New Zealand White, young adults; 1 male and 2 females.	TGAI 98.9% dinotefuran): 0.1 mL right eye. Left eye control. Washing not specified (and presumably not done).	Conjunctivitis at the 1 hour observation. No effects by 24 hours after administration. Toxicity Category IV, minimally irritating.	Kuhn 2004 MRID 46301601 Acceptable
Rabbits, Japanese White, 6 females; 15 weeks old; weight 2.67-2.95 kg; 3 rabbits in unwashed group and 3 three rabbits in washed group.	**20% SG formulation** (purity 23.0%): 0.1 g granules in left eye. Right eye control. With and without washing.	Unwashed: Corneal opacity and conjunctivitis. Washed: No effects. Category III (unwashed)	Ukon 2002a 45639112 Acceptable

Appendix 2: Toxicity After Repeated Administrations to Mammals

Species	Exposure	Response	Reference
Subchronic Dietary			
Rats, Crl:CD (SD) BR VAF/Plus; 5/sex/group	28 days: 0, 5000, 25,000, or 50,000 ppm Dinotefuran (equivalent to 0, 390, 1814,or 3720 mg/kg bw/day for males and 0, 450, 2183, or 4222 mg/kg bw/day for females) in the diet	No mortality or signs of toxicity. Decreased body weight gain at 50,000 ppm (about 50% of controls).	Weiler 1997b MRID 45654203
Rats, Crl:CD (SD) BR VAF/Plus; ≈ 7 weeks; males: 235-284 g; females: 165-228 g; 10/sex/dose,	90 days: 0, 500, 5000, 25,000, or 50,000 ppm Dinotefuran (96.5% a.i.) (equivalent to 0, 34, 336, 1623, or 3156 mg/kg bw/day for males and 0, 38, 384, 1871or 3616 mg/kg bw/day for females) in the diet	No mortality or signs of toxicity. Decreased body weights and food consumption at two highest concentrations. Decreased body weight gain at 5000 ppm. Decrease food conversion efficiency during Week 1 at 50,000 ppm. NOAEL: 500 ppm (34 mg/kg/day) for males NOAEL: 5000 ppm (384 mg/kg/day) for females. LOAEL: 5000 ppm (336 mg/kg/day) for males, based on adrenal histopathology LOAEL: 25,000 ppm (1871 mg/kg/day for females, based on reduced body weight/gains; dose-related changes in hematological and clinical pathology parameters, organ weight changes, and adrenal histopathology.	Weiler 1997a MRID 45654205 Acceptable/ Guideline
Mice, Crl:CD-l (ICR)BR VAF/Plus	28 days: 0, 5,000, 25,000, or 50,000 ppm Dinotefuran (equivalent to 0, 901, 4612, and 10,303 mg/kg bw/day for males and 0, 1043,5359, and 12,289 mg/kg bw/day for females)	One fatality at highest dose not attributed to treatment. Decreased body weight gain at 25,000 and 50,000 ppm. Slight increase in total protein and albumin of the 50,000 ppm males but on signs of kidney pathology	Weiler 1997d MRID 45654204

Species	Exposure	Response	Reference
Mice, Crl:CD-l (ICR)BR VAF/Plus; ≈7 weeks; males: 25.9-35.9 g; females: 18.8-32.2 g; 10/sex/dose group	90 days: 0, 500, 5000, 25,000 or 50,000 ppm Dinotefuran (96.5% a.i.) (equivalent to 0, 81, 844, 4442, or 10,635 mg/kg bw/day for males and 0, 102, 1064,5414, or 11,560 mg/kg bw/day for females).	No mortality or signs of toxicity. Decreased body weights and food consumption at two highest concentrations. No effects on hematology, clinical chemistry, urinalysis, organ weights, or pathology. NOAEL: 25,000 ppm (4442 mg/kg/day for males and 5414 mg/kg/day for females). LOAEL: 50,000 ppm (10,635 mg/kg/day for males and 11,560 mg/kg/day for females) based on decreased body weight/gains.	Weiler 1997c MRID 45654206
Dog, beagle; 5- to 6-months-old; males: 7.7-8.8 kg, females: 6.3-8.8 kg, 4/sex/dose group	90 days: 0, 1600, 8000, or 24,000 ppm Dinotefuran (99.1% a.i.) in diet [mean equivalents: 0, 58, 307, or 862 mg/kg bw/day (males), and 0, 58, 323, or 950 mg/kg bw/day (females)]. Additional high dose of 40,000 ppm reduced to 30,000 ppm on Day 5 and 24,000 ppm on Day 12	30,000 to 40,000 ppm x 2 weeks: decreased body weight gain and decreased food conversion efficiency (possibly due to vomiting and/or diarrhea). NOAEL: 8000 ppm (307 mg/kg/day for males) NOAEL: not determined (<58 mg/kg/day for females) LOAEL: 24,000 ppm (862 mg/kg bw /day for males), based on hemorrhagic lymph nodes and decreased body weight gain LOAEL: 16,000 ppm (58 mg/kg/ bw/day for females), based on decreased body weight/gains	Weiler 1999a MRID 45639906 Acceptable/ Guideline

Subchronic Neurotoxicity (oral)			
Rats, Cr1:CD (SD)IGS BR; 46- to 52-days-old; males: 207-297 g, females: 146-205 g; 10/sex/dose group	13 weeks: Dietary concentrations MTI-446 (93.0% a.i.) of 0, 500, 5000, or 50,000 ppm (equivalent to 0, 33, 327, or 3413 mg/kg/day for males and 0, 40, 400, or 3806 mg/kg/day for females).	No mortality or gross signs of toxicity. High Dose Body Weights: Significant ($p \leq 0.05$) decreased body weights relative to controls (79% for males and 81% for females). Decrease in food conversion efficiency relative to controls (87% for males and 82% for females.). High Dose Body Temperature: Significant decrease in females during Week 2. High Dose Neurotoxicity: Decreased motor activity and rearing in females. Mid Dose Neurotoxicity: Increased subsession motor activity in both males and females in Week 2 (200% to 429% of controls). NOAEL: 500 ppm (33 mg/kg/day for males and 40 mg/kg/day for females) LOAEL: 5000 ppm (327 mg/kg/day for males and 400 mg/kg/day for females), based on increased motor activity during week 2.	Weiler 2001a MRID 45640004 Acceptable/ Guideline

Rats, Cr1:CD (SD) IGS BR; 48- to 54-days-old; males: 212-284 g, females: 142-208 g; 10/sex/dose group for behavioral testing (FOB, motor activity); 6/sex in control and high-dose group for neuropathology testing.	Single Gavage doses MTI-446 (93% a.i.) of 0, 325, 750, or 1500 mg/kg bw with 15 day observation period.	No mortality; no clinical signs of toxicity related to treatment; no treatment-related effects on body weight/gains; and no treatment-related effects on food consumption. Transient decreases in total motor activity, relative to controls (Day 1 only) were as follows: high-dose males: 70% high-dose females: 53% mid-dose females: 68% On days 8 and 15, motor activity was comparable to controls in all treatment groups. Observations included decreases in the numbers of rears among mid-dose (46%) and high-dose (54%) females, as well as decreased body temperatures in high-dose males (1.0ºC less than controls) and high-dose females (1.1ºC less than controls). Males NOAEL: 750 mg/kg bw LOAEL: 1500 mg/kg bw, based on decreased motor activity Females: NOAEL: 325 mg/kg bw LOAEL: 750 mg/kg bw, based on decreased motor activity	Weiler 2001b MRID 45640005 Acceptable/ Guideline
Subchronic Dermal			
Rat, Crl:CD(SD)IGS BR; 52- to 58-days-old; males: 247-326 g, females: 166-218 g; 10/sex/dose group	0, 40, 200, or 1000 mg/kg bw/day MTI-446 (93% a.i.), 6 to 7 hours/day, 7 days/week for 29 days.	40 mg/kg: one male died in week 4. Not attributable to treatment. No dermal effects or signs of systemic toxicity. NOEC: 1000 mg/kg bw/day (dose limit)	Henwood 2001a,b MRID 45639908 (Full study) MRID 45639907 (range finding) Acceptable/ Guideline

Subchronic Inhalation			
Rats, Crl:WI(GLx/BRL/ Han)Br; ; 9-weeks-old at start; males: 174-226 g, females: 145-182 g; 10/sex/dose group	TGAI: **nose-only** exposure. To MTI 446 (99.1% a.i.) at concentrations of 0, 0.22, 0.66, and 2.08 mg/L for 6 hours/day for 29 days (males) and 30 days (females). The DER specifies that these exposures were equivalent to doses of approximately 60, 179, and 565 mg/kg/day.	No compound-related effects on mortality, hematology, clinical chemistry, gross pathology, or histological pathology. Observations included an increased incidence of thinning fur or hair loss in treated animals, and an increased incidence in protruding eyes in mid-dose and high-dose females only. NOAEL: 0.22 mg/L (≈60 mg/kg/day for females) NOAEL: <0.22 mg/L for males LOAEL: 0.22 mg/L (≈60 mg/kg/day for males), based on decreased body weight gain at all doses during week 1 LOAEL: 0.66 mg/L (≈179 mg/kg/day for females), based on clinical signs (protruding eyes).	Mita 2002 MRID 45639909 Acceptable/Non-guideline

Developmental/Teratology Studies			
Rabbits, New Zealand White; 5- to 6-months-old; 2.7-3.6 kg (at start of mating); 22 females/ dose group	Gavage doses MTI-446 (92.9% a.i.) of 0, 52, 125, or 300 mg/kg bw/day from Days 6 to 18 of gestation.	**Maternal:** No mortality at any dose. Hypoactivity, prone positioning, panting, erythema (nose), and tremors at 300 mg/kg bw/day. Decreases in food consumption and body weight gain at 125 and 300 mg/kg bw/day. Pathologic changes in stomach and liver at 125 and 300 mg/kg bw/day. Maternal Study NOAEL = 52 mg/kg bw/day Maternal Study LOAEL = 125 mg/kg bw/day for decreased weight gain. Maternal Single Dose NOAEL = 125 mg/kg bw/day Maternal Single Dose LOAEL = 300 mg/kg bw/day (prone position, panting, tremor, erythema) **Fetuses:** No effects at any dose. Fetal NOAEL: 300 mg/kg bw/day Fetal LOAEL: not determined.	Sakurai 1998b MRID 45654208 Acceptable/ Guideline **Used for Acute RfD in U.S. EPA/OPP 2004e**
Rats, Sprague-Dawley; ≈8 weeks; 212.22-269.37 g at start; 24 dams/dose	Gavage doses MTI-446 (92.9% a.i.) of 0, 100, 300, or 1000 mg/kg bw/day from Days 6 to 15 of gestation.	**Maternal:** No mortality at any dose. Hypoactivity in 1 dam at on Days 8 to 10 at 1000 mg/kg bw. No other signs of toxicity. Decreases in food consumption (about 88 to 90% of controls) and body weight gain (91% of controls) at 1000 mg/kg bw/day. Significant on Days 6 to 10. Maternal NOAEL = 300 mg/kg bw/day Maternal LOAEL = 1000 mg/kg bw/day. **Fetuses:** No treatment related effects at any dose. Fetal NOAEL: 1000 mg/kg bw/day Fetal LOAEL: not determined.	Sakurai 2002 MIRD 45654207 Acceptable/ Guideline

Reproduction Studies			
Rats, Wistar, (F_0) approximately 6 weeks old; (F_1) 4 weeks old; wt: males (group means) 52-65 g, females (group means 52-60 g; 25/sex/dose group	TGAI (purity 98.9%): dietary concentrations of 0, 300, 1000, 3000, or 10,000 ppm.. 0, 24.1, 79.9, 241.0, or 822.1 mg/kg bw/day for Females, 0, 26.8, 90.1, 267.9, or 907.0 mg/kg bw/day for F0 females, 0, 27.2, 90.5, 269.0, or 934.7 mg/kg bw/day for F1 males, and 0, 29.6, 96.5, 292.6, or 1004.8 mg/kg bw/day for F1 females.	Parental NOAEL: 3000 ppm () LOAEL: 10,000 ppm (822.1-934, decreased food consumption, and weight gain. Decrease (60% of controls) in ovarian primordial follicles as well as changes in the estrous cycle of dams. Offspring NOAEL: 3000 ppm LOAEL: 10,000 ppm, decreased body weight, spleen weights, thymus weights, and grip strength.	Becker 2002: Full study Edwards et al. 2001: Range finding study MRID Nos. 45639913, 45639914

Chronic Studies			
Dogs, beagle; ≈5- to 5.5-months-old; males: 8.0-9.8 kg, females: 7.1-8.9 kg; 4/sex/dose group	52 weeks: MTI-446 (Dinotefuran; 98.9% a.i.) at 0, 640, 3200, or 16,000 ppm (equivalent to 0, 20, 111, or 559 mg/kg bw/day (males) and 0, 22, 108, or 512 mg/kg bw/day (females).	Reduced body weight gain (70% of controls) at 16,000 ppm. Reduced terminal body weights at 3200 ppm (88% of controls) and 16,000 ppm (89% of controls). Reduced food conversion efficiency from Week 1 to Week 16. NOAEL females: 640 ppm NOAEL males: not determined LOAEL females: 3200 ppm (108 mg/kg bw/day), based on reduced cumulative food (weeks 1-16), reduced final body weights, reduced overall body weight/gains, and decreased thymus weights. LOAEL males: 640 ppm (20 mg/kg bw/day), based on decreased thymus weights. Body weight were not significantly decreased.	Weiler 1999b MRID 45654209 Acceptable/ Guideline **Used for Chronic RfD in U.S. EPA/OPP 2004e, with LOAEL in males of 20 mg/kg bw/day and an UF of 1000.**
EPA Commentary: *toxicologically significant, adverse effect on the utilization of food in high-dose males and in the mid-dose and high-dose females. ... Thymus weights were decreased in treated males at all doses (49-68% of controls) and in females at the mid and high doses (69% of controls). Testes weights were also decreased in males at all doses (83-89% of controls).*			

Mice, Crl:CD-l® (ICR)BR VAF/Plus; 7-weeks-old; males: 27.1-1.36 g, females: 20.0-29.5 g; 10/sex/dose group	78 weeks with partial sacrifice at 53 weeks: MTI-446 (Dinotefuran technical; 93% a.i.): 0, 25, 250, 2500, or 25,000 ppm (equivalent to 0, 3, 34, 345, or 3694 mg/kg bw/day for males and 0, 4, 45, 441, or 4728 mg/kg bw/day for females)	No effects on mortality, signs of toxicity, or pathology (including tumor incidence). 25,000 ppm: Slight decrease in terminal body weights – i.e., 95% for males and 91% for females relative to controls. In males, food consumption was somewhat higher than controls. All groups: Increase in relative ovarian weight (218-1549% of control ovarian weights) at week 53. Statistically significant except in 2500 ppm group but not dose-related. All groups: Substantial decrease in spleen weight at Week 79 (45% to 70% of controls). Dose-related only in females. EPA Commentary – *The magnitude of the decrease is dose-related in females, and is sufficiently large in males (although not dose-related) to be considered adverse at all doses in both sexes.* NOEAL: Not determined. LOAEL: 25 ppm (3 mg/kg/day for males and 4 mg/kg/day for females), based on decreased spleen weight in males and increased ovarian weight (week 53) in females.	Weiler 2000a MRID 45639917 Acceptable/ Guideline

Rats, Crl:CD (SD)BR VAF/Plus; 41- to 47-days old at start; males: 173-271 g, females: 143-204 g; 60/sex/dose group; interim sacrifice at 26, 52, and 78 weeks: 10/sex/dose group.	Study: 104 weeks with partial sacrifices as Weeks 26, 52, and 78. Dietary concentrations MTI-446 (Dinotefuran; 98.9%) of 0, 60, 200, 2000, or 20,000 ppm (corresponding to doses of 2.98, 9.89, 99.7, and 991 mg/kg bw/day, respectively, for males and 3.91, 12.5, 127.3, and 1332 mg/kg bw/day, respectively, for females).	No treatment-related effects on mortality, signs of toxicity, hematology, clinical chemistry, or urinalysis. High Dose, Body Weights: Slight but statistically significant decrease (4-9%) in body weights in males from Weeks 2 to 90. Decrease in body weight gain (5%) by end of study. More substantial impact on body weights in females: 17% less by Week 52 and 32% less by Week 104. In both sexes, decreased food consumption – 7 to 12% relative to controls. Apparent decreased food conversion efficiency in females. High Dose, Other Effects: Substantial increase in absolute ovary weight (641% of controls) and relative ovary weights (957% of controls). NOAEL: 2000 ppm LOAEL: 20,000 ppm (991 mg/kg bw/day in males), based on increased incidence of kidney pelvic mineralization and ulceration, and (1332 mg/kg bw/day for females), based on increased ovarian weight, decreased body weight/gain, and food efficiency. EPA Commentary on Carcinogenicity: *The incidence of thyroid C-cell adenoma was 7/59 (12%), 10/59 (17%), 10/60 (17%), 12/58 (21%), and 15/60 (25%) (p=0.053) in male rats administered the 0, 60, 200, 2000, and 20,000 ppm diets, respectively. The incidence at 20,000 ppm was just outside the upper range for historical controls (1.7-24%). Therefore, at the doses tested, the data showed equivocal evidence for a treatment-related increase in tumor incidence in male rats.*	Weiler 2000b MRID 45640001 Acceptable/ Guideline

Appendix 3: Toxicity of to Birds

Species	Exposure	Effects	Reference/ EPA Classific-ation
Single Dose Gavage			
Japanese quail, *Coturnix coturnix japonica*, 8 weeks; males: 156.9-210.8, females: 164.0-228.2 g; 1/sex/dose group	TGAI (97.26% purity). Gavage, 0, 200, 1000, or 2000 mg/kg.	No mortality. Somnolence at 2000 mg/kg bw for up to 3 hours after dosing.. NOEC: 1000 mg/kg bw.	Burri 2000a MRID 45639720 Supplemental due to species selection.
Acute Dietary			
Japanese quail, *Coturnix coturnix japonica*, 16-day-old chicks at start; 66-106 g; 10/dose group	TGAI (97.26% purity). Dietary limit test. 0 and 4936 ppm feed x 5 days. Dose of 1301 mg/kg bw/day based on measured food consumption (0.26 of bw).	No mortality or other signs of toxicity.	Burri 2000b MRID 45639721 Supplemental due to species selection.
Mallard duck, *Anas platyrhynchos*, 14-day-old chicks at start; 290.4-323.7 g; 10 treated birds; 20 negative controls	TGAI (99.2% purity). Dietary limit test. 0 and 4732 ppm feed x 5 days. Dose of 997.9 mg/kg bw/day based on measured food consumption (0.21 of bw).	No mortality or other signs of toxicity. MTI-446 classified as practically non-toxic to Mallard duck on subacute dietary basis.	Burri 2000c MRID 45639722 Core

Appendix 3: Toxicity to Birds *(continued)*

Species	Exposure	Effects	Reference/ EPA Classific-ation
Reproduction Studies			
Mallard duck, *Anas platyrhynchos*; 21 weeks at start; males: 921-1356 g, females: 907-1296 g; 16/sex/dose group	TGAI (99.3% purity): Dietary concentrations of 0, 764, 2150, or 5270 ppm. Vehicle: corn oil. Food consumption: 0.154 (control), 0.155 (low dose), 0.151 (mid dose), and 0.156 (high dose) kg food/kg bw.	NOEC: 2150 ppm (324.56 mg/kg bw/day) LOEC: 5270 ppm. (822.12 mg/kg bw/day) reductions in the percentages of number of hatchlings/eggs laid, number of hatchlings/eggs set, and hatchling survival/eggs set.	Mitchell et al. 2002a MRID 45639723 Core
Northern bobwhite quail, *Colinus virginianus*, 21-weeks-old at start; males: 180-222 g, females: 182-227g; 16/sex/dose group	TGAI (99.3% purity): Dietary concentrations of 0, 764, 2150, or 5270 ppm.. Food consumption: 0.0183 (control), 0.019 (low dose), 0.0.0185 (mid dose), and 0.0177 (high dose) kg food/kg bw.	NOEC: 5270 ppm (93.279 mg/kg bw/day) LOEC: not determined	Mitchell et al. 2002b MRID 45639724 Supplemental because highest dose tested did not elicit adverse effects.

