Imidacloprid: Human Health and Ecological Risk Assessment Corrected FINAL REPORT

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USDA Forest Service Contract: **AG-3187-C-12-0009**
USDA Forest Order Number: **AG-3187-D-14-0145**
SERA Internal Task No. 56-**09**

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August 31, 2015 (Original Report)
July 12, 2016 (Minor Corrections)

Preface

In July 2016, the HQs in Section 4.4.2.4.3 (Direct Spray of Insects) were revised to reflect corrections to the contact toxicity value for insects – i.e., 0.0059 mg/kg bw/day. This toxicity value had been incorrectly entered in WorksheetMaker as 0.00023 mg/kg bw/day, which is the toxicity value for oral exposures to phytophagous insects. Replacements for Attachments 3 and 4 were also provided with the current revised risk assessment. No replacements for the attachments for tree injection (Attachment 1) and soil injection (Attachment 2) are needed because these application methods did not include the direct spray scenario for the honeybee. The qualitative risk characterization for insects is unchanged.

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Note on Appendices

The appendices are in a separate document which accompanies this risk assessment – i.e., SERA TR-056-09-02b-Appendices

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
nAChR	nicotinic acetylcholine receptor
AEL	adverse-effect level
a.e.	acid equivalent
a.i.	active ingredient
a.k.a.	also known as
a.s.	active substance
APHIS	Animal and Plant Health Inspection Service
ASAE	American Society of Agricultural Engineers
BCF	bioconcentration factor
bw	body weight
calc	calculated value
CBI	confidential business information
CI	confidence interval
cm	centimeter
CNS	central nervous system
DAA	days after application
DAT	days after treatment
DBH	diameter at breast height
DER	data evaluation record
d.f.	degrees of freedom
EAB	emerald ash borer
EC	emulsifiable concentrate
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
ECOTOX	ECOTOXicology (database used by U.S. EPA/OPP)
EFED	Environmental Fate and Effects Division (U.S. EPA/OPP)
F	female
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
HRAC	Herbicide Resistance Action Committee
HWA	hemlock woolly adelgid
IARC	International Agency for Research on Cancer
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
LC_{50}	lethal concentration, 50% kill
LD_{50}	lethal dose, 50% kill
LOAEC	lowest-observed-adverse-effect concentration
LOAEL	lowest-observed-adverse-effect level
LOC	level of concern
LR_{50}	50% lethal response [EFSA/European term]
m	meter
M	male
mg	milligram
mg/kg/day	milligrams of agent per kilogram of body weight per day
mPa	millipascal, (0.001 Pa)
MOE	margin of exposure
MRID	Master Record Identification Number
MSDS	material safety data sheet
MSO	methylated seed oil
MW	molecular weight
NAWQA	USGS National Water Quality Assessment
NOAEL	no-observed-adverse-effect level
NOAEC	no-observed-adverse-effect concentration
NOS	not otherwise specified
N.R.	not reported
OM	organic matter
OPP	Office of Pesticide Programs
Pa	Pascal
ppm	parts per million
RBC	red blood cells
RED	re-registration eligibility decision
RfD	reference dose
SERA	Syracuse Environmental Research Associates
TEP	typical end-use product
TGIA	Technical grade active ingredient
TOC	total organic carbon
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
$1 \cdot 10^{-10}$	0.0000000001	One in ten billion
$1 \cdot 10^{-9}$	0.000000001	One in one billion
$1 \cdot 10^{-8}$	0.00000001	One in one hundred million
$1 \cdot 10^{-7}$	0.0000001	One in ten million
$1 \cdot 10^{-6}$	0.000001	One in one million
$1 \cdot 10^{-5}$	0.00001	One in one hundred thousand
$1 \cdot 10^{-4}$	0.0001	One in ten thousand
$1 \cdot 10^{-3}$	0.001	One in one thousand
$1 \cdot 10^{-2}$	0.01	One in one hundred
$1 \cdot 10^{-1}$	0.1	One in ten
$1 \cdot 10^{0}$	1	One
$1 \cdot 10^{1}$	10	Ten
$1 \cdot 10^{2}$	100	One hundred
$1 \cdot 10^{3}$	1,000	One thousand
$1 \cdot 10^{4}$	10,000	Ten thousand
$1 \cdot 10^{5}$	100,000	One hundred thousand
$1 \cdot 10^{6}$	1,000,000	One million
$1 \cdot 10^{7}$	10,000,000	Ten million
$1 \cdot 10^{8}$	100,000,000	One hundred million
$1 \cdot 10^{9}$	1,000,000,000	One billion
$1 \cdot 10^{10}$	10,000,000,000	Ten billion

EXECUTIVE SUMMARY

This document, which provides human health and ecological risk assessments of imidacloprid use in Forest Service programs, is an update of the risk assessment prepared in 2005 for the USDA Forest Service. Of the many application methods for imidacloprid, the most common ones used in forestry are tree injection and soil injection. Although the current standard labels for imidacloprid formulations do include bark applications, the Forest Service and their cooperators are evaluating this application method under FIFRA 2(ee) recommendations. Consequently, bark applications are considered explicitly in this document. Broadcast foliar and broadcast ground applications of imidacloprid, which are not used in Forest Service programs, are not supported by the current risk assessment. Foliar applications are covered in the document to illustrate the differences in risks associated with the more directed and focused application methods to be used by the Forest Service. The maximum labeled rate for a single application of imidacloprid is 0.4 lb a.i./acre. This application rate applies specifically to broadcast applications but is used to estimate the maximum functional application rate in units of lb a.i./acre for tree/soil injection and bark applications. The application rate of 0.4 lb a.i./acre is used throughout the current risk assessment.

Following the standard practice in all Forest Service risk assessments, risks are characterized using the hazard quotient (HQ), the ratio of the estimated exposure divided by a No-Observable-Adverse-Effect Level (NOAEL) or similar toxicity value. As the NOAEL increases over a value of 1, potential risks increase in the sense that exposures increasingly exceed the NOAEL or comparable toxicity value.

Imidacloprid is a neonicotinoid insecticide, a member of a class of insecticides that act by binding or partial binding to specific areas of the nicotinic acetylcholine receptor (nAChR). Imidacloprid will bind to nAChR in mammals, insects, and other species; however, the affinity for imidacloprid to insect nAChR is much greater than the affinity to mammalian nAChR. This difference in affinity for the nAChR is the basis for the differential toxicity of imidacloprid to insects and vertebrates, which is clearly reflected in the risk characterization for imidacloprid.

No substantial risks to workers or members of the general public are identified for tree injection, soil injection, or bark applications. Similarly, there is no basis for asserting that risks to vertebrate wildlife are substantial. This largely benign risk characterization applies to mammals, birds, and fish. Risk characterizations for reptiles and amphibians are not possible because of the limited toxicity data on these groups of organisms. Nonetheless and by analogy to methods used by U.S. EPA, there is no basis for asserting that risks to reptiles and amphibians are substantial. An explicit quantitative risk characterization for terrestrial plants is not warranted because endpoints of concern for terrestrial plants were not identified in the literature.

While risks to vertebrates and plants are minimal, risks to some sensitive groups of invertebrates, both aquatic and terrestrial, are substantial. Among the terrestrial invertebrates, risks to honeybees and phytophagous insects exceed the level of concern (HQ=1) for all the application methods considered by the Forest Service—i.e., tree injection, soil injection, and bark application (Table 34). Adverse effects on honeybee colonies are the most sensitive endpoint for bees. Consequently, risks to honeybees are characterized at the level of the colony or hive rather than the individual. The only substantial qualification to the risk characterization for honeybees

involves tree injection. For this application method, risks are dependent on the type of tree that is treated. Bees will forage on maple trees in the spring. If maple trees are injected with effective doses of imidacloprid, adverse effects on honeybees foraging on the maple flowers are high—HQs of 27,166 (8,754 - 180,390). Depending on treatment timing, risks to bees foraging on maple might not occur during the year that the maple is treated but could occur in the following year. Risks to honeybees following the injection of ash and hemlock are less certain because there is no information to suggest that the honeybees will forage on these trees. The risks associated with other types of exposures (e.g., nest building) on ash, hemlock, or other trees cannot be characterized. Based on the available information concerning the distribution of imidacloprid in hemlock, ash, and maple, the levels of imidacloprid that might be found in flowering trees could vary substantially, depending on the species of tree. Hence, potential risks to bees foraging on treated maple are clear, but risks associated with the treatment of other species of trees are less certain. For soil injection and bark application involving any species of tree, risks to honeybees are associated primarily with the contamination of flowering nontarget vegetation in the treated area. HQs exceed the level of concern for both soil injection [HQs = 203 (58 - 575)] and bark application [HQs = 20 (6 - 57)].

Risks to phytophagous insects are also substantial (Table 36). For tree injection, the HQs exceed the level of concern across the range of estimates with all lower bounds of the HQs exceeding the level of concern—i.e., lower bound HQs range from 78 to 16,174. For tree and soil injection, HQs differ substantially for hemlock (lowest HQs), ash (intermediate HQs), and maple (highest HQs). For bark application, the HQs vary with the type of vegetation that might be contaminated. Nonetheless, as with tree injection, all of the lower bounds of the HQs for bark application exceed the level of concern—i.e., lower bound HQs range from 334 to 3130.

Risks are highly variable among different groups of aquatic invertebrates. For tolerant groups of aquatic invertebrates, no adverse effects would be anticipated even in the event of an accidental spill. For sensitive groups of aquatic invertebrates, the risk characterization is much more severe (Table 37). At both the central estimates and upper bounds of the HQs, there is a clear difference among the application methods considered by the Forest Service. Bark applications pose the lowest risk with acute HQs of 2 (0.0002 - 12) and chronic HQs of 12 (0.0003 - 135). Soil injection poses substantially higher risks with acute HQs of 16 (0.001 - 209) and chronic HQs of 140 (0.008 - 800). These HQs are all based on toxicity data on Ephemeroptera, the taxonomic order of aquatic invertebrates most sensitive to imidacloprid. While HQs would be lower for less sensitive groups of aquatic invertebrates, the groups of aquatic invertebrates that appear to be at risk (HQs>1) include Ostracoda, Annelida, midges and other Diptera, Hemiptera, Amphipoda, Trichoptera, Mysida, Megaloptera, and one species of Cladocera (*Ceriodaphnia dubia*).