Appendix 4: Toxicity to Terrestrial Invertebrates

Standard toxicity studies are grouped by bees and then other species. Within each group, the entries are sorted by author.

For MRID studies, all LD_{50} and LC_{50} values are those calculated by EPA rather than those reported by the investigator unless otherwise specified.

<table>
<tr><th>Species</th><th>Exposure</th><th>Response</th><th>Reference</th></tr>
<tr><td>Bees</td><td></td><td></td><td></td></tr>
<tr><td>Honey bee, Apis mellifera</td><td>TGAI Oral Test: 0.00315,0.0063,0.0125, 0.025,0.05, and 0.1 µg a.i./bee. 48-hour observation period.

30 organisms in each group – i.e., 3 replicates of 10 bees per replicate.</td><td>EPA Values
Oral 48-hour LD_{50}:
0.018 (0.0059-0.066) µg/bee
Oral NOEC (mortality): 0.023 µg/bee
Investigator Values
Oral 48-hour LD_{50}:
0.023 (0.019-0.027) µg/bee
Oral NOEC (sublethal): 0.003 µg/bee
Dose response data (n=30).
<table>
<tr><th rowspan="2">Group or Dose (µg/bee)</th><th colspan="2">Number Dead</th></tr>
<tr><th>24 hr</th><th>48 hr</th></tr>
<tr><td>Neg. Control</td><td>0</td><td>4</td></tr>
<tr><td>Solvent Cntrl</td><td>0</td><td>5</td></tr>
<tr><td>0.00313</td><td>0</td><td>9</td></tr>
<tr><td>0.0063</td><td>2</td><td>8</td></tr>
<tr><td>0.0125</td><td>2</td><td>8</td></tr>
<tr><td>0.025</td><td>16</td><td>17</td></tr>
<tr><td>0.05</td><td>22</td><td>26</td></tr>
<tr><td>0.1</td><td>23</td><td>30</td></tr>
</table></td><td>Harnish 2000a
MRID 45639725
Supplemental</td></tr>
<tr><td>Honey bee, Apis mellifera</td><td>TGAI Contact Test (micro-applicator): 0.0063, 0.0125, 0.025, 0.05, 0.1, and 0.2 µg a.i./bee, 48-hour observation period

30 organisms in each group – i.e., 3 replicates of 10 bees per replicate.</td><td>EPA Values
4h-hour Contact LD_{50}:
0.047 (0.039-0.057) µg/bee
Contact NOEC (mortality): 0.1 µg/bee
Investigator Values
Contact LD_{50}:
0.056 (0.044-0.072) µg/bee
Contact NOEC (sublethal effects – ataxia): 0.0063 µg/bee
Dose response data.
<table>
<tr><th rowspan="2">Group or Dose (µg/bee)</th><th colspan="2">Number Dead</th></tr>
<tr><th>24 hr</th><th>48 hr</th></tr>
<tr><td>Neg. Control</td><td>0</td><td>1</td></tr>
<tr><td>Solvent Cntrl</td><td>0</td><td>0</td></tr>
<tr><td>0.0063</td><td>0</td><td>0</td></tr>
<tr><td>0.0125</td><td>1</td><td>3</td></tr>
<tr><td>0.025</td><td>4</td><td>5</td></tr>
<tr><td>0.05</td><td>14</td><td>14</td></tr>
<tr><td>0.1</td><td>22</td><td>23</td></tr>
<tr><td>0.2</td><td>28</td><td>30</td></tr>
</table></td><td>Harnish 2000a
MRID 45639725
Core</td></tr>
<tr><td colspan="4">Note on Harnish 2000a: The full study is not available but the investigator NOEC of 0.0063 µg/bee appears to be based on sublethal effects. Based on lethality, the NOEC is 0.0125 using the Fisher Exact test with pooled controls – i.e., 1/60 vs 3/30 has a p-value of 0.106061 and 0.0124 µg/be is a NOEC based on lethality. For the 0.025 dose group, the corresponding p-value (3/60 vs 5/30) is 0.014687 – i.e., 0.025 is an FEL based on lethality.</td></tr>
</table>

<table>
<tr><th>Species</th><th>Exposure</th><th>Response</th><th>Reference</th></tr>
<tr><td>Honey bee, Apis mellifera</td><td>20% WG formulation
Oral Test: 0.005, 0.011, 0.021, 0.046, 0.088, and 0.173 /µg a.i./bee. 48-hour observation period</td><td>EPA Values
Oral LD_{50}: 0.032 (0.025-0.040) µg/bee
Oral NOEC (mortality): 0.0046 µg/bee
Investigator Values
Oral LD_{50}: 0.032 (0.025-0.041) µg/bee
Oral NOEC (sublethal): 0.005 µg/bee</td><td>Harnish 2000b
MRID 45639726
Supplemental/ Non-guideline</td></tr>
<tr><td>Honey bee, Apis mellifera</td><td>20% WG formulation
Contact Test (direct spray): .0125, 0.025, 0.05, 0.1, 0.2, and 0.4 /µg a.i./bee. 48-hour observation period.

30 organisms in each group – i.e., 3 replicates of 10 bees per replicate.</td><td>EPA Values
Contact LD50: 0.061 (0.050-0.073) µg/bee
Contact NOEC (mortality): 0.01 µg/bee

Investigator Values
Contact LD50: 0.065 (0.053-0.080) µg/bee
Contact NOEC (sublethal – ataxia): 0.0125 µg/bee</td><td>Harnish 2000b
MRID 45639726
Core</td></tr>
<tr><td>Honey bee, Apis mellifera</td><td>20 % formulation.
Residues on alfalfa. Single nominal application of 150 g formulation/ha (60.75 g a.i./A). Plants harvested from test plots at 3, 8, 24, and 48 hours after treatment. Bees (25 per cage) exposed in test chamber to 15 g of chopped foliage per cage.

The test chambers consisted of “cricket boxes”. The following description is given in the study: ...disposable paper containers (cricket boxes) measuring approximately 9 cm in diameter and 15 cm in height. Test chamber tops were covered with Petri dishes approximately 9 cm in diameter.</td><td>RT_{25} values (residual time to cause 25% mortality) for residues aged for specific periods:
3 hr Residue: 6.7 (3.3-14) hours
8 hr Residue: 4.8 (2.4-9.6) hours
24 hr Residue: 24 (14-44) hours
48 hr Residue: 90 (75-110) hours
Differences in response between 48 hour residues and controls were not statistically significant.
% Mortality
<table>
<tr><th rowspan="2">Residue Period</th><th colspan="4">Duration of Exposure to Residue</th></tr>
<tr><th>3</th><th>8</th><th>24</th><th>48</th></tr>
<tr><td></td><td colspan="4">Dinotefuran Groups</td></tr>
<tr><td>3 h</td><td>0</td><td>76</td><td>92</td><td>95</td></tr>
<tr><td>8 h</td><td>0</td><td>94</td><td>96</td><td>98</td></tr>
<tr><td>24 h</td><td>1</td><td>55</td><td>83</td><td>97</td></tr>
<tr><td>48 h</td><td>0</td><td>2</td><td>7</td><td>12</td></tr>
<tr><td></td><td colspan="4">Matched Control Groups</td></tr>
<tr><td>3 h</td><td>0</td><td>0</td><td>0</td><td>7</td></tr>
<tr><td>8 h</td><td>0</td><td>1</td><td>4</td><td>12</td></tr>
<tr><td>24 h</td><td>0</td><td>12</td><td>30</td><td>73</td></tr>
<tr><td>48 h</td><td>0</td><td>2</td><td>7</td><td>12</td></tr>
</table>
48-h residues were also assayed at 100 hours: Dinotefuran group, 42% mortality; Matched control group, 45% mortality.</td><td>Hummel 2001

MRID 45639728

Core</td></tr>
</table>

<table>
<tr><th>Species</th><th>Exposure</th><th>Response</th><th>Reference</th></tr>
<tr><td colspan="4">Working Note on Hummel 2001: The application rate is in grams per acre and not g/ha. The application rate is equivalent to 0.06075 kg./acre or about 0.134 lb a.i./acre. This is characterized as 102% of the maximum proposed label use rate. The maximum rate considered in the Forest Service risk assessment is 0.54 lb/acre. On the 20 SG label, the highest single application rate is 0.2 lb a.i./acre. Description of the test chamber from Julie Horton (Landis) via email on January 27, 2009.</td></tr>
<tr><td>Honey bee, Apis mellifera</td><td>20% WG formulation
Oral Test: 0.00056, 0.0013, 0.0028, 0.0061, 0.013, and 0.029 µg a.i./bee.

30 organisms in each group – i.e., 3 replicates of 10 bees per replicate.</td><td>EPA Values
Oral LD_{50}: 0.0063 (0.001-7.7) µg/bee
NOEC (mortality): 0.0061 µg/bee
Note: The upper bound of the LD_{50} appears to be a typo. See d/r data below.

Investigator Values
Oral LD_{50}: 0.0076 (0.004-0.12) µg/bee
NOEC (sublethal): 0.0013 µg/bee

Dose response data (n=30).
<table>
<tr><th rowspan="2">Group or Dose (µg/bee)</th><th colspan="2">Number Dead</th></tr>
<tr><th>24 hr</th><th>48 hr</th></tr>
<tr><td>Solvent Cntrl</td><td>6</td><td>6</td></tr>
<tr><td>0.00056</td><td>4</td><td>4</td></tr>
<tr><td>0.0013</td><td>1</td><td>1</td></tr>
<tr><td>0.0028</td><td>4</td><td>5</td></tr>
<tr><td>0.0061</td><td>13</td><td>13</td></tr>
<tr><td>0.013</td><td>29</td><td>29</td></tr>
<tr><td>0.029</td><td>27</td><td>27</td></tr>
</table>
Note: Oral LD_{50} of a.i. is 0.018 (0.0059-0.066) µg/bee (Harnish 2000a).</td><td>Thompson 1998
MRID 45639727
Supplemental/ Non-guideline</td></tr>
<tr><td>Honey bee, Apis mellifera</td><td>20% WG formulation
Contact Test (direct spray): 0.0014,0.0032,0.0072,0.016, 0.036, and 0.080 µg a.i./bee.

30 organisms in each group – i.e., 3 replicates of 10 bees per replicate.

Note: The NOEC for mortality from EPA appears to be incorrect. Using the Fisher Exact test, the p-value for the response at 0.08 µg/bee (26/30), relative to control (0/30), is 3.92×10^{-13}.</td><td>EPA Values
Contact LD_{50}: 0.024 (0.018-0.031) µg/bee
Contact NOEC (mortality): 0.08 µg/bee.

Investigator Values
Contact LD_{50}: 0.023 (0.014-0.046) µg/bee
Contact NOEC (sublethal – stumbling): 0.0032 µg/bee.
Dose response data (n=30).
<table>
<tr><th rowspan="2">Group or Dose (µg/bee)</th><th colspan="2">Number Dead</th></tr>
<tr><th>24 hr</th><th>48 hr</th></tr>
<tr><td>Solvent Cntrl</td><td>0</td><td>0</td></tr>
<tr><td>0.0014</td><td>0</td><td>1</td></tr>
<tr><td>0.0032</td><td>1</td><td>1</td></tr>
<tr><td>0.0072</td><td>2</td><td>2</td></tr>
<tr><td>0.016</td><td>13</td><td>19</td></tr>
<tr><td>0.036</td><td>19</td><td>19</td></tr>
<tr><td>0.080</td><td>26</td><td>26</td></tr>
</table>
Note: Contact LD_{50} of a.i. is 0.047 (0.039-0.057) µg/bee (Harnish 2000a).
Based on EPA values, the confidence intervals do no overlap.</td><td>Thompson 1998
MRID 45639727
Core</td></tr>
<tr><td colspan="4">Working Note: The Harnish 2000b study suggests that the formulation is less toxic than the a.i. The older study by Thompson suggests the opposite.</td></tr>
</table>

Species	Exposure	Response	Reference
OTHER INSECTS			
Predaceous mite, *Typhlodromus pyri*	MTI-446 20% SG (formulation): application rates of (spray to glass cage) of 15,20,30,40, and 60 g a.i./ha for 7 days and observed for an additional 7 days for reproductive effects.	Mortality rates of : 39, 32, 79, 47, and 96%, LC_{50}=30.1 g/ha [0.027 lb a.i./acre]. Decrease reproduction at 15 and 20 g a.i./ha. NOAEL: not determined. LOAEL: : 15 g/ha. [Equiv to 0.013 lb a.i./acre]	Aldershof 2000a Supplemental
Parasitoid wasp, *Aphidius rhopalosiphi*	MTI-446 20% SG (formulation): application rates (spray of glass cage) of 2, 7, 20, 70, and 200 mg a.i./ha for 2 days and observed for an additional 11 days for mortality and reproductive effects (parasitism).	Adjusted mortality rates of -7, -2, 9, 50, and 74%. Reduced parasitism at 20 mg/ha. LC_{50} (EPA): 77.2 mg/ha [0.00007 lb a.i./acre] NOEC (mortality): 7 mg a.i./ha [0.0000062 lb a.i./acre] LOEC: 20 mg a.i./ha [0.000018 lb a.i./acre]	Aldershof 2000b Supplemental
Predacious bug, *Orius laevigatus*	MTI-446 20% SG (formulation): spray of glass cage at rates of 1.36,2.72,5,8.8, and 13.6 mg a.i./ha for 9 days and observed for an additional 12 days for effects on fecundity.	LC_{50}: 13.3 mg a.i./ha [0.000012 lb a.i./acre] NOEC: not determined LOEC: 1.36 mg a.i./ha [0.0000012 lb a.i./acre]	Aldershof 2000c Supplemental
American cockroach (*Periplaneta americana*), body weight not specified	QSAR Study of dinotefuran and analogous. Abdominal injection of 3 animals at each dose with or without piperonyl butoxide or NIA [propargyl propyl benzenephosphonate]. Minimum lethal dose define as the dose that killed or paralyzed 2/3 animals within 24 hours.	**Dinotefuran alone:** Log(1/MLD *mol*): 8.36 [Table 2 of paper] The MLD 0.473 mg **Dinotefuran with PB:** Log(1/MLD *mol*): 8.86 [Table 2 of paper] The MLD is 0.287 mg **Dinotefuran with NIA:** Log(1/MLD *mol*): 9.66 [Table 2 of paper] The MLD is 0.0129 mg Data on PB and NIA discussed in text of this risk assessment.	Kiriyama and Nishimura 2002
Working Note on Kiriyama and Nishimura 2002: Units of *mol* are assumed to be millimoles. Not stated if "Log" is common (base 10) or natural (base e) but only the natural log makes sense. In the paper, Dinotefuran is Compound 7. Imidacloprid is Compound 2. See Fig 1 of paper. See Mathematica file, **Kiriyama Studies.nb** for QA of conversions. The details on synergists are in Table 2 of this risk assessment. No need to repeat above.			