A major limitation in the risk assessment for aquatic invertebrates is that exposures associated with tree injection are not quantified, except for accidental spills. Risks associated with non-accidental exposures following tree injection would most likely involve water contamination secondary to leaf fall from treated trees. Given the high HQs for sensitive species of aquatic invertebrates with other application methods, risks to some sensitive species of aquatic invertebrates following tree injection cannot be dismissed. Whether tree injection might be associated with adverse effects in aquatic invertebrates would depend greatly on the volume of

the water contaminated by falling leaves, the total number of leaves transported to that body of water, and the concentration of imidacloprid in the leaves.

The risk characterization for imidacloprid focuses on the potential for direct toxic effects. Nonetheless, there is a potential for secondary effects in virtually all groups of nontarget organisms. Terrestrial applications of any effective insecticide, including imidacloprid, are likely to alter insect and some other invertebrate populations within the treatment area. This alteration could have secondary effects on terrestrial or aquatic animals and plants, including changes in food availability and habitat quality. These secondary effects may be beneficial to some species and detrimental to others; moreover, the magnitude of secondary effects is likely to vary over time. In the case of imidacloprid, an analysis of bird populations suggests adverse effects on terrestrial invertebrates may reduce populations of insectivorous birds.

1. INTRODUCTION

1.1. Chemical Specific Information

This document provides a human health and ecological risk assessment that evaluates the environmental consequences of using imidacloprid in Forest Service programs. This risk assessment is an update to a previous USDA Forest Service risk assessment of imidacloprid (SERA 2005).

A dominating factor in the previous and current Forest Service risk assessment is the limited uses of imidacloprid by the Forest Service in concert with the focused application methods to be used in most Forest Service programs. As discussed further in Section 2, imidacloprid is labelled for broadcast applications to numerous agricultural crops. Broadcast applications of imidacloprid are potentially hazardous to many nontarget species (e.g., U.S. EPA/OPP 2010a; U.S. EPA/OPP/EFED 2008a). As also detailed in Section 2, the Forest Service will use imidacloprid primarily for the control of the hemlock woolly adelgid (HWA, *Adelges tsugae*), a pest of hemlocks (*Tsuga spp.*) and other important insect pests on trees. Most applications of imidacloprid in Forest Service programs will involve tree or soil injection, thus, limiting exposures and consequent risks to nontarget species. Neither broadcast foliar nor broadcast ground applications of imidacloprid will be made in Forest Service programs. Consequently, the current Forest Service risk assessment does not support broadcast applications of imidacloprid. Nonetheless, as in the previous Forest Service risk assessment, broadcast application methods are discussed and considered in this updated risk assessment. This approach is taken solely for the sake of comparison of risks associated with focused application methods (i.e., tree or soil injection) to potential risks associated with broadcast applications. Much of the literature and commentary on imidacloprid reflects concerns with broadcast applications; accordingly, it is important to distinguish and contrast, quantitatively, when possible, the substantially reduced risks in focused applications, relative to the higher risks associated with broadcast applications.

In the preparation of this risk assessment, an updated literature search of imidacloprid was conducted in TOXLINE covering 2005 to January 2015. Initially, more than 4000 citations were identified based on CAS Number and synonyms. The use of synonyms (which included formulation names) identified many publications not relevant to imidacloprid. Narrowing the search to exclude synonyms yielded just fewer than 1000 citations. As with the previous Forest Service risk assessment of imidacloprid, no attempt is made to consider all of the new literature; instead, the focus of this updated risk assessment is the literature that specifically addresses the potential risks of imidacloprid to humans and nontarget species. For the most part, literature dealing with the efficacy of imidacloprid is not addressed in detail except to note, when possible, apparent differences in sensitivity between target and nontarget species.

Other relevant sources in the open literature were identified through recent reviews and risk assessments in the open literature (e.g., Blacquiere et al. 2012; CCME 2007; CDPR 2006; Cresswell 2011; Decourtye and Devillers 2010; EFSA 2013a,b; EFSA 2015; Furlan and Kreutzweiser 2015; Gervais et al. 2010; Gibbons et al. 2015. Hopwood et al. 2013; HSDB 2010; Kegley et al. 2014; Marrs and Maynard 2013; Mineau and Palmer 2013; Thany 2010; Tomizawa and Casida 2005, 2011) as well on commentaries on the impact of imidacloprid and other neonicotinoids on bees (Cressey 2013, 2015; Cresswell and Thompson 2012; Dicks 2013;

Eisenstein 2015; Elbert et al. 2008; Entine 2014a,b; Godfray et al. 2014; Goulson 2013; Gross 2013; Maxim and van der Sluijs 2007; Mole 2014; Stokstad 2012, 2013; Tomizawa and Casida 2011; Sanchez-Bayo 2014). Generally, reviews and commentaries are used only to identify published studies to ensure adequate coverage of the literature. The authors of some of the reviews and related documents had access to unpublished literature not included in EPA documents (discussed further below). For example, the review by the European Food Safety Authority (EFSA 2013a) includes studies required by European regulatory agencies but not by the U.S. EPA. In such cases, information taken from reviews is used directly in this risk assessment and is noted specifically in the text and references (Section 5) as appropriate.