Species	Exposure	Response	Reference
Housefly (*Musca domestica*), adult female	QSAR Study of dinotefuran and analogous. Injection into thorax. Metabolic inhibitors – piperonyl butoxide or NIA [propargyl propyl benzenephosphonate] – applied topically one hour prior to injection. Injection consisted of 0.22 µL at the specified molar concentrations.	**Results with no inhibitors** ***Dinotefuran*** Log(1/EC_{50} *mol*): 4.29 LD_{50}: 0.61 µg/fly ***Imidacloprid*** Log(1/EC_{50} *mol*): 4.70 LD_{50}: 0.51 µg/fly **Results with both inhibitors** ***Dinotefuran*** Log(1/EC_{50} *mol*): 5.02 LD_{50}: 0.29 µg/fly ***Imidacloprid*** Log(1/EC_{50} *mol*): 5.93 LD_{50}: 0.15 µg/fly All of the above results are in Table 2 of paper (p. 1097). Details for other inhibitors discussed in Section 4.1.2.3.2.	Kiriyama et al. 2003
Working Note on Kiriyama et al. 2003: Dinotefuran is Compound 3; Imidacloprid is Compound 1. See note on Kiriyama and Nishimura 2002 for assumptions concerning units and logs. See working notes above on other Kiriyama study. EC50 values converted to doses (mg) in **Kiriyama Studies.nb**. Body weight not specified. The weight of female houseflies is about 40 mg (Figure 1, p. 774 in Zanuncio et al. 2005). Thus, the LD50 for dinotefuran alone would be about 0.61 µg/40 mg ≈ 0.015 µg/mg ≈ 0.015 mg/g ≈ 15 mg/kg.			
American cockroach (*Periplaneta americana*)	Injections (10 animals/dose) preceded by topical application of piperonyl butoxide. Knockdown and mortality determined at 3 and 24 hours.	Reported 24h LD_{50}s, nMol/g (±)dinotefuran: 0.173 nMol/g bw (+)dinotefuran: 0.0545 nMol/g bw (-)dinotefuran: 2.67 nMol/g bw Dose conversion: 24h LD_{50}s, mg/kg bw (±)dinotefuran: 0.035 mg/kg bw (+)dinotefuran: 0.011 mg/kg bw (-)dinotefuran: 0.54 mg/kg bw	Mori et al. 2002
Working Note on Mori et al. 2002: See Mathematica file, **nMoles.nb**. Note that reported knockdown KD50s in Table 1 of paper are higher than LD50 values.			
Whitefly (*Bemisia tabaci*) Various strains	*Systemic Uptake Bioassay:* Dietary exposures by treating cotton leaves with agents at specified concentrations in solution and allowing uptake for 24 hours prior to use. **Concentrations of the agents in leaves are not reported.** Mortality assayed at 24 and 48 hours.	Dinotefuran more toxic than imidacloprid base treatment concentrations. Above from Table 1, IM-R strain. Dinotefuran also more toxic than imidacloprid to field populations (see Figures 1 to 4 of paper).	Prabhaker et al. 2005

	Dino, µg/ml	Imid, µg/ml
24h-LC_{50}	3.72	498
24h-LC_{90}	99	1102
48h-LC_{50}	0.098	293
48h-LC_{90}	4.56	843

Species	Exposure	Response	Reference
Working Note on Prabhaker et al. 2005: Dinotefuran is more toxic than imidacloprid. If I understand the experimental procedure, however, the actual concentrations of the two agents in the leaves may not have been directly comparable.			
American cockroach (*Periplaneta americana*)	Methods identical to Mori et al. 2002. Piperonyl butoxide applied 1 hour prior to dosing. Compounds injected into thorax. 4 to 8 animals per dose. Mortality assayed at 48 hours post-treatment	Dinotefuran: 48-hour LD_{50}: 0.28 (0.15-0.46) nmoles/g. Equivalent to 0.057 (0.030-0.093) mg/kg bw. Imidacloprid: LD_{50}: 0.7 (0.45-1.57) nmoles/g. Equivalent to 0.18 (0.12-0.40) mg/kg bw.	Tan et al. 2007
Working Note on Tan et al. 2007: See **nMoles.nb** for check of dose conversion from nmole/g bw to mg/kg bw. This is just like the conversion for Mori.			
German cockroach (*Blattella Germanica*)	Methods identical to Mori et al. 2002. Piperonyl butoxide applied 1 hour prior to dosing. Compounds injected into thorax. 30 organisms per compound. Single dose of 4 nmole/g cockroach.	Dinotefuran: 90% mortality at 48 hours. Dinotefuran dose of 4 µg/g equivalent to 0.8088 mg/kg. [808.8 ng/g = 0.8088 µg/g = 0.8088 mg/kg] Imidacloprid: no mortality at 48 hours.	Tan et al. 2007
Asian long-horned beetle (*Anoplophora glabripennis*)	Test concentrations of 1, 10, 100, 500, and 1000 ppm applied to maple leaves. Dried maple leaves folded to prevent direct contact with dinotefuran. Concentration of dinotefuran in maple leaves of 0.02, 0.53, 3.18, 10.46, and 19.47 ppm.	72 hour oral toxicity values: **Dinotefuran** LC_{50}: 2.2 (1.13-3.58) ppm LC_{90}: 22.7 (12.08-69.30) ppm **Imidacloprid** LC_{50}: 1.9 (0.78-4.7) ppm LC_{90}: 7.1 (2.73-29.86) ppm (See Table 8, p. 2298, of Wang paper).	Wang et al. 2005

Appendix 5: Toxicity to Fish

Freshwater Acute

Species	Exposure	Effects	Reference
Rainbow trout (*Oncorhynchus mykiss*), juvenile; 1.9 g (average wet weight); 5.5 cm (average length at start); 20/dose group	TGAI (97.26% purity): 0 or 99.5 mg/L for 96 hours under static conditions.	No mortality in control or exposed organisms. No signs of toxicity. NOEC: 99.5 mg/L	Peither 1999 MRID: 45639714 Core
Bluegill Sunfish (*Lepomis macrochirus*), juvenile; 1.2 ± 0.23 g (average wet weight); 4.2 ± 0.37 cm (average length at start); 20/dose group	TGAI (97.26% purity): 0 or 99.3 mg/L for 96 hours under static conditions.	No mortality in control or exposed organisms. No signs of toxicity. NOEC: 99.3 mg/L	Peither 2000b MRID 45639715 Core
Common carp (*Cyprinus carpio*); juvenile; 2.2 ± 0.28 g (average wet weight); 5.2 ± 0.24 cm (average length at start); 20/dose group	TGAI (97.26% purity): 0 or 99.1 mg/L for 96 hours under static conditions.	No mortality in control or exposed organisms. No signs of toxicity. NOEC: 99.1 mg/L	Peither 2000c MRID 45639716 Core

Saltwater Acute

Species	Exposure	Effects	Reference
Sheepshead Minnow (*Cyprinodon variegatus*), 0.35 g (wet); 2.8 cm (mean of controls at end of study)	TGAI (purity 99.2%): 0 or 109 mg/L for 96 hours under flow-through conditions.	LC_{50}: >109 mg/L NOEC: 109 mg/L No signs of toxicity.	Blankinship 2001b MRID 45639717 Supplemental (mean fish weight less than required initial range of 0.5-5 g)

Freshwater Chronic

Species	Exposure	Effects	Reference
Rainbow trout (*Oncorhynchus mykiss*); newly fertilized embryos (≈3-hours-old); 60 embryos/treatment, divided into 15 embryos/cup, 1 cup/chamber, and 4 replicate chambers/treatment	TGAI (purity 98.9%): Nominal concentrations of 0 or 10 mg/L for 94 days (34 days hatching and 60 days post-hatching) under flow-through conditions. See note below.	No effects on fertilization success, hatching success, time to hatch, time to swim up, post-hatch survival, terminal length, wet weights or dry weights.	Peither 2001 MRID 45639719 **INVALID**
Peither 2001, EFED Notes on Classification: Highly variable analytical results ranging from 6.36 mg/L at Day 76 to 12.9 mg/L on Day 0. *Low recoveries (compared to the general trend) were observed on Days 48,69, 76, and 84 of the study. The study author reported that no explanation was known for these low recoveries. Furthermore, the study was conducted at only one toxicant level, and this level did not adversely affect a life-stage. For these reasons, this study is not scientifically valid and does not fulfill the guideline requirement for a fish early-life stage toxicity study [§72-4(a)]. This study is classified as INVALID.*			

Appendix 6: Toxicity to Aquatic Invertebrates

All concentrations are measured rather than nominal in units of a.i. unless otherwise specified.

Freshwater Acute

Species	Exposure	Effects	Reference/ Classification
Daphnia magna; neonates (6- to 24-hours old); 5/dose group; 4 replicates	TGAI (purity 97.26%): 0 or 968.3 mg/L for 48 hours under static conditions.	No mortality or other signs of toxicity in test or control animals. NOEC: 968.3 mg/L	Peither 2000a MRID 45639709 Core
DN Phosphate			
Daphnia magna; neonates (6- to 24-hours old); 5/dose group; 2 replicates (except 6 replicates for 100 mg/L)	**DN Phosphate**: 0 , 10 or 110.6 mg/L for 48 hours under static conditions.	10% immobility at 110.6 mg/L. NOEC: 10 mg/L LOEC: 110.6 mg/L based on immobility in 1/10 animals vs. 0/10 immobility in control. Note that 0/10 vs 1/10 is not statistically significant using the Fisher Exact test [p=0.5],	Kelly et al. 2002 MRID 45639710 Core

Saltwater Acute

Species	Exposure	Effects	Reference/ Classification
Mysid shrimp (*Mysidopsis bahia*), <24 hours old, 20/level, divided into two replicates of 10 mysids each	TGAI (purity 99.2%); Measured concentrations: 0, 0.065, 0.13, 0.25, 0.49, 1.0, or 2.0 mg/L x 96 hours under flow-through conditions.	LC_{50}: 0.79 (0.49 to 1.0) mg/L NOEC: 0.49 mg/L (mortality and signs of toxicity) Sublethal effects: Erratic swimming and loss of equilibrium at 1.0 and 2.0 mg/L. Lethargy at 1.0 mg/L but not at 2 mg/L..	Blankinship et al. 2001a MRID 45639713 Core
Eastern oyster (*Crassostrea virginica*); 30.6-45.0 mm; 2 replicates/ treatment group	TGAI (purity not reported): 0, 15, 24, 47, 75, or 141 mg/L x 96 hours under flow-through conditions.	No effect on shell deposition. NOEC: 141 mg/L Categorized as **practically nontoxic** to the Eastern oyster on an acute toxicity basis.	Drottar et al. 2001 MRID 45639711 Core

Freshwater Chronic

Species	Exposure	Effects	Reference/ Classification
Daphnia magna; <24-hours-old; 10/concentration	TGAI (purity 97.26%): 0, 6.25, 12.5, 20, 50, or 100 mg/L nominal for 3 weeks under static renewal conditions. 100 mg/L assayed at 95.3 mg/L	No significant or substantial differences in mean number of young per adult, day to first brood, or mean length. NOEC: 100 mg/L nominal (95.3 mg/L measured)	Peither 2000d MRID 45639718 Core

Appendix 7: Toxicity to Aquatic Plants

Species	Exposure	Effects	Reference
Algae			
Pseudokirchneriella subcapitata (Selenastrum capricornutum)	**MNG Metabolite**: Nominal 0, 1.0, 10.0, or 100.0 mg/L for 96 hours under static conditions. 100 mg/L nominal = 98.7 mg/L measured	NOEC: 98.7 mg/L LOEC: not determined	Kelly and Ferguson 2002a MRID 45639733, Supplemental
Pseudokirchneriella subcapitata (Selenastrum capricornutum)	**DN Phosphate**: 0, 1.0, 10.0, or 100.0 mg/L for 96 hours. 100 mg/L nominal = 100.4 mg/L measured	NOEC: 100.5 mg/L LOEC: not determined	Kelly and Ferguson 2002b MRID 45639734, Supplemental
Pseudokirchneriella subcapitata (Selenastrum capricornutum)	TGAI (purity 97.26%): 6.25, 12.5,25, 50, or 100 mg/L (nominal) under static conditions. 100 mg/L assayed at 97.6 mg/L.	NOEC: 25 mg/L (cell density, most sensitive endpoint)	Seyfried 2000 MRID 45639732 Core
Macrophytes			
Lemna gibba	TGAI (purity 99.2%); Concentrations of 11, 20, 35, 62, or 110 mg/L for 7 days under static renewal conditions. Mean measured concentrations averaged 101% of nominal 100 mg/L test concentration.	NOEC: 110 mg/L for dry weight, growth rate, and biomass. LOEC: not determined	Batscher 2002 MRID 45639731 Supplemental: Scientifically sound but not consistent with guidelines

Appendix 8: Details of Gleams-Driver Runs for Dinotefuran

Run 1: Foliar Broadcast Application at 1 lb/acre

Table 1-1: Effective Offsite Application Rate (lb/acre)

Site	Clay	Loam	Sand
Dry and Warm Location	0.0041 (0 - 0.0266)	0 (0 - 4.30E-06)	0 (0 - 1.43E-06)
Dry and Temperate Location	0.0022 (0.000199 - 0.0075)	0 (0 - 2.76E-06)	0 (0 - 6.00E-07)
Dry and Cold Location	0.00153 (0.000105 - 0.0184)	0 (0 - 0)	0 (0 - 0)
Average Rainfall and Warm Location	0.04 (0.0122 - 0.119)	1.04E-05 (3.30E-07 - 0.000296)	1.48E-06 (5.80E-08 - 2.71E-05)
Average Rainfall and Temperate Location	0.0315 (0.0099 - 0.109)	8.10E-06 (0 - 0.000295)	1.39E-06 (7.80E-08 - 2.07E-05)
Average Rainfall and Cool Location	0.0236 (0.0078 - 0.057)	1.71E-07 (0 - 0.000069)	3.08E-07 (0 - 1.08E-05)
Wet and Warm Location	0.0221 (0.0068 - 0.086)	1.21E-06 (6.00E-08 - 0.000232)	1.00E-07 (0 - 0.000021)
Wet and Temperate Location	0.0198 (0.0064 - 0.058)	9.00E-07 (0 - 0.000091)	3.20E-07 (0 - 1.07E-05)
Wet and Cool Location	0.097 (0.053 - 0.134)	0.000138 (2.15E-07 - 0.00038)	2.01E-05 (1.80E-07 - 0.000033)
		Average of Central Values:	0.00896
		25th Percentile of Lower Bounds:	0
		Maximum Value:	0.134
		Summary of Values:	0.009 (0 - 0.134)

Run 1: Foliar Broadcast Application at 1 lb/acre

Table 1-2: Concentration in Top 12 Inches of Soil (ppm)

Site	**Clay**	**Loam**	**Sand**
Dry and Warm Location	0.238 (0.232 - 0.245)	0.218 (0.212 - 0.225)	0.215 (0.2 - 0.222)
Dry and Temperate Location	0.236 (0.23 - 0.241)	0.216 (0.208 - 0.221)	0.209 (0.184 - 0.219)
Dry and Cold Location	0.226 (0.223 - 0.232)	0.207 (0.204 - 0.21)	0.2 (0.191 - 0.209)
Average Rainfall and Warm Location	0.209 (0.188 - 0.224)	0.18 (0.173 - 0.198)	0.173 (0.17 - 0.176)
Average Rainfall and Temperate Location	0.204 (0.192 - 0.215)	0.177 (0.173 - 0.187)	0.173 (0.172 - 0.174)
Average Rainfall and Cool Location	0.2 (0.189 - 0.209)	0.176 (0.174 - 0.183)	0.173 (0.173 - 0.173)
Wet and Warm Location	0.188 (0.184 - 0.189)	0.173 (0.173 - 0.173)	0.173 (0.17 - 0.173)
Wet and Temperate Location	0.188 (0.186 - 0.189)	0.173 (0.173 - 0.173)	0.173 (0.172 - 0.173)
Wet and Cool Location	0.174 (0.163 - 0.188)	0.17 (0.164 - 0.173)	0.153 (0.128 - 0.173)
		Average of Central Values:	0.1924
		25th Percentile of Lower Bounds:	0.1725
		Maximum Value:	0.245
		Summary of Values:	0.192 (0.1725 - 0.245)

Run 1: Foliar Broadcast Application at 1 lb/acre

Table 1-3: Concentration in Top 60 Inches of Soil (ppm)

Site	Clay	Loam	Sand
Dry and Warm Location	0.048 (0.046 - 0.049)	0.044 (0.042 - 0.045)	0.043 (0.042 - 0.045)
Dry and Temperate Location	0.047 (0.047 - 0.048)	0.043 (0.043 - 0.044)	0.043 (0.042 - 0.044)
Dry and Cold Location	0.045 (0.045 - 0.046)	0.042 (0.041 - 0.042)	0.042 (0.041 - 0.042)
Average Rainfall and Warm Location	0.045 (0.039 - 0.046)	0.042 (0.041 - 0.042)	0.039 (0.036 - 0.041)
Average Rainfall and Temperate Location	0.045 (0.042 - 0.045)	0.042 (0.041 - 0.042)	0.038 (0.036 - 0.041)
Average Rainfall and Cool Location	0.045 (0.043 - 0.045)	0.041 (0.041 - 0.042)	0.037 (0.035 - 0.04)
Wet and Warm Location	0.044 (0.04 - 0.045)	0.036 (0.035 - 0.038)	0.035 (0.035 - 0.035)
Wet and Temperate Location	0.044 (0.042 - 0.045)	0.036 (0.035 - 0.039)	0.035 (0.035 - 0.035)
Wet and Cool Location	0.04 (0.038 - 0.043)	0.037 (0.036 - 0.039)	0.035 (0.035 - 0.035)
		Average of Central Values:	0.0412
		25th Percentile of Lower Bounds:	0.036
		Maximum Value:	0.049
		Summary of Values:	0.041 (0.036 - 0.049)

Run 1: Foliar Broadcast Application at 1 lb/acre

Table 1-4: Maximum Penetration into Soil Column (inches)

Site	Clay	Loam	Sand
Dry and Warm Location	18 (8 - 36)	18 (4 - 48)	18 (8 - 60)
Dry and Temperate Location	24 (12 - 42)	24 (8 - 60)	42 (12 - 60)
Dry and Cold Location	30 (24 - 36)	36 (24 - 42)	54 (36 - 60)
Average Rainfall and Warm Location	60 (48 - 60)	60 (60 - 60)	60 (60 - 60)
Average Rainfall and Temperate Location	60 (48 - 60)	60 (60 - 60)	60 (60 - 60)
Average Rainfall and Cool Location	60 (54 - 60)	60 (60 - 60)	60 (60 - 60)
Wet and Warm Location	60 (60 - 60)	60 (60 - 60)	60 (60 - 60)
Wet and Temperate Location	60 (60 - 60)	60 (60 - 60)	60 (60 - 60)
Wet and Cool Location	60 (60 - 60)	60 (60 - 60)	60 (60 - 60)
		Average of Central Values:	49.8
		25th Percentile of Lower Bounds:	24
		Maximum Value:	60
		Summary of Values:	49.8 (24 - 60)

Run 1: Foliar Broadcast Application at 1 lb/acre

Table 1-5: Pond Maximum Peak Concentration in Surface Water (ug/L or ppb)