In addition to the open literature, a substantial number of unpublished studies were submitted to the U.S. EPA/OPP in support of the registration of imidacloprid. In the previous Forest Service risk assessment (SERA 2005), 903 registrant studies were identified. Of these, 213 submissions—i.e., full copies of the studies submitted to the U.S. EPA—were kindly provided by the U.S. EPA Office of Pesticide Programs. Summaries of these submissions from the previous Forest Service risk assessment are included in the current risk assessment and are cited in the bibliography (Section 5) as MRID05. MRID is an acronym for Master Record Identification Number, a unique number assigned to each registrant-submitted study.

A web site maintained by the U.S. EPA/OPP (http://iaspub.epa.gov/apex/pesticides) includes reviews and summaries of studies submitted to the Agency in support of the registration of imidacloprid (n=159). These reviews most often take the form of Data Evaluation Records (DERs). While the nature and complexity of DERs varies according to the nature and complexity of the particular studies, each DER involves an independent assessment of the study to ensure that the EPA Guidelines are followed and that the results are expressed accurately. In many instances, the U.S. EPA/OPP will reanalyze raw data from the study as a check or elaboration of data analyses presented in the study. In addition, each DER undergoes internal review (and sometimes several layers of review). The DERs prepared by the U.S. EPA form the basis of EPA risk assessments, and available DERs are used in the current Forest Service risk assessment.

In addition to the above sources of information on registrant studies, other information on registrant-submitted studies is taken from risk assessments and related documents prepared by the EPA since the prior Forest Service risk assessment (e.g., U.S. EPA/OPP 2010a,b, 2014; U.S. EPA/OPP/EFED 2007a, 2008a; U.S. EPA/OPP/HED 2007a, 2008a,b; U.S. EPA/OPP/SRRD 2008a). In the interest of transparency, information on registrant studies based either on copies of full studies or DERs is cited in the standard author/date format, supplemented by the MRID number. Information taken only from EPA documents is cited using the MRID number and a reference to the EPA document in which the information is summarized.

The Forest Service is aware of and is sensitive to concerns with risk assessments that use 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 that are submitted to the U.S. EPA for pesticide registration are minor. The design of studies that are submitted for pesticide registration is based on strict guidelines for both the conduct and reporting of studies. 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 that substantially exceed the levels typically seen in open literature publications. Lastly, each study that is submitted to the U.S. EPA is reviewed by the U.S. EPA for adherence to the relevant study guidelines. As discussed above, these reviews most often take the form of Data Evaluation Records (DERs).

There are real and legitimate concerns with risk assessments that are based solely on registrant-submitted studies; however, data quality and data integrity are not substantial concerns. The major limitation of risk assessments based solely on registrant-submitted studies involves the nature and diversity of the available 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 following standardized protocols.

For some pesticides, including imidacloprid, numerous published studies are available, many of which are generated by academics with 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. As discussed above, the open literature on imidacloprid is substantial and has expanded greatly since the previous Forest Service risk assessment. Whereas the original Forest Service risk assessment on imidacloprid covered a little more than 150 open literature publications, more than 340 open literature publications for the period of 2005 to date were selected for detailed review in the current update.

The potential impact of imidacloprid on bees illustrates the greatly expanded literature on this pesticide. Imidacloprid is a neonicotinoid insecticide (Section 2), and one emerging issue with neonicotinoids involves adverse effects on both honeybees and other pollinators. As noted by U.S. EPA/OPP/EFED (2008a),

> *The Agency is currently in collaboration with other Agencies and researchers regarding the issue of pesticides, particularly the neonicotinoids, and their adverse effects on honeybees. The Agency is exploring all possible causes of Colony Collapse Disorder in bees, including the possible impact of pesticides, including imidacloprid.*
>
> U.S. EPA/OPP/EFED (2008)