Site	**Clay**	**Loam**	**Sand**
Dry and Warm Location	3.7 (0 - 29.5)	0 (0 - 0.005)	0 (0 - 0.1)
Dry and Temperate Location	1.72 (0.17 - 8.3)	0 (0 - 0.003)	0 (0 - 1)
Dry and Cold Location	1.34 (0.11 - 20)	0 (0 - 0)	0 (0 - 0.013)
Average Rainfall and Warm Location	33 (7.8 - 89)	4.1 (0.11 - 21.3)	83 (31.4 - 157)
Average Rainfall and Temperate Location	26.4 (6.8 - 91)	1.48 (0.023 - 15)	50 (25 - 141)
Average Rainfall and Cool Location	21.5 (5.7 - 53)	2.74 (0.06 - 8.6)	62 (36 - 92)
Wet and Warm Location	15.5 (7.4 - 39)	33 (20.8 - 52)	102 (76 - 138)
Wet and Temperate Location	17.2 (6.1 - 42)	30 (19.8 - 43)	53 (44 - 75)
Wet and Cool Location	26.1 (16.4 - 35)	43 (17.8 - 76)	90 (79 - 134)
		Average of Central Values:	26
		25th Percentile of Lower Bounds:	0.0115
		Maximum Value:	157
		Summary of Values:	26 (0.0115 - 157)

Run 1: Foliar Broadcast Application at 1 lb/acre

Table 1-6: Pond Annual Average Concentration in Surface Water (ug/L or ppb)

Site	**Clay**	**Loam**	**Sand**
Dry and Warm Location	0.4 (0 - 3.16)	0 (0 - 0.0008)	0 (0 - 0.014)
Dry and Temperate Location	0.24 (0.015 - 1)	0 (0 - 0.0006)	0 (0 - 0.16)
Dry and Cold Location	0.16 (0.011 - 1.85)	0 (0 - 0)	0 (0 - 0.002)
Average Rainfall and Warm Location	4.4 (1.65 - 11.9)	1.05 (0.026 - 6.4)	26.8 (12.2 - 45)
Average Rainfall and Temperate Location	3.8 (1.26 - 11.5)	0.4 (0.006 - 4.6)	19.4 (9 - 45)
Average Rainfall and Cool Location	2.72 (1 - 5.8)	0.8 (0.023 - 3.8)	21.5 (11.6 - 35)
Wet and Warm Location	4.6 (2.55 - 8.3)	16.9 (10.1 - 24.2)	29.4 (19.4 - 48)
Wet and Temperate Location	4.2 (1.96 - 7.8)	14.2 (9.9 - 17.8)	12.3 (7.3 - 20.8)
Wet and Cool Location	2.99 (2.24 - 5.2)	15.1 (7.5 - 23.9)	41 (26.3 - 49)
		Average of Central Values:	8.24
		25th Percentile of Lower Bounds:	0.003
		Maximum Value:	49
		Summary of Values:	8.24 (0.003 - 49)

Run 1: Foliar Broadcast Application at 1 lb/acre

Table 1-7: Stream Maximum Peak Concentration in Surface Water (ug/L or ppb)

Site	**Clay**	**Loam**	**Sand**
Dry and Warm Location	11.3 (0 - 55)	0 (0 - 0.012)	0 (0 - 0.15)
Dry and Temperate Location	4.6 (0.6 - 29.2)	0 (0 - 0.008)	0 (0 - 1.34)
Dry and Cold Location	5.8 (0.28 - 62)	0 (0 - 0)	0 (0 - 0.02)
Average Rainfall and Warm Location	67 (21.9 - 126)	1.79 (0.1 - 7.3)	39 (21.6 - 53)
Average Rainfall and Temperate Location	61 (21.8 - 114)	0.8 (0.027 - 4.4)	23.3 (14.9 - 47)
Average Rainfall and Cool Location	47 (13.3 - 98)	1.21 (0.07 - 2.73)	23.9 (16.4 - 40)
Wet and Warm Location	36 (11 - 96)	13.1 (9.8 - 16.3)	53 (44 - 61)
Wet and Temperate Location	44 (9.8 - 89)	12.8 (10 - 15.2)	45 (41 - 49)
Wet and Cool Location	90 (70 - 122)	18.2 (8 - 27.4)	74 (61 - 77)
		Average of Central Values:	24.9
		25th Percentile of Lower Bounds:	0.0135
		Maximum Value:	126
		Summary of Values:	24.9 (0.0135 - 126)

Run 1: Foliar Broadcast Application at 1 lb/acre

Table 1-8: Stream Annual Average Concentration in Surface Water (ug/L or ppb)

Site	**Clay**	**Loam**	**Sand**
Dry and Warm Location	0.04 (0 - 0.2)	0 (0 - 0.00004)	0 (0 - 0.0005)
Dry and Temperate Location	0.027 (0.0025 - 0.1)	0 (0 - 0.000023)	0 (0 - 0.014)
Dry and Cold Location	0.022 (0.0012 - 0.2)	0 (0 - 0)	0 (0 - 0.00011)
Average Rainfall and Warm Location	0.3 (0.17 - 0.6)	0.05 (0.0012 - 0.24)	1.32 (0.7 - 2.56)
Average Rainfall and Temperate Location	0.31 (0.12 - 0.5)	0.025 (0.0003 - 0.17)	1.17 (0.6 - 2.31)
Average Rainfall and Cool Location	0.22 (0.09 - 0.4)	0.05 (0.0012 - 0.21)	1.35 (0.8 - 2.46)
Wet and Warm Location	0.6 (0.4 - 1)	1.46 (1.14 - 1.84)	3.3 (2.55 - 4.6)
Wet and Temperate Location	0.5 (0.3 - 0.8)	1.42 (1.1 - 1.87)	2.54 (2 - 3.7)
Wet and Cool Location	0.7 (0.5 - 0.9)	1.71 (1 - 2.88)	5.3 (3.7 - 6.1)
		Average of Central Values:	0.83
		25th Percentile of Lower Bounds:	0.00015
		Maximum Value:	6.1
		Summary of Values:	0.83 (0.00015 - 6.1)

Run 2: Two Foliar Broadcast Applications at 1 lb/acre 14 Days Apart

Table 2-1: Effective Offsite Application Rate (lb/acre)

Site	Clay	Loam	Sand
Dry and Warm Location	0.0083 (0 - 0.054)	0 (0 - 8.80E-06)	0 (0 - 2.92E-06)
Dry and Temperate Location	0.0047 (0.00041 - 0.0165)	0 (0 - 5.60E-06)	0 (0 - 1.25E-06)
Dry and Cold Location	0.0035 (0.000244 - 0.038)	0 (0 - 0)	0 (0 - 0)
Average Rainfall and Warm Location	0.07 (0.0302 - 0.147)	2.36E-05 (9.00E-07 - 0.000298)	3.60E-06 (1.32E-07 - 2.95E-05)
Average Rainfall and Temperate Location	0.069 (0.0268 - 0.168)	0.000021 (0 - 0.00035)	3.60E-06 (2.47E-07 - 2.51E-05)
Average Rainfall and Cool Location	0.043 (0.015 - 0.091)	4.10E-07 (0 - 0.000069)	7.40E-07 (0 - 1.46E-05)
Wet and Warm Location	0.049 (0.0175 - 0.117)	7.50E-06 (2.39E-07 - 0.000264)	5.30E-07 (4.80E-09 - 2.48E-05)
Wet and Temperate Location	0.038 (0.0148 - 0.115)	2.13E-06 (0 - 0.000237)	7.50E-07 (8.50E-10 - 2.23E-05)
Wet and Cool Location	0.167 (0.1 - 0.246)	0.000205 (7.90E-06 - 0.00067)	2.63E-05 (7.20E-06 - 0.000046)
		Average of Central Values:	0.01677
		25th Percentile of Lower Bounds:	0
		Maximum Value:	0.246
		Summary of Values:	0.0168 (0 - 0.246)

Run 2: Two Foliar Broadcast Applications at 1 lb/acre 14 Days Apart

Table 2-2: Concentration in Top 12 Inches of Soil (ppm)

Site	Clay	Loam	Sand
Dry and Warm Location	0.47 (0.45 - 0.48)	0.43 (0.42 - 0.45)	0.42 (0.39 - 0.44)
Dry and Temperate Location	0.46 (0.45 - 0.48)	0.42 (0.4 - 0.45)	0.41 (0.36 - 0.44)
Dry and Cold Location	0.44 (0.43 - 0.47)	0.4 (0.4 - 0.43)	0.39 (0.37 - 0.43)
Average Rainfall and Warm Location	0.4 (0.37 - 0.42)	0.35 (0.33 - 0.38)	0.33 (0.286 - 0.34)
Average Rainfall and Temperate Location	0.39 (0.36 - 0.41)	0.34 (0.33 - 0.37)	0.34 (0.282 - 0.34)
Average Rainfall and Cool Location	0.38 (0.37 - 0.41)	0.34 (0.33 - 0.35)	0.34 (0.302 - 0.34)
Wet and Warm Location	0.36 (0.35 - 0.37)	0.33 (0.32 - 0.34)	0.32 (0.253 - 0.34)
Wet and Temperate Location	0.37 (0.36 - 0.43)	0.34 (0.33 - 0.4)	0.34 (0.32 - 0.39)
Wet and Cool Location	0.33 (0.286 - 0.36)	0.294 (0.211 - 0.34)	0.209 (0.163 - 0.32)
		Average of Central Values:	0.368
		25th Percentile of Lower Bounds:	0.311
		Maximum Value:	0.48
		Summary of Values:	0.37 (0.311 - 0.48)

Run 2: Two Foliar Broadcast Applications at 1 lb/acre 14 Days Apart

Table 2-3: Concentration in Top 60 Inches of Soil (ppm)

Site	Clay	Loam	Sand
Dry and Warm Location	0.094 (0.091 - 0.096)	0.086 (0.083 - 0.089)	0.085 (0.082 - 0.088)
Dry and Temperate Location	0.093 (0.091 - 0.097)	0.085 (0.083 - 0.089)	0.084 (0.082 - 0.089)
Dry and Cold Location	0.088 (0.087 - 0.095)	0.081 (0.08 - 0.086)	0.081 (0.08 - 0.086)
Average Rainfall and Warm Location	0.086 (0.081 - 0.088)	0.081 (0.079 - 0.082)	0.075 (0.068 - 0.08)
Average Rainfall and Temperate Location	0.086 (0.079 - 0.088)	0.081 (0.08 - 0.082)	0.074 (0.069 - 0.079)
Average Rainfall and Cool Location	0.087 (0.084 - 0.088)	0.081 (0.08 - 0.081)	0.072 (0.069 - 0.078)
Wet and Warm Location	0.084 (0.079 - 0.086)	0.07 (0.067 - 0.073)	0.067 (0.067 - 0.067)
Wet and Temperate Location	0.085 (0.082 - 0.087)	0.07 (0.068 - 0.079)	0.067 (0.067 - 0.079)
Wet and Cool Location	0.077 (0.073 - 0.083)	0.069 (0.068 - 0.073)	0.067 (0.058 - 0.067)
		Average of Central Values:	0.0799
		25th Percentile of Lower Bounds:	0.0685
		Maximum Value:	0.097
		Summary of Values:	0.08 (0.0685 - 0.097)

Run 2: Two Foliar Broadcast Applications at 1 lb/acre 14 Days Apart

Table 2-4: Maximum Penetration into Soil Column (inches)

Site	Clay	Loam	Sand
Dry and Warm Location	18 (8 - 36)	18 (4 - 48)	18 (8 - 60)
Dry and Temperate Location	30 (12 - 42)	24 (8 - 60)	42 (12 - 60)
Dry and Cold Location	30 (24 - 36)	36 (24 - 42)	54 (36 - 60)
Average Rainfall and Warm Location	60 (54 - 60)	60 (60 - 60)	60 (60 - 60)
Average Rainfall and Temperate Location	60 (54 - 60)	60 (60 - 60)	60 (60 - 60)
Average Rainfall and Cool Location	60 (60 - 60)	60 (60 - 60)	60 (60 - 60)
Wet and Warm Location	60 (60 - 60)	60 (60 - 60)	60 (60 - 60)
Wet and Temperate Location	60 (60 - 60)	60 (60 - 60)	60 (60 - 60)
Wet and Cool Location	60 (60 - 60)	60 (60 - 60)	60 (60 - 60)
		Average of Central Values:	50
		25th Percentile of Lower Bounds:	24
		Maximum Value:	60
		Summary of Values:	50 (24 - 60)

Run 2: Two Foliar Broadcast Applications at 1 lb/acre 14 Days Apart

Table 2-5: Stream, Maximum Peak Concentration in Surface Water (ug/L or ppb)

Site	Clay	Loam	Sand
Dry and Warm Location	23 (0 - 96)	0 (0 - 0.024)	0 (0 - 0.3)
Dry and Temperate Location	9.6 (1.26 - 52)	0 (0 - 0.017)	0 (0 - 2.74)
Dry and Cold Location	11.8 (0.6 - 128)	0 (0 - 2.5E-06)	0 (0 - 0.07)
Average Rainfall and Warm Location	83 (43 - 134)	3.4 (0.5 - 14.1)	72 (41 - 111)
Average Rainfall and Temperate Location	86 (27 - 133)	1.62 (0.1 - 8.8)	46 (29.8 - 92)
Average Rainfall and Cool Location	66 (23.9 - 112)	2.33 (0.4 - 5.4)	49 (33 - 80)
Wet and Warm Location	60 (22.5 - 108)	26.3 (20.1 - 34)	103 (90 - 119)
Wet and Temperate Location	63 (22.6 - 129)	26.4 (20.7 - 34)	91 (84 - 108)
Wet and Cool Location	96 (73 - 124)	25 (14.6 - 45)	101 (78 - 119)
		Average of Central Values:	38.7
		25th Percentile of Lower Bounds:	0.05
		Maximum Value:	134
		Summary of Values:	38.7 (0.05 - 134)

Run 2: Two Foliar Broadcast Applications at 1 lb/acre 14 Days Apart

Table 2-6: Stream, Annual Average Concentration in Surface Water (ug/L or ppb)

Site	Clay	Loam	Sand
Dry and Warm Location	0.09 (0 - 0.3)	0 (0 - 0.00007)	0 (0 - 0.0011)
Dry and Temperate Location	0.06 (0.005 - 0.2)	0 (0 - 0.00005)	0 (0 - 0.028)
Dry and Cold Location	0.05 (0.0029 - 0.4)	0 (0 - 7.0E-09)	0 (0 - 0.0004)
Average Rainfall and Warm Location	0.6 (0.3 - 0.9)	0.08 (0.008 - 0.5)	2.61 (1.3 - 5)
Average Rainfall and Temperate Location	0.6 (0.29 - 0.9)	0.05 (0.0008 - 0.4)	2.22 (1.09 - 4.7)
Average Rainfall and Cool Location	0.4 (0.18 - 0.8)	0.11 (0.013 - 0.4)	2.7 (1.6 - 4.7)
Wet and Warm Location	1.16 (0.7 - 1.89)	2.92 (2.32 - 3.7)	6.7 (5.1 - 9.1)
Wet and Temperate Location	1.04 (0.6 - 1.78)	2.92 (2.22 - 3.8)	5.3 (4.1 - 7.4)
Wet and Cool Location	1.31 (0.8 - 1.58)	2.64 (1.74 - 4.8)	8.9 (6.8 - 10.9)
		Average of Central Values:	1.57
		25th Percentile of Lower Bounds:	0.0004
		Maximum Value:	10.9
		Summary of Values:	1.57 (0.0004 - 10.9)

Run 2: Two Foliar Broadcast Applications at 1 lb/acre 14 Days Apart

Table 2-7: Pond, Maximum Peak Concentration in Surface Water (ug/L or ppb)

Site	Clay	Loam	Sand
Dry and Warm Location	7.6 (0 - 60)	0 (0 - 0.024)	0 (0 - 0.22)
Dry and Temperate Location	3.6 (0.3 - 17.5)	0 (0 - 0.017)	0 (0 - 1.96)
Dry and Cold Location	3.01 (0.24 - 42)	0 (0 - 2.5E-06)	0 (0 - 0.03)
Average Rainfall and Warm Location	52 (18 - 101)	3.4 (0.5 - 14.1)	152 (65 - 314)
Average Rainfall and Temperate Location	54 (15.9 - 133)	1.62 (0.1 - 8.8)	97 (46 - 264)
Average Rainfall and Cool Location	36 (10.3 - 76)	2.33 (0.4 - 5.4)	121 (73 - 184)
Wet and Warm Location	34 (17.2 - 65)	26.3 (20.1 - 34)	196 (151 - 258)
Wet and Temperate Location	36 (9.8 - 85)	26.4 (20.7 - 34)	109 (90 - 153)
Wet and Cool Location	34 (23.2 - 44)	25 (14.6 - 45)	164 (130 - 269)
		Average of Central Values:	43.9
		25th Percentile of Lower Bounds:	0.05
		Maximum Value:	314
		Summary of Values:	43.9 (0.05 - 314)

Run 2: Two Foliar Broadcast Applications at 1 lb/acre 14 Days Apart

Table 2-8: Pond, Annual Average Concentration in Surface Water (ug/L or ppb)

Site	Clay	Loam	Sand
Dry and Warm Location	0.8 (0 - 5.6)	0 (0 - 0.00007)	0 (0 - 0.03)
Dry and Temperate Location	0.5 (0.031 - 2.02)	0 (0 - 0.00005)	0 (0 - 0.3)
Dry and Cold Location	0.4 (0.027 - 3.8)	0 (0 - 7.0E-09)	0 (0 - 0.005)
Average Rainfall and Warm Location	8.2 (3.7 - 15)	0.08 (0.008 - 0.5)	50 (24.7 - 96)
Average Rainfall and Temperate Location	7.8 (3.4 - 17.1)	0.05 (0.0008 - 0.4)	38 (17.5 - 86)
Average Rainfall and Cool Location	4.8 (1.85 - 10.1)	0.11 (0.013 - 0.4)	43 (23.7 - 70)
Wet and Warm Location	9.4 (5.9 - 15.8)	2.92 (2.32 - 3.7)	58 (39 - 89)
Wet and Temperate Location	8.3 (4 - 15.3)	2.92 (2.22 - 3.8)	24.6 (15 - 42)
Wet and Cool Location	6.5 (4.8 - 9.2)	2.64 (1.74 - 4.8)	75 (61 - 90)
		Average of Central Values:	12.7
		25th Percentile of Lower Bounds:	0.0004
		Maximum Value:	96
		Summary of Values:	12.7 (0.0004 - 96)

Run 3: Ground Broadcast Application at 1 lb/acre

Table 3-1: Effective Offsite Application Rate (lb/acre)

Site	Clay	Loam	Sand
Dry and Warm Location	0.0056 (0 - 0.037)	0 (0 - 5.70E-06)	0 (0 - 1.90E-06)
Dry and Temperate Location	0.00302 (0.000274 - 0.0104)	0 (0 - 3.70E-06)	0 (0 - 7.90E-07)
Dry and Cold Location	0.00211 (0.000145 - 0.026)	0 (0 - 0)	0 (0 - 0)
Average Rainfall and Warm Location	0.053 (0.0168 - 0.215)	1.33E-05 (4.40E-07 - 0.00057)	1.79E-06 (7.80E-08 - 0.000042)
Average Rainfall and Temperate Location	0.042 (0.0135 - 0.168)	1.07E-05 (0 - 0.00046)	1.79E-06 (1.02E-07 - 0.000033)
Average Rainfall and Cool Location	0.033 (0.0107 - 0.078)	2.27E-07 (0 - 0.000092)	4.00E-07 (0 - 9.60E-06)
Wet and Warm Location	0.0284 (0.009 - 0.128)	1.61E-06 (8.00E-08 - 0.000243)	1.30E-07 (0 - 0.000042)
Wet and Temperate Location	0.0268 (0.0083 - 0.089)	1.20E-06 (0 - 0.000121)	4.30E-07 (0 - 2.13E-05)
Wet and Cool Location	0.128 (0.074 - 0.205)	0.000081 (2.10E-07 - 0.00064)	3.03E-05 (2.04E-08 - 0.000047)
		Average of Central Values:	0.01193
		25th Percentile of Lower Bounds:	0
		Maximum Value:	0.215
		Summary of Values:	0.0119 (0 - 0.215)

Run 3: Ground Broadcast Application at 1 lb/acre

Table 3-2: Concentration in Top 12 Inches of Soil (ppm)

Site	Clay	Loam	Sand
Dry and Warm Location	0.33 (0.32 - 0.34)	0.289 (0.281 - 0.299)	0.285 (0.265 - 0.295)
Dry and Temperate Location	0.33 (0.32 - 0.33)	0.286 (0.276 - 0.294)	0.277 (0.244 - 0.29)
Dry and Cold Location	0.311 (0.307 - 0.32)	0.274 (0.271 - 0.278)	0.266 (0.253 - 0.277)
Average Rainfall and Warm Location	0.29 (0.272 - 0.309)	0.239 (0.23 - 0.262)	0.229 (0.229 - 0.233)
Average Rainfall and Temperate Location	0.281 (0.266 - 0.294)	0.236 (0.23 - 0.248)	0.229 (0.229 - 0.23)
Average Rainfall and Cool Location	0.276 (0.26 - 0.288)	0.233 (0.23 - 0.242)	0.229 (0.229 - 0.23)
Wet and Warm Location	0.259 (0.258 - 0.26)	0.229 (0.229 - 0.229)	0.229 (0.228 - 0.229)
Wet and Temperate Location	0.26 (0.259 - 0.261)	0.229 (0.229 - 0.229)	0.229 (0.229 - 0.229)
Wet and Cool Location	0.25 (0.224 - 0.26)	0.229 (0.223 - 0.229)	0.223 (0.194 - 0.229)
		Average of Central Values:	0.2603
		25th Percentile of Lower Bounds:	0.229
		Maximum Value:	0.34
		Summary of Values:	0.26 (0.229 - 0.34)

Run 3: Ground Broadcast Application at 1 lb/acre

Table 3-3: Concentration in Top 60 Inches of Soil (ppm)

Site	Clay	Loam	Sand
Dry and Warm Location	0.066 (0.064 - 0.068)	0.058 (0.056 - 0.06)	0.057 (0.056 - 0.059)
Dry and Temperate Location	0.065 (0.064 - 0.067)	0.058 (0.057 - 0.059)	0.057 (0.056 - 0.058)
Dry and Cold Location	0.062 (0.061 - 0.064)	0.055 (0.054 - 0.056)	0.055 (0.054 - 0.056)
Average Rainfall and Warm Location	0.062 (0.059 - 0.063)	0.055 (0.055 - 0.056)	0.052 (0.047 - 0.055)
Average Rainfall and Temperate Location	0.062 (0.059 - 0.063)	0.055 (0.055 - 0.056)	0.051 (0.047 - 0.054)
Average Rainfall and Cool Location	0.062 (0.059 - 0.062)	0.055 (0.055 - 0.055)	0.05 (0.047 - 0.053)
Wet and Warm Location	0.061 (0.054 - 0.062)	0.048 (0.046 - 0.051)	0.046 (0.046 - 0.046)
Wet and Temperate Location	0.061 (0.059 - 0.062)	0.048 (0.046 - 0.052)	0.046 (0.046 - 0.046)
Wet and Cool Location	0.057 (0.052 - 0.061)	0.049 (0.047 - 0.052)	0.046 (0.046 - 0.046)
		Average of Central Values:	0.0555
		25th Percentile of Lower Bounds:	0.047
		Maximum Value:	0.068
		Summary of Values:	0.056 (0.047 - 0.068)

Run 3: Ground Broadcast Application at 1 lb/acre

Table 3-4: Maximum Penetration into Soil Column (inches)

Site	Clay	Loam	Sand
Dry and Warm Location	18 (8 - 36)	18 (4 - 48)	18 (8 - 60)
Dry and Temperate Location	24 (12 - 42)	24 (8 - 60)	42 (12 - 60)
Dry and Cold Location	30 (24 - 36)	36 (24 - 42)	54 (36 - 60)
Average Rainfall and Warm Location	60 (54 - 60)	60 (60 - 60)	60 (60 - 60)
Average Rainfall and Temperate Location	60 (54 - 60)	60 (60 - 60)	60 (60 - 60)
Average Rainfall and Cool Location	60 (54 - 60)	60 (60 - 60)	60 (60 - 60)
Wet and Warm Location	60 (60 - 60)	60 (60 - 60)	60 (60 - 60)
Wet and Temperate Location	60 (60 - 60)	60 (60 - 60)	60 (60 - 60)
Wet and Cool Location	60 (60 - 60)	60 (60 - 60)	60 (60 - 60)
		Average of Central Values:	49.8
		25th Percentile of Lower Bounds:	24
		Maximum Value:	60
		Summary of Values:	49.8 (24 - 60)

Run 3: Ground Broadcast Application at 1 lb/acre

Table 3-5: Stream, Maximum Peak Concentration in Surface Water (ug/L or ppb)

Site	Clay	Loam	Sand
Dry and Warm Location	15.6 (0 - 77)	0 (0 - 0.016)	0 (0 - 0.22)
Dry and Temperate Location	6.3 (0.9 - 40)	0 (0 - 0.011)	0 (0 - 1.78)
Dry and Cold Location	7.9 (0.4 - 87)	0 (0 - 2.1E-06)	0 (0 - 0.03)
Average Rainfall and Warm Location	92 (30.2 - 201)	2.37 (0.29 - 9.7)	52 (28.6 - 70)
Average Rainfall and Temperate Location	85 (31.4 - 180)	1.12 (0.04 - 5.8)	30.9 (19.7 - 62)
Average Rainfall and Cool Location	65 (18.4 - 149)	1.61 (0.1 - 3.6)	32 (21.8 - 53)
Wet and Warm Location	55 (14.6 - 185)	17.3 (13.1 - 21.7)	70 (58 - 81)
Wet and Temperate Location	61 (13.5 - 160)	17 (13.2 - 20.1)	59 (55 - 65)
Wet and Cool Location	173 (97 - 197)	24.5 (11.1 - 37)	99 (81 - 102)
		Average of Central Values:	35.8
		25th Percentile of Lower Bounds:	0.02
		Maximum Value:	201
		Summary of Values:	35.8 (0.02 - 201)

Run 3: Ground Broadcast Application at 1 lb/acre

Table 3-6: Stream, Annual Average Concentration in Surface Water (ug/L or ppb)

Site	Clay	Loam	Sand
Dry and Warm Location	0.06 (0 - 0.28)	0 (0 - 0.00005)	0 (0 - 0.0007)
Dry and Temperate Location	0.04 (0.003 - 0.13)	0 (0 - 0.00003)	0 (0 - 0.018)
Dry and Cold Location	0.03 (0.0016 - 0.26)	0 (0 - 6.0E-09)	0 (0 - 0.00014)
Average Rainfall and Warm Location	0.5 (0.23 - 0.9)	0.06 (0.005 - 0.3)	1.74 (0.9 - 3.4)
Average Rainfall and Temperate Location	0.4 (0.17 - 0.7)	0.03 (0.0005 - 0.23)	1.55 (0.7 - 3.07)
Average Rainfall and Cool Location	0.31 (0.13 - 0.7)	0.07 (0.0016 - 0.28)	1.79 (1.04 - 3.3)
Wet and Warm Location	0.8 (0.5 - 1.48)	1.94 (1.52 - 2.44)	4.4 (3.4 - 6.1)
Wet and Temperate Location	0.7 (0.4 - 1.16)	1.88 (1.45 - 2.48)	3.4 (2.66 - 4.9)
Wet and Cool Location	0.9 (0.7 - 1.2)	2.29 (1.29 - 3.8)	7 (4.9 - 8)
		Average of Central Values:	1.11
		25th Percentile of Lower Bounds:	0.00025
		Maximum Value:	8
		Summary of Values:	1.11 (0.00025 - 8)

Run 3: Ground Broadcast Application at 1 lb/acre

Table 3-7: Pond, Maximum Peak Concentration in Surface Water (ug/L or ppb)

Site	Clay	Loam	Sand
Dry and Warm Location	5.1 (0 - 41)	0 (0 - 0.007)	0 (0 - 0.14)
Dry and Temperate Location	2.36 (0.23 - 11.4)	0 (0 - 0.004)	0 (0 - 1.27)
Dry and Cold Location	1.85 (0.15 - 27.6)	0 (0 - 9.0E-07)	0 (0 - 0.018)
Average Rainfall and Warm Location	46 (10.8 - 164)	5.4 (0.4 - 28.3)	110 (42 - 208)
Average Rainfall and Temperate Location	35 (9.4 - 145)	2.05 (0.06 - 19.9)	66 (33 - 187)
Average Rainfall and Cool Location	29.7 (7.9 - 75)	3.7 (0.08 - 11.5)	82 (48 - 123)
Wet and Warm Location	21 (9.9 - 59)	44 (27.7 - 69)	135 (101 - 183)
Wet and Temperate Location	23.8 (8.5 - 80)	40 (26.2 - 57)	71 (58 - 99)
Wet and Cool Location	36 (21.3 - 60)	57 (24.3 - 102)	119 (106 - 178)
		Average of Central Values:	34.7
		25th Percentile of Lower Bounds:	0.03
		Maximum Value:	208
		Summary of Values:	34.7 (0.03 - 208)

Run 3: Ground Broadcast Application at 1 lb/acre

Table 3-8: Pond, Annual Average Concentration in Surface Water (ug/L or ppb)

Site	Clay	Loam	Sand
Dry and Warm Location	0.6 (0 - 4.4)	0 (0 - 0.0011)	0 (0 - 0.021)
Dry and Temperate Location	0.3 (0.021 - 1.31)	0 (0 - 0.0007)	0 (0 - 0.22)
Dry and Cold Location	0.22 (0.015 - 2.64)	0 (0 - 1.6E-07)	0 (0 - 0.0026)
Average Rainfall and Warm Location	6 (2.3 - 21.3)	1.44 (0.07 - 8.5)	36 (16.3 - 60)
Average Rainfall and Temperate Location	5.1 (1.74 - 17.4)	0.6 (0.009 - 6.1)	26.3 (11.9 - 60)
Average Rainfall and Cool Location	3.7 (1.31 - 8.7)	1.15 (0.03 - 5.1)	28.5 (15.3 - 47)
Wet and Warm Location	6.3 (3.7 - 13.7)	22.5 (13.4 - 32)	40 (26 - 63)
Wet and Temperate Location	5.8 (2.74 - 11.1)	18.8 (13.2 - 23.6)	16.2 (9.7 - 27.4)
Wet and Cool Location	4.1 (3.14 - 7.2)	20.5 (10.1 - 32)	54 (35 - 65)
		Average of Central Values:	11
		25th Percentile of Lower Bounds:	0.0045
		Maximum Value:	65
		Summary of Values:	11 (0.0045 - 65)

Run 4: Soil Injection at 1 lb/acre

Table 5-1: Effective Offsite Application Rate (lb/acre)

Site	Clay	Loam	Sand
Dry and Warm Location	0.00073 (0 - 0.0061)	0 (0 - 1.99E-06)	0 (0 - 9.80E-07)
Dry and Temperate Location	0.00099 (0.0001 - 0.0033)	0 (0 - 3.60E-06)	0 (0 - 7.80E-07)
Dry and Cold Location	0.00033 (0.00005 - 0.00307)	0 (0 - 0)	0 (0 - 0)
Average Rainfall and Warm Location	0.0129 (0.009 - 0.0188)	5.10E-06 (4.30E-07 - 2.77E-05)	1.01E-06 (6.90E-08 - 6.10E-06)
Average Rainfall and Temperate Location	0.0124 (0.008 - 0.0191)	7.70E-06 (0 - 2.86E-05)	1.30E-06 (1.00E-07 - 5.20E-06)
Average Rainfall and Cool Location	0.0064 (0.00311 - 0.0125)	2.23E-07 (0 - 1.26E-05)	2.89E-07 (0 - 2.90E-06)
Wet and Warm Location	0.0045 (0.00269 - 0.007)	9.60E-07 (7.10E-08 - 0.000008)	9.60E-08 (0 - 1.04E-06)
Wet and Temperate Location	0.0055 (0.00255 - 0.0101)	9.90E-07 (0 - 1.89E-05)	3.60E-07 (0 - 3.70E-06)
Wet and Cool Location	0.00178 (0.00071 - 0.0041)	8.30E-07 (2.25E-08 - 3.40E-06)	1.88E-07 (2.65E-09 - 5.60E-07)
		Average of Central Values:	0.001687
		25th Percentile of Lower Bounds:	0
		Maximum Value:	0.0191
		Summary of Values:	0.00169 (0 - 0.0191)

Run 4: Soil Injection at 1 lb/acre

Table 5-2: Concentration in Top 12 Inches of Soil (ppm)

Site	Clay	Loam	Sand
Dry and Warm Location	0.33 (0.32 - 0.34)	0.289 (0.28 - 0.299)	0.284 (0.265 - 0.295)
Dry and Temperate Location	0.33 (0.32 - 0.33)	0.286 (0.273 - 0.293)	0.278 (0.244 - 0.29)
Dry and Cold Location	0.31 (0.305 - 0.32)	0.273 (0.269 - 0.277)	0.265 (0.252 - 0.276)
Average Rainfall and Warm Location	0.291 (0.277 - 0.308)	0.238 (0.23 - 0.261)	0.229 (0.229 - 0.232)
Average Rainfall and Temperate Location	0.282 (0.27 - 0.297)	0.235 (0.23 - 0.248)	0.229 (0.229 - 0.23)
Average Rainfall and Cool Location	0.277 (0.268 - 0.289)	0.233 (0.23 - 0.242)	0.229 (0.229 - 0.229)
Wet and Warm Location	0.259 (0.259 - 0.26)	0.229 (0.229 - 0.229)	0.229 (0.228 - 0.229)
Wet and Temperate Location	0.26 (0.259 - 0.261)	0.229 (0.229 - 0.229)	0.229 (0.229 - 0.229)
Wet and Cool Location	0.259 (0.259 - 0.261)	0.228 (0.223 - 0.229)	0.222 (0.194 - 0.229)
		Average of Central Values:	0.2604
		25th Percentile of Lower Bounds:	0.229
		Maximum Value:	0.34
		Summary of Values:	0.26 (0.229 - 0.34)

Run 4: Soil Injection at 1 lb/acre

Table 5-3: Concentration in Top 60 Inches of Soil (ppm)

Site	Clay	Loam	Sand
Dry and Warm Location	0.065 (0.063 - 0.067)	0.058 (0.056 - 0.06)	0.057 (0.056 - 0.059)
Dry and Temperate Location	0.065 (0.064 - 0.067)	0.058 (0.056 - 0.059)	0.057 (0.056 - 0.058)
Dry and Cold Location	0.062 (0.061 - 0.064)	0.055 (0.054 - 0.055)	0.055 (0.054 - 0.055)
Average Rainfall and Warm Location	0.062 (0.062 - 0.063)	0.055 (0.054 - 0.055)	0.052 (0.047 - 0.055)
Average Rainfall and Temperate Location	0.062 (0.062 - 0.063)	0.055 (0.055 - 0.055)	0.051 (0.047 - 0.054)
Average Rainfall and Cool Location	0.062 (0.062 - 0.062)	0.055 (0.055 - 0.055)	0.05 (0.047 - 0.053)
Wet and Warm Location	0.061 (0.059 - 0.062)	0.048 (0.046 - 0.05)	0.046 (0.046 - 0.046)
Wet and Temperate Location	0.061 (0.059 - 0.062)	0.048 (0.046 - 0.051)	0.046 (0.046 - 0.046)
Wet and Cool Location	0.062 (0.061 - 0.062)	0.049 (0.047 - 0.052)	0.046 (0.046 - 0.046)
		Average of Central Values:	0.0557
		25th Percentile of Lower Bounds:	0.047
		Maximum Value:	0.067
		Summary of Values:	0.056 (0.047 - 0.067)

Run 4: Soil Injection at 1 lb/acre

Table 5-4: Maximum Penetration into Soil Column (inches)

Site	Clay	Loam	Sand
Dry and Warm Location	18 (8 - 36)	18 (4 - 48)	18 (8 - 60)
Dry and Temperate Location	24 (12 - 42)	24 (8 - 60)	42 (12 - 60)
Dry and Cold Location	30 (24 - 36)	36 (24 - 42)	54 (36 - 60)
Average Rainfall and Warm Location	60 (54 - 60)	60 (60 - 60)	60 (60 - 60)
Average Rainfall and Temperate Location	60 (54 - 60)	60 (60 - 60)	60 (60 - 60)
Average Rainfall and Cool Location	60 (54 - 60)	60 (60 - 60)	60 (60 - 60)
Wet and Warm Location	60 (60 - 60)	60 (60 - 60)	60 (60 - 60)
Wet and Temperate Location	60 (60 - 60)	60 (60 - 60)	60 (60 - 60)
Wet and Cool Location	60 (60 - 60)	60 (60 - 60)	60 (60 - 60)
		Average of Central Values:	49.8
		25th Percentile of Lower Bounds:	24
		Maximum Value:	60
		Summary of Values:	49.8 (24 - 60)