The 2005 Forest Service risk assessment included less than a dozen published studies on the impact of imidacloprid on honeybees. Since 2005, many additional studies have been published in the open literature on the potential impact of imidacloprid on honeybees (Alaux et al. 2010; Bacandritsos et al. 2010; Barbara et al. 2005; Beliën et al. 2009; Boily et al. 2013; Chauzat et al. 2006, 2009, 2011; Cresswell 2011, 2012, 2014; Faucon et al. 2005; Gobin et al. 2008; Gregorc et al. 2012; Halm et al. 2006; Han et al. 2010a,b, 2012; Maxim and Van Der Sluijs 2007; Nguyen et al. 2009; Palmer et al. 2013; Pettis et al. 2012; Rocher and Marchand-Geneste 2008; Teeters et al. 2012; Williamson and Wright 2013; Williamson et al. 2013; Yang et al. 2008). Additional studies have been published on the potential impact of imidacloprid on bumblebees (Cresswell 2012, 2014; Feltham et al. 2014; Laycock et al. 2012, 2014; Mommaerts et al. 2010; Tobback et al. 2011; Whitehorn et al. 2012; Wilson et al. 2013), Africanized honeybees (de Almeida Rossi et al. 2013), as well as other bee species (Abbott et al. 2008; Wang et al. 2010). For bees as well as other groups of nontarget organisms, the more recent open literature plays an important role in this updated risk assessment.

The related aspect of the more recent open literature on imidacloprid involves studies conducted outside of the United States. The more recent literature on bees, other nontarget species, as well as other topics of concern to this risk assessment is dominated by studies conducted outside of the United States. There is no *a priori* basis for minimizing the significance of the studies on imidacloprid conducted outside the United States; accordingly, these studies are covered in the same manner as studies conducted within the United States. Nonetheless, some of the non-U.S. literature is inconsistent with the U.S. literature, particularly the studies conducted in the United States and submitted to and reviewed by the U.S. EPA/OPP and other governmental organizations (U.S. EPA/OPP/HED 2007a, 2008a, 2010a; CalEPA 2012). In some cases, the non-U.S. literature does not fully describe the source or purity of technical grade imidacloprid. In publications involving formulations, studies from the non-U.S. literature on imidacloprid do not use formulations marketed in the United States. Consequently, the relevance of this literature to the current Forest Service risk assessment may be questioned. Because of these considerations, an attempt is made to clearly identify studies conducted outside of the United States, including designations of where the studies were conducted, the source and purity of the imidacloprid, and which formulations of imidacloprid were used. In addition, studies submitted to and reviewed by the U.S. EPA are clearly identified by citing both standard author/year information as well as the MRID numbers for the studies designated by the U.S. EPA, as discussed above. The description of conflicting information is generally presented in the hazard identifications (Sections 3.1 and 4.1). The resolution of conflicting information is generally presented in the dose-response assessments (Sections 3.3 and 4.3) with additional discussions as necessary in the risk characterizations (Sections 3.4 and 4.4).

A final aspect of the emerging literature on imidacloprid involves the ongoing regulatory activities of EPA, which reviews pesticide registrations on a 15-year cycle. The registration review for imidacloprid is underway but is not scheduled for completion until 2016 (U.S. EPA/OPP 2010a, p. 3). While preliminary assessments supporting the registration review of imidacloprid are available (U.S. EPA/OPP/EFED 2008a; U.S. EPA/OPP/HED 2008a), it is likely that additional studies will be submitted to the U.S. EPA/OPP as part of the registration review. For example, U.S. EPA/OPP/EFED (2008a, p. 15) indicates that field tests for pollinators

following U.S. EPA/OPP protocols (e.g., U.S. EPA/OPP 2014d) are needed; however, references to or summaries of completed field studies have not been identified.

1.2. General Information

This document has four major sections, including this introduction (Section 1), the program description (Section 2), risk assessment for human health effects (Section 3), and risk assessment for ecological effects or effects on wildlife species (Section 4). Each of the two risk assessment sections has four major subsections, including an identification of the hazards, an assessment of potential exposure to this compound, an assessment of the dose-response relationships, and a characterization of the risks associated with plausible levels of exposure.

This is a technical support document which addresses some specialized technical areas. Nevertheless an effort was made to ensure that the document can be understood by individuals who do not have specialized training in the chemical and biological sciences. Certain technical concepts, methods, and terms common to all parts of the risk assessment are described in plain language in a separate document (SERA 2014a). The human health and ecological risk assessments presented in this document are not, and are not intended to be, comprehensive summaries of all of the available information. Nonetheless, the information presented in the appendices and the discussions in chapters 2, 3, and 4 of the risk assessment are intended to be detailed enough to support an independent review of the risk analyses.

The Forest Service periodically updates pesticide risk assessments and welcomes input from the general public and other interested parties on the selection of studies included in risk assessments. This input is helpful, however, only if recommendations for including additional studies specify why and/or how the new or not previously included information would be likely to alter the conclusions reached in the risk assessments.

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. Simple calculations are included in the body of the document [typically in brackets]. The results of some calculations within brackets may contain an inordinate number of significant figures in the interest of transparency (i.e., to allow readers to reproduce and check the calculations). In all cases, these numbers are not used directly but are rounded to the number of significant figures (typically two or three) that can be justified by the data.