Run 4: Soil Injection at 1 lb/acre

Table 5-5: Stream, Maximum Peak Concentration in Surface Water (ug/L or ppb)

Site	Clay	Loam	Sand
Dry and Warm Location	2.02	0	0
	(0 - 7.3)	(0 - 0.009)	(0 - 0.22)
Dry and Temperate	1.96	0	0
Location	(0.5 - 4.7)	(0 - 0.011)	(0 - 1.79)
Dry and Cold Location	1.22	0	0
	(0.14 - 9.4)	(0 - 2.1E-06)	(0 - 0.03)
Average Rainfall and	7.8	2.38	52
Warm Location	(5.6 - 13)	(0.29 - 9.7)	(28.6 - 70)
Average Rainfall and	8.5	1.12	30.7
Temperate Location	(5.3 - 11.7)	(0.04 - 5.8)	(19.8 - 62)
Average Rainfall and	5.9	1.59	31.6
Cool Location	(3.2 - 9.5)	(0.1 - 3.6)	(22.1 - 53)
Wet and Warm Location	4.8	17.4	70
	(3.3 - 7.8)	(13.1 - 21.7)	(58 - 81)
Wet and Temperate	6.4	16.9	59
Location	(4.1 - 11)	(13.1 - 20.1)	(54 - 65)
Wet and Cool Location	3.8	24.6	99
	(2.72 - 6.2)	(11.2 - 37)	(81 - 102)
		Average of Central Values:	16.6
		25th Percentile of Lower Bounds:	0.02
		Maximum Value:	102
		Summary of Values:	16.6 (0.02 - 102)

Run 4: Soil Injection at 1 lb/acre

Table 5-6: Stream, Annual Average Concentration in Surface Water (ug/L or ppb)

Site	Clay	Loam	Sand
Dry and Warm Location	0.008 (0 - 0.05)	0 (0 - 0.000024)	0 (0 - 0.0007)
Dry and Temperate Location	0.012 (0.0018 - 0.04)	0 (0 - 0.00003)	0 (0 - 0.018)
Dry and Cold Location	0.006 (0.0007 - 0.03)	0 (0 - 6.0E-09)	0 (0 - 0.00015)
Average Rainfall and Warm Location	0.11 (0.08 - 0.16)	0.06 (0.004 - 0.3)	1.75 (0.9 - 3.4)
Average Rainfall and Temperate Location	0.11 (0.08 - 0.15)	0.03 (0.0005 - 0.23)	1.55 (0.7 - 3.05)
Average Rainfall and Cool Location	0.07 (0.03 - 0.1)	0.07 (0.0016 - 0.29)	1.78 (1.03 - 3.3)
Wet and Warm Location	0.7 (0.4 - 1.05)	1.94 (1.53 - 2.45)	4.4 (3.4 - 6.1)
Wet and Temperate Location	0.6 (0.27 - 1)	1.86 (1.45 - 2.45)	3.4 (2.65 - 4.9)
Wet and Cool Location	0.5 (0.29 - 0.8)	2.3 (1.3 - 3.8)	7 (4.9 - 8.1)
		Average of Central Values:	1.05
		25th Percentile of Lower Bounds:	0.00025
		Maximum Value:	8.1
		Summary of Values:	1.05 (0.00025 - 8.1)

Run 4: Soil Injection at 1 lb/acre

Table 5-7: Pond, Maximum Peak Concentration in Surface Water (ug/L or ppb)

Site	Clay	Loam	Sand
Dry and Warm Location	0.7 (0 - 4.9)	0 (0 - 0.004)	0 (0 - 0.14)
Dry and Temperate Location	0.8 (0.11 - 2.37)	0 (0 - 0.004)	0 (0 - 1.28)
Dry and Cold Location	0.31 (0.05 - 3.06)	0 (0 - 9.0E-07)	0 (0 - 0.018)
Average Rainfall and Warm Location	6.3 (4.1 - 11.9)	5.4 (0.4 - 28.1)	110 (42 - 207)
Average Rainfall and Temperate Location	7 (4.3 - 12.3)	2.01 (0.06 - 19.9)	66 (33 - 187)
Average Rainfall and Cool Location	3.8 (1.84 - 7.3)	3.8 (0.08 - 11.5)	82 (47 - 123)
Wet and Warm Location	10.3 (6.1 - 15.3)	43 (27.9 - 69)	135 (101 - 183)
Wet and Temperate Location	8.6 (3.6 - 15.1)	39 (26.2 - 57)	70 (58 - 100)
Wet and Cool Location	7.3 (5 - 12.3)	57 (24.3 - 102)	119 (106 - 178)
		Average of Central Values:	28.8
		25th Percentile of Lower Bounds:	0.025
		Maximum Value:	207
		Summary of Values:	28.8 (0.025 - 207)

Run 4: Soil Injection at 1 lb/acre

Table 5-8: Pond, Annual Average Concentration in Surface Water (ug/L or ppb)

Site	Clay	Loam	Sand
Dry and Warm Location	0.08 (0 - 0.6)	0 (0 - 0.0005)	0 (0 - 0.021)
Dry and Temperate Location	0.11 (0.013 - 0.4)	0 (0 - 0.0007)	0 (0 - 0.22)
Dry and Cold Location	0.04 (0.005 - 0.31)	0 (0 - 1.6E-07)	0 (0 - 0.0026)
Average Rainfall and Warm Location	1.55 (1.11 - 2.22)	1.45 (0.07 - 8.6)	36 (16.3 - 60)
Average Rainfall and Temperate Location	1.53 (0.9 - 2.12)	0.6 (0.009 - 6.1)	26.3 (11.9 - 60)
Average Rainfall and Cool Location	0.8 (0.4 - 1.37)	1.15 (0.03 - 5.1)	28.6 (15.2 - 47)
Wet and Warm Location	4.7 (2.83 - 7.3)	22.5 (13.4 - 32)	40 (26.1 - 64)
Wet and Temperate Location	3.8 (1.57 - 6.2)	18.8 (13.2 - 23.5)	16.3 (9.7 - 27.3)
Wet and Cool Location	2.87 (1.8 - 3.8)	20.6 (10.2 - 32)	54 (35 - 65)
		Average of Central Values:	10.4
		25th Percentile of Lower Bounds:	0.0025
		Maximum Value:	65
		Summary of Values:	10.4 (0.0025 - 65)

Appendix 9: Risk Characterization for Workers

Attachment 1a - Aerial Broadcast Foliar Safari 20 SG - One Application.xls

	A	B	C	D	E	F
1	**Worksheet E01: Summary of Worker Hazard Quotients (Toxicity)**					
2	**Application Rate:**	**0.2**	**lb a.i./acre**			E01aV5-1Wrkr
3	**Scenario**	**Receptor**	**Hazard Quotients**			**Toxicity Value**
4			**Central**	**Lower**	**Upper**	
5	**Accidental/Incidental Exposures**					
6	Contaminated Gloves, 1 min.	Worker	2E-05	2E-06	8E-05	**1.25**
7	Contaminated Gloves, 1 hour	Worker	1E-03	1E-04	5E-03	**1.25**
8	Spill on Hands, 1 hour	Worker	3E-04	3E-05	2E-03	**1.25**
9	Spill on lower legs, 1 hour	Worker	8E-04	7E-05	4E-03	**1.25**
10	**General Exposures**					
11		Worker	1E-02	2E-04	7E-02	**0.22**

Attachment 1b - Aerial Broadcast Foliar Safari 20 SG - Two Applications.xls

	A	B	C	D	E	F
1	**Worksheet E01: Summary of Worker Hazard Quotients (Toxicity)**					
2	**Application Rate:**	**0.2**	**lb a.i./acre**			E01aV5-1Wrkr
3	**Scenario**	**Receptor**	**Hazard Quotients**			**Toxicity Value**
4			**Central**	**Lower**	**Upper**	
5	**Accidental/Incidental Exposures**					
6	Contaminated Gloves, 1 min.	Worker	2E-05	2E-06	8E-05	**1.25**
7	Contaminated Gloves, 1 hour	Worker	1E-03	1E-04	5E-03	**1.25**
8	Spill on Hands, 1 hour	Worker	3E-04	3E-05	2E-03	**1.25**
9	Spill on lower legs, 1 hour	Worker	8E-04	7E-05	4E-03	**1.25**
10	**General Exposures**					
11		Worker	1E-02	2E-04	7E-02	**0.22**

Attachment 2 - Aerial Broadcast Soil (Granular) Safari 2 G.xls

	A	B	C	D	E	F
1	**Worksheet E01: Summary of Worker Hazard Quotients (Toxicity)**					
2	**Application Rate:**	**0.54**	**lb a.i./acre**			E01aV5-1Wrkr
3	**Scenario**	**Receptor**	**Hazard Quotients**			**Toxicity Value**
4			**Central**	**Lower**	**Upper**	
5	**Accidental/Incidental Exposures**					
6	Contaminated Gloves, 1 min.	Worker	3E-03	1E-03	6E-03	**1.25**
7	Contaminated Gloves, 1 hour	Worker	0.2	8E-02	0.4	**1.25**
8	Spill on Hands, 1 hour	Worker	No exposure assessment.			
9	Spill on lower legs, 1 hour	Worker	No exposure assessment.			
10	**General Exposures**					
11		Worker	4E-02	6E-04	0.2	**0.22**

Attachment 3 - Bark Application Safari 20 SG.xls

	A	B	C	D	E	F
1	**Worksheet E01: Summary of Worker Hazard Quotients (Toxicity)**					
2	**Application Rate:**	**0.054**	**lb a.i./acre**			E01aV5-1Wrkr
3	**Scenario**	**Receptor**	**Hazard Quotients**			**Toxicity Value**
4			**Central**	**Lower**	**Upper**	
5	**Accidental/Incidental Exposures**					
6	Contaminated Gloves, 1 min.	Worker	2E-03	9E-04	4E-03	**1.25**
7	Contaminated Gloves, 1 hour	Worker	0.1	5E-02	0.3	**1.25**
8	Spill on Hands, 1 hour	Worker	3E-02	1E-02	0.1	**1.25**
9	Spill on lower legs, 1 hour	Worker	9E-02	3E-02	0.2	**1.25**
10	**General Exposures**					
11		Worker	7E-03	7E-04	2E-02	**0.22**

Attachment 4 - Soil Injection Safari 20 SG.xls

	A	B	C	D	E	F
1	**Worksheet E01: Summary of Worker Hazard Quotients (Toxicity)**					
2	**Application Rate:**	**0.54**	**lb a.i./acre**			E01aV5-1Wrkr
3	**Scenario**	**Receptor**	**Hazard Quotients**			**Toxicity Value**
4			**Central**	**Lower**	**Upper**	
5	**Accidental/Incidental Exposures**					
6	Contaminated Gloves, 1 min.	Worker	6E-03	3E-03	1E-02	**1.25**
7	Contaminated Gloves, 1 hour	Worker	0.3	0.2	0.8	**1.25**
8	Spill on Hands, 1 hour	Worker	0.1	4E-02	0.3	**1.25**
9	Spill on lower legs, 1 hour	Worker	0.3	9E-02	0.7	**1.25**
10	**General Exposures**					
11		Worker	3E-02	1E-03	0.2	**0.22**

Attachment 5 - Tree Injection Safari 20 SG.xls

	A	B	C	D	E	F
1	**Worksheet E01: Summary of Worker Hazard Quotients (Toxicity)**					
2	**Application Rate:**	**0.054**	**lb a.i./acre**			E01aV5-1Wrkr
3	**Scenario**	**Receptor**	**Hazard Quotients**			**Toxicity Value**
4			**Central**	**Lower**	**Upper**	
5	**Accidental/Incidental Exposures**					
6	Contaminated Gloves, 1 min.	Worker	2E-03	1E-03	5E-03	**1.25**
7	Contaminated Gloves, 1 hour	Worker	0.1	6E-02	0.3	**1.25**
8	Spill on Hands, 1 hour	Worker	4E-02	1E-02	0.1	**1.25**
9	Spill on lower legs, 1 hour	Worker	1E-01	3E-02	0.3	**1.25**
10	**General Exposures**					
11		Worker	3E-03	1E-04	2E-02	**0.22**

Appendix 10: Risk Characterization for General Public

Attachment 1a - Aerial Broadcast Foliar Safari 20 SG - One Application.xls

	A	B	C	D	E	F
1	**Worksheet E03: Summary of Hazard Quotients (Toxicity) for the General Public**					
2	**Application Rate:**	**0.2**	**lb a.i./acre**			E03aV5
3	**Scenario**	**Receptor**	**Hazard Quotients**			**Toxicity Value**
4			**Central**	**Lower**	**Upper**	
5	**Accidental Acute Exposures (dose in mg/kg/event)**					
6	Direct Spray of Child, whole body	Child	1E-02	1E-03	7E-02	**1.25**
7	Direct Spray of Woman, feet and lower legs	Adult Female	1E-03	1E-04	7E-03	**1.25**
8	Water consumption (spill)	Child	5E-03	2E-04	3E-02	**1.25**
9	Fish consumption (spill)	Adult Male	5E-04	2E-05	2E-03	**1.25**
10	Fish consumption (spill)	Subsistence Populations	2E-03	1E-04	1E-02	**1.25**
11	**Non-Accidental Acute Exposures (dose in mg/kg/event)**					
12	Vegetation Contact, shorts and T-shirt	Adult Female	5E-03	7E-05	2E-02	**1.25**
13	Contaminated Fruit	Adult Female	2E-03	9E-04	3E-02	**1.25**
14	Contaminated Vegetation	Adult Female	3E-02	2E-03	0.2	**1.25**
15	Swimming, one hour	Adult Female	5E-07	1E-10	7E-06	**1.25**
16	Water consumption	Child	3E-04	9E-08	3E-03	**1.25**
17	Fish consumption	Adult Male	3E-05	1E-08	2E-04	**1.25**
18	Fish consumption	Subsistence Populations	1E-04	6E-08	8E-04	**1.25**
19	**Chronic/Longer Term Exposures (dose in mg/kg/day)**					
20	Contaminated Fruit	Adult Female	1E-02	3E-04	0.3	**0.02**
21	Contaminated Vegetation	Adult Female	0.2	6E-04	**2**	**0.02**
22	Water consumption	Adult Male	2E-03	6E-08	2E-02	**0.02**
23	Fish consumption	Adult Male	4E-05	1E-09	2E-04	**0.02**
24	Fish consumption	Subsistence Populations	3E-04	1E-08	2E-03	**0.02**

Attachment 1b - Aerial Broadcast Foliar Safari 20 SG - Two Applications.xls

	A	B	C	D	E	F
1	**Worksheet E03: Summary of Hazard Quotients (Toxicity) for the General Public**					
2	**Application Rate:**	**0.2**	**lb a.i./acre**			E03aV5
3	**Scenario**	**Receptor**	**Hazard Quotients**			**Toxicity Value**
4			**Central**	**Lower**	**Upper**	
5	**Accidental Acute Exposures (dose in mg/kg/event)**					
6	Direct Spray of Child, whole body	Child	1E-02	1E-03	7E-02	**1.25**
7	Direct Spray of Woman, feet and lower legs	Adult Female	1E-03	1E-04	7E-03	**1.25**
8	Water consumption (spill)	Child	5E-03	2E-04	3E-02	**1.25**
9	Fish consumption (spill)	Adult Male	5E-04	2E-05	2E-03	**1.25**
10	Fish consumption (spill)	Subsistence Populations	2E-03	1E-04	1E-02	**1.25**
11	**Non-Accidental Acute Exposures (dose in mg/kg/event)**					
12	Vegetation Contact, shorts and T-shirt	Adult Female	5E-03	7E-05	2E-02	**1.25**
13	Contaminated Fruit	Adult Female	2E-03	9E-04	4E-02	**1.25**
14	Contaminated Vegetation	Adult Female	3E-02	2E-03	0.3	**1.25**
15	Swimming, one hour	Adult Female	8E-07	4E-10	1E-05	**1.25**
16	Water consumption	Child	5E-04	4E-07	6E-03	**1.25**
17	Fish consumption	Adult Male	5E-05	5E-08	3E-04	**1.25**
18	Fish consumption	Subsistence Populations	2E-04	3E-07	2E-03	**1.25**
19	**Chronic/Longer Term Exposures (dose in mg/kg/day)**					
20	Contaminated Fruit	Adult Female	1E-02	3E-04	0.5	**0.02**
21	Contaminated Vegetation	Adult Female	0.2	6E-04	**4**	**0.02**
22	Water consumption	Adult Male	4E-03	8E-08	3E-02	**0.02**
23	Fish consumption	Adult Male	6E-05	2E-09	4E-04	**0.02**
24	Fish consumption	Subsistence Populations	5E-04	1E-08	3E-03	**0.02**

Attachment 2 - Aerial Broadcast Soil (Granular) Safari 2 G.xls

	A	B	C	D	E	F
1	**Worksheet E03: Summary of Hazard Quotients (Toxicity) for the General Public**					
2	**Application Rate:**	**0.54**	**lb a.i./acre**			E03aV5
3	**Scenario**	**Receptor**	**Hazard Quotients**			**Toxicity Value**
4			**Central**	**Lower**	**Upper**	
5	**Accidental Acute Exposures (dose in mg/kg/event)**					
6	Direct Spray of Child, whole body	Child	No exposure assessment.			
7	Direct Spray of Woman, feet and lower legs	Adult Female	No exposure assessment.			
8	Water consumption (spill)	Child	**1.1**	0.3	**3**	**1.25**
9	Fish consumption (spill)	Adult Male	1E-01	4E-02	0.2	**1.25**
10	Fish consumption (spill)	Subsistence Populations	0.5	0.2	1.0	**1.25**
11	**Non-Accidental Acute Exposures (dose in mg/kg/event)**					
12	Vegetation Contact, shorts and T-shirt	Adult Female	No exposure assessment.			
13	Contaminated Fruit	Adult Female	2E-04	9E-05	3E-03	**1.25**
14	Contaminated Vegetation	Adult Female	3E-03	2E-04	2E-02	**1.25**
15	Swimming, one hour	Adult Female	2E-06	7E-10	2E-05	**1.25**
16	Water consumption	Child	1E-03	6E-07	1E-02	**1.25**
17	Fish consumption	Adult Male	1E-04	9E-08	6E-04	**1.25**
18	Fish consumption	Subsistence Populations	5E-04	4E-07	3E-03	**1.25**
19	**Chronic/Longer Term Exposures (dose in mg/kg/day)**					
20	Contaminated Fruit	Adult Female	1E-03	3E-05	4E-02	**0.02**
21	Contaminated Vegetation	Adult Female	2E-02	7E-05	0.3	**0.02**
22	Water consumption	Adult Male	8E-03	2E-06	6E-02	**0.02**
23	Fish consumption	Adult Male	1E-04	5E-08	8E-04	**0.02**
24	Fish consumption	Subsistence Populations	1E-03	4E-07	6E-03	**0.02**

Attachment 3 - Bark Application Safari 20 SG.xls

	A	B	C	D	E	F
1	**Worksheet E03: Summary of Hazard Quotients (Toxicity) for the General Public**					
2	**Application Rate:**	**0.054**	**lb a.i./acre**			E03aV5
3	**Scenario**	**Receptor**	**Hazard Quotients**			**Toxicity Value**
4			**Central**	**Lower**	**Upper**	
5	**Accidental Acute Exposures (dose in mg/kg/event)**					
6	Direct Spray of Child, whole body	Child	**1.3**	0.5	**4**	**1.25**
7	Direct Spray of Woman, feet and lower legs	Adult Female	0.1	5E-02	0.4	**1.25**
8	Water consumption (spill)	Child	0.6	8E-02	**1.8**	**1.25**
9	Fish consumption (spill)	Adult Male	6E-02	1E-02	0.1	**1.25**
10	Fish consumption (spill)	Subsistence Populations	0.3	5E-02	0.5	**1.25**
11	**Non-Accidental Acute Exposures (dose in mg/kg/event)**					
12	Vegetation Contact, shorts and T-shirt	Adult Female	1E-03	5E-04	2E-03	**1.25**
13	Contaminated Fruit	Adult Female	5E-04	5E-04	8E-03	**1.25**
14	Contaminated Vegetation	Adult Female	7E-03	1E-03	6E-02	**1.25**
15	Swimming, one hour	Adult Female	2E-07	7E-11	2E-06	**1.25**
16	Water consumption	Child	1E-04	6E-08	1E-03	**1.25**
17	Fish consumption	Adult Male	1E-05	9E-09	6E-05	**1.25**
18	Fish consumption	Subsistence Populations	5E-05	4E-08	3E-04	**1.25**
19	**Chronic/Longer Term Exposures (dose in mg/kg/day)**					
20	Contaminated Fruit	Adult Female	4E-04	4E-04	1E-02	**0.02**
21	Contaminated Vegetation	Adult Female	5E-03	1E-03	9E-02	**0.02**
22	Water consumption	Adult Male	8E-04	2E-07	6E-03	**0.02**
23	Fish consumption	Adult Male	1E-05	5E-09	8E-05	**0.02**
24	Fish consumption	Subsistence Populations	1E-04	4E-08	6E-04	**0.02**

Attachment 4 - Soil Injection Safari 20 SG.xls

	A	B	C	D	E	F
1	**Worksheet E03: Summary of Hazard Quotients (Toxicity) for the General Public**					
2	**Application Rate:**	**0.54**	**lb a.i./acre**			E03aV5
3	**Scenario**	**Receptor**	**Hazard Quotients**			**Toxicity Value**
4			**Central**	**Lower**	**Upper**	
5	**Accidental Acute Exposures (dose in mg/kg/event)**					
6	Direct Spray of Child, whole body	Child	No exposure assessment.			
7	Direct Spray of Woman, feet and lower legs	Adult Female	No exposure assessment.			
8	Water consumption (spill)	Child	**1.8**	0.2	**6**	**1.25**
9	Fish consumption (spill)	Adult Male	0.2	3E-02	0.3	**1.25**
10	Fish consumption (spill)	Subsistence Populations	0.8	0.2	**1.6**	**1.25**
11	**Non-Accidental Acute Exposures (dose in mg/kg/event)**					
12	Vegetation Contact, shorts and T-shirt	Adult Female	No exposure assessment.			
13	Contaminated Fruit	Adult Female	No exposure assessment.			
14	Contaminated Vegetation	Adult Female	No exposure assessment.			
15	Swimming, one hour	Adult Female	1E-06	6E-10	2E-05	**1.25**
16	Water consumption	Child	9E-04	5E-07	1E-02	**1.25**
17	Fish consumption	Adult Male	8E-05	7E-08	6E-04	**1.25**
18	Fish consumption	Subsistence Populations	4E-04	4E-07	3E-03	**1.25**
19	**Chronic/Longer Term Exposures (dose in mg/kg/day)**					
20	Contaminated Fruit	Adult Female	No exposure assessment.			
21	Contaminated Vegetation	Adult Female	No exposure assessment.			
22	Water consumption	Adult Male	8E-03	1E-06	6E-02	**0.02**
23	Fish consumption	Adult Male	1E-04	3E-08	8E-04	**0.02**
24	Fish consumption	Subsistence Populations	9E-04	2E-07	6E-03	**0.02**

Attachment 5 - Tree Injection Safari 20 SG.xls
NO EXPOSURE ASSESSMENTS

Appendix 11: Risk Characterization for Mammals and Birds

Attachment 1a - Aerial Broadcast Foliar Safari 20 SG - One Application.xls

	A	B	C	D	E	F	G
1	Summary of Hazard Quotients (Toxicity) for the Terrestrial Animals						
2	Application Rate:	0.2	lb a.i./acre			G01V5	
3	Scenario	Receptor	Hazard Quotients			Toxicity Value	
4			Central	Lower	Upper		
5	Accidental Acute Exposures						
6	Direct Spray						
7	first-order absorption	Small mammal	1E-02	5E-03	3E-02	125	NOAEL
8	100% absorption	Small mammal	4E-02	4E-02	4E-02	125	NOAEL
9	Contaminated Water						
10	Spill	Small Mammal	1E-04	5E-06	4E-04	125	NOAEL
11	Spill	Small Bird	2E-05	1E-06	1E-04	997.9	NOAEL
12	Consumption of contaminated Fish						
13	Spill	Fish-eating bird	3E-05	7E-07	2E-04	997.9	NOAEL
14	Non-Accidental Acute Exposures						
15	Contaminated Vegetation						
16	Fruit	Small Mammal	2E-03	9E-04	4E-03	125	NOAEL
17	Grass	Small Mammal	2E-02	9E-03	7E-02	125	NOAEL
18	Grass	Large Mammal	3E-02	1E-02	8E-02	125	NOAEL
19	Grass	Large Bird	5E-03	2E-03	2E-02	997.9	NOAEL
20	Contaminated Water						
21		Small Mammal	6E-06	3E-09	4E-05	125	NOAEL
22		Small Bird	1E-06	6E-10	9E-06	997.9	NOAEL
23	Contaminated Insects						
24		Small Mammal	4E-02	1E-02	0.1	125	NOAEL
25		Small Bird	8E-03	3E-03	2E-02	997.9	NOAEL
26	Consumption of small mammal (after direct spray) by predator						
27		Carnivorous mammal	3E-03	3E-03	3E-03	125	NOAEL
28		Carnivorous bird	6E-04	6E-04	6E-04	997.9	NOAEL
29	Consumption of contaminated Fish						
30		Fish-eating bird	2E-06	4E-10	1E-05	997.9	NOAEL
31	Chronic/Longer Term Exposures						
32	Contaminated Vegetation						
33	On-site	Small Mammal	1E-03	2E-05	1E-02	2	NOAEL
34	Off-Site		2E-04	2E-06	2E-03	2	NOAEL
35	On-Site	Large Mammal	5E-02	4E-04	0.9	2	NOAEL
36	Off-Site		3E-02	3E-04	0.2	2	NOAEL
37	On-Site	Large Bird	5E-04	3E-06	9E-03	325	NOAEL
38	Off-Site		3E-04	3E-06	2E-03	325	NOAEL
39	Contaminated Water						
40		Small Mammal	1E-04	4E-09	7E-04	2	NOAEL
41		Small Bird	1E-06	5E-11	8E-06	325	NOAEL
42	Consumption of contaminated Fish						
43		Fish-eating bird	2E-06	3E-11	1E-05	325	NOAEL

Attachment 1b - Aerial Broadcast Foliar Safari 20 SG - Two Applications.xls

	A	B	C	D	E	F	G
1	**Summary of Hazard Quotients (Toxicity) for the Terrestrial Animals**						
2	**Application Rate:**	**0.2**	**lb a.i./acre**			G01V5	
3	**Scenario**	**Receptor**	**Hazard Quotients**			**Toxicity Value**	
4			**Central**	**Lower**	**Upper**		
5	**Accidental Acute Exposures**						
6	**Direct Spray**						
7	first-order absorption	Small mammal	1E-02	5E-03	3E-02	**125**	NOAEL
8	100% absorption	Small mammal	4E-02	4E-02	4E-02	**125**	NOAEL
9	**Contaminated Water**						
10	Spill	Small Mammal	1E-04	5E-06	4E-04	**125**	NOAEL
11	Spill	Small Bird	2E-05	1E-06	1E-04	**997.9**	NOAEL
12	**Consumption of contaminated Fish**						
13	Spill	Fish-eating bird	3E-05	7E-07	2E-04	**997.9**	NOAEL
14	**Non-Accidental Acute Exposures**						
15	**Contaminated Vegetation**						
16	Fruit	Small Mammal	2E-03	9E-04	6E-03	**125**	NOAEL
17	Grass	Small Mammal	3E-02	9E-03	1E-01	**125**	NOAEL
18	Grass	Large Mammal	3E-02	1E-02	0.1	**125**	NOAEL
19	Grass	Large Bird	6E-03	2E-03	2E-02	**997.9**	NOAEL
20	**Contaminated Water**						
21		Small Mammal	1E-05	1E-08	7E-05	**125**	NOAEL
22		Small Bird	2E-06	3E-09	2E-05	**997.9**	NOAEL
23	**Contaminated Insects**						
24		Small Mammal	4E-02	1E-02	0.1	**125**	NOAEL
25		Small Bird	8E-03	3E-03	2E-02	**997.9**	NOAEL
26	**Consumption of small mammal (after direct spray) by predator**						
27		Carnivorous mammal	3E-03	3E-03	3E-03	**125**	NOAEL
28		Carnivorous bird	6E-04	6E-04	6E-04	**997.9**	NOAEL
29	**Consumption of contaminated Fish**						
30		Fish-eating bird	3E-06	2E-09	3E-05	**997.9**	NOAEL
31	**Chronic/Longer Term Exposures**						
32	**Contaminated Vegetation**						
33	On-site	Small Mammal	1E-03	2E-05	1E-02	**2**	NOAEL
34	Off-Site		2E-04	2E-06	3E-03	**2**	NOAEL
35	On-Site	Large Mammal	6E-02	4E-04	**1.3**	**2**	NOAEL
36	Off-Site		3E-02	3E-04	0.3	**2**	NOAEL
37	On-Site	Large Bird	6E-04	3E-06	1E-02	**325**	NOAEL
38	Off-Site		3E-04	3E-06	3E-03	**325**	NOAEL
39	**Contaminated Water**						
40		Small Mammal	2E-04	6E-09	1E-03	**2**	NOAEL
41		Small Bird	2E-06	7E-11	2E-05	**325**	NOAEL
42	**Consumption of contaminated Fish**						
43		Fish-eating bird	2E-06	4E-11	3E-05	**325**	NOAEL

Attachment 2 - Aerial Broadcast Soil (Granular) Safari 2 G.xls

	A	B	C	D	E	F	G
1	**Summary of Hazard Quotients (Toxicity) for the Terrestrial Animals**						
2	**Application Rate:**	**0.54**	**lb a.i./acre**			G01V5	
3	**Scenario**	**Receptor**	**Hazard Quotients**			**Toxicity Value**	
4			**Central**	**Lower**	**Upper**		
5	**Accidental Acute Exposures**						
6	**Direct Spray**						
7	first-order absorption	Small mammal	No exposure assessment.				
8	100% absorption	Small mammal	No exposure assessment.				
9	**Contaminated Water**						
10	Spill	Small Mammal	2E-02	8E-03	4E-02	**125**	NOAEL
11	Spill	Small Bird	5E-03	2E-03	1E-02	**997.9**	NOAEL
12	**Consumption of contaminated Fish**						
13	Spill	Fish-eating bird	5E-03	1E-03	2E-02	**997.9**	NOAEL
14	**Non-Accidental Acute Exposures**						
15	**Contaminated Vegetation**						
16	Fruit	Small Mammal	2E-04	1E-04	5E-04	**125**	NOAEL
17	Grass	Small Mammal	3E-03	9E-04	7E-03	**125**	NOAEL
18	Grass	Large Mammal	3E-03	1E-03	8E-03	**125**	NOAEL
19	Grass	Large Bird	6E-04	2E-04	2E-03	**997.9**	NOAEL
20	**Contaminated Water**						
21		Small Mammal	2E-05	2E-08	1E-04	**125**	NOAEL
22		Small Bird	5E-06	4E-09	3E-05	**997.9**	NOAEL
23	**Contaminated Insects**						
24		Small Mammal	4E-03	1E-03	1E-02	**125**	NOAEL
25		Small Bird	8E-04	3E-04	2E-03	**997.9**	NOAEL
26	**Consumption of small mammal (after direct spray) by predator**						
27		Carnivorous mammal	9E-03	9E-03	9E-03	**125**	NOAEL
28		Carnivorous bird	2E-03	2E-03	2E-03	**997.9**	NOAEL
29	**Consumption of contaminated Fish**						
30		Fish-eating bird	6E-06	2E-09	5E-05	**997.9**	NOAEL
31	**Chronic/Longer Term Exposures**						
32	**Contaminated Vegetation**						
33	On-site	Small Mammal	1E-04	2E-06	1E-03	**2**	NOAEL
34	Off-Site		2E-05	2E-07	2E-04	**2**	NOAEL
35	On-Site	Large Mammal	5E-03	4E-05	1E-01	**2**	NOAEL
36	Off-Site		3E-03	4E-05	2E-02	**2**	NOAEL
37	On-Site	Large Bird	5E-05	4E-07	9E-04	**325**	NOAEL
38	Off-Site		3E-05	4E-07	2E-04	**325**	NOAEL
39	**Contaminated Water**						
40		Small Mammal	4E-04	2E-07	3E-03	**2**	NOAEL
41		Small Bird	5E-06	2E-09	3E-05	**325**	NOAEL
42	**Consumption of contaminated Fish**						
43		Fish-eating bird	5E-06	1E-09	5E-05	**325**	NOAEL

Attachment 3 - Bark Application Safari 20 SG.xls

	A	B	C	D	E	F	G
1	**Summary of Hazard Quotients (Toxicity) for the Terrestrial Animals**						
2	**Application Rate:**	**0.054**	**lb a.i./acre**			G01V5	
3	**Scenario**	**Receptor**	**Hazard Quotients**			**Toxicity Value**	
4			**Central**	**Lower**	**Upper**		
5	**Accidental Acute Exposures**						
6	**Direct Spray**						
7	first-order absorption	Small mammal	4E-03	1E-03	7E-03	**125**	NOAEL
8	100% absorption	Small mammal	1E-02	1E-02	1E-02	**125**	NOAEL
9	**Contaminated Water**						
10	Spill	Small Mammal	1E-02	2E-03	2E-02	**125**	NOAEL
11	Spill	Small Bird	3E-03	6E-04	6E-03	**997.9**	NOAEL
12	**Consumption of contaminated Fish**						
13	Spill	Fish-eating bird	3E-03	3E-04	9E-03	**997.9**	NOAEL
14	**Non-Accidental Acute Exposures**						
15	**Contaminated Vegetation**						
16	Fruit	Small Mammal	5E-04	5E-04	1E-03	**125**	NOAEL
17	Grass	Small Mammal	7E-03	7E-03	2E-02	**125**	NOAEL
18	Grass	Large Mammal	7E-03	7E-03	2E-02	**125**	NOAEL
19	Grass	Large Bird	1E-03	1E-03	4E-03	**997.9**	NOAEL
20	**Contaminated Water**						
21		Small Mammal	2E-06	2E-09	1E-05	**125**	NOAEL
22		Small Bird	5E-07	4E-10	3E-06	**997.9**	NOAEL
23	**Contaminated Insects**						
24		Small Mammal	1E-02	1E-02	3E-02	**125**	NOAEL
25		Small Bird	2E-03	2E-03	6E-03	**997.9**	NOAEL
26	**Consumption of small mammal (after direct spray) by predator**						
27		Carnivorous mammal	9E-04	9E-04	9E-04	**125**	NOAEL
28		Carnivorous bird	2E-04	2E-04	2E-04	**997.9**	NOAEL
29	**Consumption of contaminated Fish**						
30		Fish-eating bird	6E-07	2E-10	5E-06	**997.9**	NOAEL
31	**Chronic/Longer Term Exposures**						
32	**Contaminated Vegetation**						
33	On-site	Small Mammal	4E-05	2E-05	4E-04	**2**	NOAEL
34	Off-Site		2E-07	5E-08	3E-06	**2**	NOAEL
35	On-Site	Large Mammal	2E-03	5E-04	3E-02	**2**	NOAEL
36	Off-Site		2E-05	1E-05	3E-04	**2**	NOAEL
37	On-Site	Large Bird	2E-05	5E-06	3E-04	**325**	NOAEL
38	Off-Site		2E-07	1E-07	3E-06	**325**	NOAEL
39	**Contaminated Water**						
40		Small Mammal	4E-05	2E-08	3E-04	**2**	NOAEL
41		Small Bird	5E-07	2E-10	3E-06	**325**	NOAEL
42	**Consumption of contaminated Fish**						
43		Fish-eating bird	5E-07	1E-10	5E-06	**325**	NOAEL