Some of the calculations, however, are cumbersome. For those calculations, EXCEL workbooks (i.e., sets of EXCEL worksheets) are included as attachments to this risk assessment. The workbooks included with the current risk assessment are discussed in Section 2.4. The worksheets in these workbooks provide the detail for the estimates cited in the body of the document. Documentation for the use of these workbooks is presented in SERA (2011a).

The EXCEL workbooks are integral parts of the risk assessment. The worksheets contained in these workbooks are designed to isolate the numerous calculations from the risk assessment narrative. In general, all calculations of exposure scenarios and quantitative risk

characterizations are derived and contained in the worksheets. In these worksheets as well as in the text of this risk assessment, the hazard quotient is the ratio of the estimated exposure to a toxicity value, typically a no adverse effect level or concentration (i.e., NOAEL or NOAEC). Both the rationale for the calculations and the interpretation of the hazard quotients are contained in this risk assessment document.

2. PROGRAMS DESCRIPTION

2.1. Overview

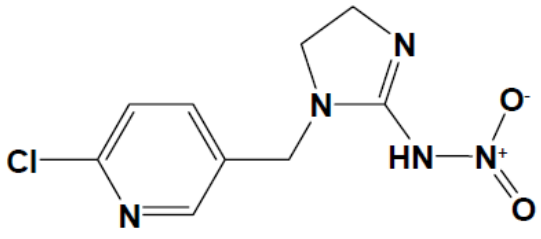
The Forest Service uses imidacloprid primarily in the control of the hemlock woolly adelgid (*Adelges tsugae*), a pest of hemlocks (*Tsuga* spp.). Imidacloprid may also be used in programs to control the emerald ash borer (*Agrilus planipennis*), engraver beetles (*Ips avulsus*), Asian longhorned beetle (*Anoplophora glabripennis*), spotted oak borer (*Agrilus auroguttatus*) and polyphagous shot-hole borer (*Euwallacea* species). While the current risk assessment focuses on the most common use in the control of the hemlock woolly adelgid, uses of imidacloprid on any target species designated on standard product labels, special local needs labels, or other similar authorizations including FIFRA 2(ee) recommendations are encompassed by the current risk assessment to the extent allowed by the available data.

Many different application methods are available for imidacloprid. The most common methods used in forestry applications are tree injection and soil injection. Tree injection involves the use of specialized application devices to insert liquid imidacloprid under pressure directly into the tree. Similarly, soil injection involves other specialized application devices that insert metered amounts of imidacloprid into the soil, below the soil surface. Broadcast foliar or broadcast ground applications of imidacloprid are not used in Forest Service programs and are not supported by the current risk assessment. Nonetheless, foliar applications are included in this risk assessment to contrast potential risks in the more directed applications methods used by the Forest Service with risks associated with directed foliar or broadcast applications.

The maximum annual application rate for imidacloprid is 0.5 lb/acre but the maximum rate for a single application is 0.4 lb/acre. While the application methods used in Forest Service programs do not typically express application rates in units of lb a.i./acre, the maximum labeled rates of 0.4 lb a.i./acre (single application) and 0.5 lb a.i./acre (cumulative annual application) are applicable to and limiting in other application methods. Because applications of imidacloprid are very labor intensive, the Forest Service will not apply any imidacloprid formulation more than once per year. Thus, the maximum application rate considered in this risk assessment is 0.4 lb a.i./acre. Based on very detailed use statistics from California, the forestry uses of imidacloprid are only about 1.4% of agricultural uses. In addition, many agricultural uses may involve broadcast applications. As noted above, broadcast applications will not be used in Forest Service risk assessments and broadcast applications are not supported by the current risk assessment.

2.2. Chemical Description and Commercial Formulations

Imidacloprid is the common name for 1-[(6-chloro-3-pyridinyl)methyl]-N-nitro-2-imidazolidinimine.



Imidacloprid was developed in 1985 by Bayer (Kagabu 2011). Structurally, imidacloprid is classified as a chloronicotinyl nitroguanidine (NPIC 2010). Functionally, imidacloprid is

classified as a neonicotinoid (IRAC Group 4A). Neonicotinoids are neurotoxic insecticides that act by binding tightly to nicotinic acetylcholine receptors (nAChRs) interfering with the binding of acetylcholine, a natural neurotransmitter, thus, interfering with normal nerve function (Kimura-Kuroda et al. 2012; Tomizawa and Casida 2004,2005; IRAC 2013).

Other neonicotinoid insecticides include acetamiprid, clothianidin, dinotefuran, thiacloprid, nitenpyram, nithiazine, thiacloprid, and thiamethoxam (Goulson 2013; Hopwood et al. 2013; U.S. EPA/OPP 2014b). In addition to the previous Forest Service risk assessment on imidacloprid (SERA 2005), a Forest Service risk assessment is available on dinotefuran (SERA 2009b). When imidacloprid is applied to either soil or foliage, the compound is systematically taken up by the plant over time. When a sucking insect such as HWA feeds on the plant after the imidacloprid has reached effective levels in the plant, it consumes imidacloprid residues from the plant and is killed (i.e., imidacloprid is a systemic insecticide).

This risk assessment is focused on Forest Service use of imidacloprid in the control of the HWA. The control of the HWA is one of the most common and most studied forestry uses for imidacloprid (Benton et al. 2015; Coots et al. 2013; Cowles et al. 2006; Dilling et al. 2009, 2010; Eisenback et al. 2009, 2010, 2014; Joseph et al. 2011a,b; Knoepp et al. 2012). As the name implies, the hemlock woolly adelgid is a pest of hemlocks (*Tsuga spp.*). The HWA sucks sap from growing hemlock twigs. In severe infestations, the resulting loss of needles and twigs can damage the health of the tree (Webb et al, 2003). While the hemlock woolly adelgid can be found in both the Pacific Northwest and the Eastern United States, damage to hemlocks appears to be most severe in the East (Hoover 2000).

Imidacloprid is also used in forestry to control other insect pests including engraver beetles such as *Ips avulsus* (Grosman and Upton 2006), the emerald ash borer, (Kreutzweiser et al. 2007; McCullough et al. 2013; Rebek et al. 2008; Smitley et al. 2010a,b) and the Asian longhorned beetle (*Anoplophora glabripennis*) (Kreutzweiser et al. 2008a; Poland et al. 2006a,b; Russell et al. 2010; Ugine et al. 2011, 2012). Bakke (2014) has indicated that Forest Service uses in California may include the control of invasive wood borers including the gold spotted oak borer (*Agrilus auroguttatus*) and polyphagous shot-hole borer (*Euwallacea* species). Notwithstanding the focus of the current risk assessment on the control of the HWA, the current risk assessment may support the use of imidacloprid on some other forest pests in that application rates, and application methods for the control of forest pests are functionally identical to the application rates and methods used to control the HWA. In terms of application rates, rates for soil or tree injection as well as bark applications will typically be expressed in units of formulation volume per inch DBH (diameter at breast height). Depending on the pest and tree species, application rates in units of formulation volume per inch DBH may be different from application rates for the control of HWA on hemlock. Nonetheless, the current risk assessment will support such uses. As discussed further in Section 2.4, the maximum labeled rate for a single application of imidacloprid is 0.4 lb a.i./acre. This application rate explicitly applies to broadcast applications but is applicable to any application method including tree/soil injection as well as bark applications.

The chemical and physical properties of imidacloprid are summarized in Table 1. Imidacloprid is relatively soluble in water (i.e., reported water solubilities of about 500 to 600 mg/L) with a

correspondingly low solubility in organic solvents (i.e., reported K_{ow} values of about 3.7 to 8.3). Because of the low K_{ow}, imidacloprid is not expected to bioconcentrate and the U.S. EPA/OPP has waived the requirement for a bioconcentration study in fish (U.S. EPA/OPP/EFED 2007a, p. 54; 2008a, p. 34). The supposition of the low potential for imidacloprid to bioconcentrate in fish is supported by a publication from the Chinese literature (Ding et al. 2004), with the abstract of the study reporting bioconcentration factors of 0.97 to 1.5 L/kg zebra fish. Imidacloprid is only moderately bound to soil (K_{oc} values of about 100 to 600) and has a potential to leach to ground water (U.S. EPA/OPP/EFED 2007a, p. 31). As with many pesticides, soil sorption is inversely related to the concentration of the pesticide in soil (Cox et al. 1998a,b) and the degree of soil sorption increases over time (Oi 1999).

Imidacloprid was developed as an insecticide in the early 1990s (Elbert et al. 1990) and was introduced as a commercial insecticide in 1991 by Bayer AG (Tomlin 2004). Furthermore, imidacloprid has been used as an insecticide in the United States since 1994 (Gervais et al. 2010). The U.S. Patent for imidacloprid (Patent No. 4,742,060) was issued on May 3, 1988 to Nihon Tokushu Noyaku Seizo KK. The patent holders name was changed to Bayer CropScience K.K., Japan on Sep 8, 2003. U.S. patents generally are issued for a period of 20 years. Thus, it appears that imidacloprid came off patent in 2008; however, an explicit documentation for the duration of the imidacloprid patent has not been identified. In any event, imidacloprid is clearly off patent at this time (2015). The Pesticide Action Network (PAN) lists 696 active U.S. registrations for imidacloprid formulations. While Bayer CropScience and Bayer Environmental Science (a subunit of Bayer CropScience) remain major suppliers of imidacloprid formulations, several other companies provide numerous formulations of imidacloprid.

Representative formulations of imidacloprid explicitly covered in the current risk assessment are summarized in Table 2. This list of formulations is essentially identical to the list of formulations covered in the previous Forest Service risk assessment except for differences in some of the companies listed as suppliers. The list includes granular, liquid, and powder formulations that may be applied as tree or soil injection as well as soil or foliar broadcast. As discussed further in Section 2.3, tree injection and soil injection are likely to be the predominant types of applications used in Forest Service programs. Only one of the formulations in Table 2 is labeled for aerial broadcast applications (i.e., Provado 1.6 Flowable). As noted in Section 1.1, the Forest Service will not use broadcast applications of imidacloprid in Forest Service programs and the current risk assessment considers but does not support the use of broadcast applications of imidacloprid.