Attachment 4 - Soil Injection Safari 20 SG.xls

	A	B	C	D	E	F	G
1	**Summary of Hazard Quotients (Toxicity) for the Terrestrial Animals**						
2	**Application Rate:**	**0.54**	**lb a.i./acre**			G01V5	
3	**Scenario**	**Receptor**	**Hazard Quotients**			**Toxicity Value**	
4			**Central**	**Lower**	**Upper**		
5	**Accidental Acute Exposures**						
6	**Direct Spray**						
7	first-order absorption	Small mammal	No exposure assessment.				
8	100% absorption	Small mammal	No exposure assessment.				
9	**Contaminated Water**						
10	Spill	Small Mammal	4E-02	7E-03	7E-02	**125**	NOAEL
11	Spill	Small Bird	8E-03	2E-03	2E-02	**997.9**	NOAEL
12	**Consumption of contaminated Fish**						
13	Spill	Fish-eating bird	9E-03	9E-04	3E-02	**997.9**	NOAEL
14	**Non-Accidental Acute Exposures**						
15	**Contaminated Vegetation**						
16	Fruit	Small Mammal	No exposure assessment.				
17	Grass	Small Mammal	No exposure assessment.				
18	Grass	Large Mammal	No exposure assessment.				
19	Grass	Large Bird	No exposure assessment.				
20	**Contaminated Water**						
21		Small Mammal	2E-05	2E-08	1E-04	**125**	NOAEL
22		Small Bird	4E-06	4E-09	3E-05	**997.9**	NOAEL
23	**Contaminated Insects**						
24		Small Mammal	No exposure assessment.				
25		Small Bird	No exposure assessment.				
26	**Consumption of small mammal (after direct spray) by predator**						
27		Carnivorous mammal	No exposure assessment.				
28		Carnivorous bird	No exposure assessment.				
29	**Consumption of contaminated Fish**						
30		Fish-eating bird	5E-06	2E-09	5E-05	**997.9**	NOAEL
31	**Chronic/Longer Term Exposures**						
32	**Contaminated Vegetation**						
33	On-site	Small Mammal	No exposure assessment.				
34	Off-Site		No exposure assessment.				
35	On-Site	Large Mammal	No exposure assessment.				
36	Off-Site		No exposure assessment.				
37	On-Site	Large Bird	No exposure assessment.				
38	Off-Site		No exposure assessment.				
39	**Contaminated Water**						
40		Small Mammal	4E-04	1E-07	3E-03	**2**	NOAEL
41		Small Bird	4E-06	1E-09	3E-05	**325**	NOAEL
42	**Consumption of contaminated Fish**						
43		Fish-eating bird	5E-06	6E-10	5E-05	**325**	NOAEL

Attachment 5 - Tree Injection Safari 20 SG.xls
NO EXPOSURE ASSESSMENTS

Appendix 12: Risk Characterization for Aquatic Organisms

Attachment 1a - Aerial Broadcast Foliar Safari 20 SG - One Application.xls

	A	B	C	D	E	F	G
1	**Worksheet G03: Summary of Hazard Quotients for Aquatic Species**						
2	**Application Rate:**	**0.2**	**lb a.i./acre**			AqToxSumV5	
3	**Exposures**		**Concentrations** (mg/L)				
4		**Scenario**	**Central**	**Lower**	**Upper**	**Worksheet**	
5		**Accidental**	0.09084	0.004542	0.36336	D05	
6		**Peak EEC**	0.0052	0.0000024	0.032	D06	
7		**Chronic**	0.00164	0.00000006	0.0098	D07	
8	**Receptor**	**Type**	**Hazard Quotients**			**Toxicity Value**	**Toxicity Endpoint**
9			**Central**	**Lower**	**Upper**		
10	**Accidental Acute Exposures**						
11	Fish	Sensitive	No toxicity data.			N/A	
12		Tolerant	9E-04	5E-05	4E-03	**99.1**	NOEC
13	Amphibian	Sensitive	No toxicity data.			N/A	
14		Tolerant	No toxicity data.			N/A	
15	Invertebrate	Sensitive	0.2	9E-03	0.7	**0.49**	NOAEC
16		Tolerant	9E-05	5E-06	4E-04	**968.3**	NOAEC
17	Macrophyte	Sensitive	No toxicity data.			N/A	
18		Tolerant	9E-04	5E-05	4E-03	**100**	NOEC
19	Algae	Sensitive	No toxicity data.			N/A	
20		Tolerant	4E-03	2E-04	1E-02	**25**	NOEC
21	**Non-Accidental Acute Exposures**						
22	Fish	Sensitive	No toxicity data.			N/A	
23		Tolerant	5E-05	2E-08	3E-04	**99.1**	NOEC
24	Amphibian	Sensitive	No toxicity data.			N/A	
25		Tolerant	No toxicity data.			N/A	
26	Invertebrate	Sensitive	1E-02	5E-06	7E-02	**0.49**	NOAEC
27		Tolerant	5E-06	2E-09	3E-05	**968.3**	NOAEC
28	Macrophyte	Sensitive	No toxicity data.			N/A	
29		Tolerant	5E-05	2E-08	3E-04	**100**	NOEC
30	Algae	Sensitive	No toxicity data.			N/A	
31		Tolerant	2E-04	1E-07	1E-03	**25**	NOEC
32	**Chronic/Longer Term Exposures**						
33	Fish	Sensitive	No toxicity data.			N/A	
34		Tolerant	2E-05	6E-10	1E-04	**10**	NOEC
35	Amphibian	Sensitive	No toxicity data.			N/A	
36		Tolerant	No toxicity data.			N/A	
37	Invertebrate	Sensitive	3E-03	1E-07	2E-02	**0.051**	NOAEL
38		Tolerant	2E-06	6E-11	1E-05	**95.3**	NOAEL
39	Macrophyte	Sensitive	No toxicity data.			N/A	
40		Tolerant	2E-05	6E-10	1E-04	**100**	NOEC
41	Algae	Sensitive	No toxicity data.			N/A	
42		Tolerant	7E-05	2E-09	4E-04	**25**	NOEC

Attachment 1b - Aerial Broadcast Foliar Safari 20 SG - Two Applications.xls

	A	B	C	D	E	F	G
1	**Worksheet G03: Summary of Hazard Quotients for Aquatic Species**						
2	**Application Rate:**	**0.2**	**lb a.i./acre**			AqToxSumV5	
3	**Exposures**		**Concentrations** (mg/L)				
4		**Scenario**	**Central**	**Lower**	**Upper**	**Worksheet**	
5		**Accidental**	0.09084	0.004542	0.36336	D05	
6		**Peak EEC**	0.0088	0.00001	0.062	D06	
7		**Chronic**	0.0026	0.00000008	0.0192	D07	
8	**Receptor**	**Type**	**Hazard Quotients**			**Toxicity Value**	**Toxicity Endpoint**
9			**Central**	**Lower**	**Upper**		
10	**Accidental Acute Exposures**						
11	Fish	Sensitive	No toxicity data.			N/A	
12		Tolerant	9E-04	5E-05	4E-03	**99.1**	NOEC
13	Amphibian	Sensitive	No toxicity data.			N/A	
14		Tolerant	No toxicity data.			N/A	
15	Invertebrate	Sensitive	0.2	9E-03	0.7	**0.49**	NOAEC
16		Tolerant	9E-05	5E-06	4E-04	**968.3**	NOAEC
17	Macrophyte	Sensitive	No toxicity data.			N/A	
18		Tolerant	9E-04	5E-05	4E-03	**100**	NOEC
19	Algae	Sensitive	No toxicity data.			N/A	
20		Tolerant	4E-03	2E-04	1E-02	**25**	NOEC
21	**Non-Accidental Acute Exposures**						
22	Fish	Sensitive	No toxicity data.			N/A	
23		Tolerant	9E-05	1E-07	6E-04	**99.1**	NOEC
24	Amphibian	Sensitive	No toxicity data.			N/A	
25		Tolerant	No toxicity data.			N/A	
26	Invertebrate	Sensitive	2E-02	2E-05	0.1	**0.49**	NOAEC
27		Tolerant	9E-06	1E-08	6E-05	**968.3**	NOAEC
28	Macrophyte	Sensitive	No toxicity data.			N/A	
29		Tolerant	9E-05	1E-07	6E-04	**100**	NOEC
30	Algae	Sensitive	No toxicity data.			N/A	
31		Tolerant	4E-04	4E-07	2E-03	**25**	NOEC
32	**Chronic/Longer Term Exposures**						
33	Fish	Sensitive	No toxicity data.			N/A	
34		Tolerant	3E-05	8E-10	2E-04	**10**	NOEC
35	Amphibian	Sensitive	No toxicity data.			N/A	
36		Tolerant	No toxicity data.			N/A	
37	Invertebrate	Sensitive	5E-03	2E-07	4E-02	**0.051**	NOAEL
38		Tolerant	3E-06	8E-11	2E-05	**95.3**	NOAEL
39	Macrophyte	Sensitive	No toxicity data.			N/A	
40		Tolerant	3E-05	8E-10	2E-04	**100**	NOEC
41	Algae	Sensitive	No toxicity data.			N/A	
42		Tolerant	1E-04	3E-09	8E-04	**25**	NOEC

Attachment 2 - Aerial Broadcast Soil (Granular) Safari 2 G.xls

	A	B	C	D	E	F	G
1	**Worksheet G03: Summary of Hazard Quotients for Aquatic Species**						
2	**Application Rate:**	**0.54**	**lb a.i./acre**			AqToxSumV5	Prog!ApRt_C
3	**Exposures**		**Concentrations** (mg/L)				
4		**Scenario**	**Central**	**Lower**	**Upper**	**Worksheet**	
5		**Accidental**	18.144	7.2576	36.288	D05	
6		**Peak EEC**	0.01944	0.0000162	0.1134	D06	
7		**Chronic**	0.00594	0.00000243	0.0351	D07	
8	**Receptor**	**Type**	**Hazard Quotients**			**Toxicity Value**	**Toxicity Endpoint**
9			**Central**	**Lower**	**Upper**		
10	**Accidental Acute Exposures**						
11	Fish	Sensitive	No toxicity data.			N/A	
12		Tolerant	0.2	7E-02	0.4	**99.1**	NOEC
13	Amphibian	Sensitive	No toxicity data.			N/A	
14		Tolerant	No toxicity data.			N/A	
15	Invertebrate	Sensitive	**37**	**15**	**74**	**0.49**	NOAEC
16		Tolerant	2E-02	7E-03	4E-02	**968.3**	NOAEC
17	Macrophyte	Sensitive	No toxicity data.			N/A	
18		Tolerant	0.2	7E-02	0.4	**100**	NOEC
19	Algae	Sensitive	No toxicity data.			N/A	
20		Tolerant	0.7	0.3	**1.5**	**25**	NOEC
21	**Non-Accidental Acute Exposures**						
22	Fish	Sensitive	No toxicity data.			N/A	
23		Tolerant	2E-04	2E-07	1E-03	**99.1**	NOEC
24	Amphibian	Sensitive	No toxicity data.			N/A	
25		Tolerant	No toxicity data.			N/A	
26	Invertebrate	Sensitive	4E-02	3E-05	0.2	**0.49**	NOAEC
27		Tolerant	2E-05	2E-08	1E-04	**968.3**	NOAEC
28	Macrophyte	Sensitive	No toxicity data.			N/A	
29		Tolerant	2E-04	2E-07	1E-03	**100**	NOEC
30	Algae	Sensitive	No toxicity data.			N/A	
31		Tolerant	8E-04	6E-07	5E-03	**25**	NOEC
32	**Chronic/Longer Term Exposures**						
33	Fish	Sensitive	No toxicity data.			N/A	
34		Tolerant	6E-05	2E-08	4E-04	**10**	NOEC
35	Amphibian	Sensitive	No toxicity data.			N/A	
36		Tolerant	No toxicity data.			N/A	
37	Invertebrate	Sensitive	1E-02	5E-06	7E-02	**0.051**	NOAEL
38		Tolerant	6E-06	3E-09	4E-05	**95.3**	NOAEL
39	Macrophyte	Sensitive	No toxicity data.			N/A	
40		Tolerant	6E-05	2E-08	4E-04	**100**	NOEC
41	Algae	Sensitive	No toxicity data.			N/A	
42		Tolerant	2E-04	1E-07	1E-03	**25**	NOEC

Attachment 3 - Bark Application Safari 20 SG.xls

	A	B	C	D	E	F	G
1	**Worksheet G03: Summary of Hazard Quotients for Aquatic Species**						
2	**Application Rate:**	**1**	**lb a.i./acre**			AqToxSumV5	
3	**Exposures**		**Concentrations** (mg/L)				
4		**Scenario**	**Central**	**Lower**	**Upper**	**Worksheet**	
5		**Accidental**	10.22972973	2.045945946	20.45945946	D05	
6		**Peak EEC**	0.001944	0.00000162	0.01134	D06	
7		**Chronic**	0.000594	0.000000243	0.00351	D07	
8	**Receptor**	**Type**	**Hazard Quotients**			**Toxicity Value**	**Toxicity Endpoint**
9			**Central**	**Lower**	**Upper**		
10	**Accidental Acute Exposures**						
11	Fish	Sensitive	No toxicity data.			N/A	
12		Tolerant	0.1	2E-02	0.2	**99.1**	NOEC
13	Amphibian	Sensitive	No toxicity data.			N/A	
14		Tolerant	No toxicity data.			N/A	
15	Invertebrate	Sensitive	**21**	**4**	**42**	**0.49**	NOAEC
16		Tolerant	1E-02	2E-03	2E-02	**968.3**	NOAEC
17	Macrophyte	Sensitive	No toxicity data.			N/A	
18		Tolerant	0.1	2E-02	0.2	**100**	NOEC
19	Algae	Sensitive	No toxicity data.			N/A	
20		Tolerant	0.4	8E-02	0.8	**25**	NOEC
21	**Non-Accidental Acute Exposures**						
22	Fish	Sensitive	No toxicity data.			N/A	
23		Tolerant	2E-05	2E-08	1E-04	**99.1**	NOEC
24	Amphibian	Sensitive	No toxicity data.			N/A	
25		Tolerant	No toxicity data.			N/A	
26	Invertebrate	Sensitive	4E-03	3E-06	2E-02	**0.49**	NOAEC
27		Tolerant	2E-06	2E-09	1E-05	**968.3**	NOAEC
28	Macrophyte	Sensitive	No toxicity data.			N/A	
29		Tolerant	2E-05	2E-08	1E-04	**100**	NOEC
30	Algae	Sensitive	No toxicity data.			N/A	
31		Tolerant	8E-05	6E-08	5E-04	**25**	NOEC
32	**Chronic/Longer Term Exposures**						
33	Fish	Sensitive	No toxicity data.			N/A	
34		Tolerant	6E-06	2E-09	4E-05	**10**	NOEC
35	Amphibian	Sensitive	No toxicity data.			N/A	
36		Tolerant	No toxicity data.			N/A	
37	Invertebrate	Sensitive	1E-03	5E-07	7E-03	**0.051**	NOAEL
38		Tolerant	6E-07	3E-10	4E-06	**95.3**	NOAEL
39	Macrophyte	Sensitive	No toxicity data.			N/A	
40		Tolerant	6E-06	2E-09	4E-05	**100**	NOEC
41	Algae	Sensitive	No toxicity data.			N/A	
42		Tolerant	2E-05	1E-08	1E-04	**25**	NOEC

Attachment 4 - Soil Injection Safari 20 SG.xls

	A	B	C	D	E	F	G
1	**Worksheet G03: Summary of Hazard Quotients for Aquatic Species**						
2	**Application Rate:**	**1**	**lb a.i./acre**			AqToxSumV5	
3	**Exposures**		**Concentrations** (mg/L)				
4		**Scenario**	**Central**	**Lower**	**Upper**	**Worksheet**	
5		**Accidental**	30.68918919	6.137837838	61.37837838	D05	
6		**Peak EEC**	0.01566	0.0000135	0.108	D06	
7		**Chronic**	0.0054	0.00000135	0.0351	D07	
8	**Receptor**	**Type**	**Hazard Quotients**			**Toxicity Value**	**Toxicity Endpoint**
9			**Central**	**Lower**	**Upper**		
10	**Accidental Acute Exposures**						
11	Fish	Sensitive	No toxicity data.			N/A	
12		Tolerant	0.3	6E-02	0.6	**99.1**	NOEC
13	Amphibian	Sensitive	No toxicity data.			N/A	
14		Tolerant	No toxicity data.			N/A	
15	Invertebrate	Sensitive	**63**	**13**	**125**	**0.49**	NOAEC
16		Tolerant	3E-02	6E-03	6E-02	**968.3**	NOAEC
17	Macrophyte	Sensitive	No toxicity data.			N/A	
18		Tolerant	0.3	6E-02	0.6	**100**	NOEC
19	Algae	Sensitive	No toxicity data.			N/A	
20		Tolerant	**1.2**	0.2	**2**	**25**	NOEC
21	**Non-Accidental Acute Exposures**						
22	Fish	Sensitive	No toxicity data.			N/A	
23		Tolerant	2E-04	1E-07	1E-03	**99.1**	NOEC
24	Amphibian	Sensitive	No toxicity data.			N/A	
25		Tolerant	No toxicity data.			N/A	
26	Invertebrate	Sensitive	3E-02	3E-05	0.2	**0.49**	NOAEC
27		Tolerant	2E-05	1E-08	1E-04	**968.3**	NOAEC
28	Macrophyte	Sensitive	No toxicity data.			N/A	
29		Tolerant	2E-04	1E-07	1E-03	**100**	NOEC
30	Algae	Sensitive	No toxicity data.			N/A	
31		Tolerant	6E-04	5E-07	4E-03	**25**	NOEC
32	**Chronic/Longer Term Exposures**						
33	Fish	Sensitive	No toxicity data.			N/A	
34		Tolerant	5E-05	1E-08	4E-04	**10**	NOEC
35	Amphibian	Sensitive	No toxicity data.			N/A	
36		Tolerant	No toxicity data.			N/A	
37	Invertebrate	Sensitive	1E-02	3E-06	7E-02	**0.051**	NOAEL
38		Tolerant	6E-06	1E-09	4E-05	**95.3**	NOAEL
39	Macrophyte	Sensitive	No toxicity data.			N/A	
40		Tolerant	5E-05	1E-08	4E-04	**100**	NOEC
41	Algae	Sensitive	No toxicity data.			N/A	
42		Tolerant	2E-04	5E-08	1E-03	**25**	NOEC

Attachment 5 - Tree Injection Safari 20 SG.xls

NO EXPOSURE ASSESSMENTS