The list of formulations in Table 2 is not intended to be exclusive. Many other formulations of imidacloprid are available commercially, and new formulations of imidacloprid are likely to become available in the future. The Forest Service may elect to use other formulations of imidacloprid registered for forestry applications. If other formulations are used in Forest Service programs, however, attempts should be made to identify information on the inerts in the formulations as well as the toxicity of the formulations to ensure that the formulation under consideration is comparable to the formulations explicitly designated in Table 2.

2.3. Application Methods

2.3.1. Tree Injection

Tree injection is a highly focused application method that minimizes exposures to most nontarget organisms (including humans) because the pesticide is applied directly to and inside of the tree. Tree injections involve the use of specialized equipment to inject a solution of the pesticide into the tree cambium. The pesticide is then transported throughout the tree primarily in xylem sap. The Forest Service has identified two formulations of imidacloprid that are labelled for tree injection: Imicide (J.J. Mauget Co) and IMA-jet (ArborJet). Each of these formulations is applied using specialized injection equipment developed by the formulators. As discussed by Kuhns (2011), both systems involve injection under pressure; nonetheless, the Mauget injection systems use a lower application pressure than the ArborJet system.

In both systems, imidacloprid is injected as a liquid under pressure directly into the tree. Holes with a diameter of about 11/64 inch are drilled into the tree at a slight downward angle to a depth of about 3/8 to ½ inch. The holes are drilled about 6 to 8 inches above the ground. The number of holes per tree depends on the tree diameter. After injection, the liquid insecticide is rapidly absorbed into the tree and translocated to the branches and foliage or needles. IMA-jet is injected into tree roots or into trunk tissue immediately above the trunk flare. The Arboplug is a self-sealing cylindrical container that can be injected directly into tree tissue (http://arborjet.com/products/arborplug.htm). The Arborplug is set into 5/8" deep holes drilled into the sapwood. The infusion process is initiated by piercing an internal septum in the Arborplug. For both formulations, the number of injections and volume of formulation are dependent on the size of the tree.

Efficacy studies, discussed further in Section 4.2.3, are available involving tree injections of imidacloprid for the control of HWA (e.g., Eisenback et al. 2014) and the Asian longhorned beetle (Ugine et al. 2012).

2.3.2. Soil Injection

As summarized in Table 2, imidacloprid may be applied to soil by broadcast application, mechanical incorporation, soil drench, or soil injection. All of these application methods involve an attempt to achieve an effective concentration of imidacloprid in the soil. Imidacloprid is then transported from the roots to the twigs where the target insects will feed.

Soil injection is the most focused/localized of the soil application methods. As with tree injection, soil injection involves the use of specialized equipment to inject or insert imidacloprid 2 to 4 inches below the soil surface (Kuhns 2011). Also as with tree injection, the application rate for soil injection is based on the size of the tree with labeled rates specified as about 0.7 to 1.5 g a.i./ inch DBH (diameter at breast height).

Soil drench is less labor intensive than soil injection but similar in terms of intent and effect (i.e., imidacloprid is incorporated into the soil column). The formulation is applied to the soil (either as a granular or liquid) and then watered in. This application method is recommended for Marathon WP, Merit 2F, Marathon II, Merit 75 WP, and Merit 75 WPS. The product labels for some formulations suggest that soil drench will be used primarily in nursery environments rather than general forestry. For example, soil drench is recommended for Marathon WP in adelgid

control for containerized plants. Other formulations, like Merit 2F, recommend soil drench for trees. All of the soil drench applications require a prescribed amount of water, typically on the order of 10 gallons per 1000 square feet. For two of the formulations labeled for soil drench in Table 2 (i.e., Marathon 60 WP and Marathon II), the application rates for soil drench may be expressed in units of a.i./acre (i.e., about 0.38 lb a.i./acre). For Merit 2F, the application rate is given as identical to soil injection (i.e., 0.72 to 1.4 g a.i./inch DBH). The requirement for irrigation in soil drench application limits the use of this application method to areas where water is readily available. Soil drench of imidacloprid in Forest Service programs are most likely to be used in treating isolated high-value hemlocks located on developed areas. Soil applications of imidacloprid may provide protection of hemlocks from the HWA for up to about 4 years (Benton et al. 2015).

While both soil injection and soil drench applications may be viewed as focused application methods relative to broadcast applications, soil injection and soil drench applications involve potentially greater exposures to most nontarget organisms, compared with tree injections (Kuhns 2011). The differences in exposures to nontarget organisms are discussed further in Section 4.2 (exposure assessment for nontarget organisms).

Soil broadcast applications involve spreading the formulation under the plants to be protected. Either rainfall or direct irrigation may be used to "activate" the imidacloprid (i.e., to transport the imidacloprid from the surface of the soil into the root zone of the plant). Soil broadcast applications may be made with granular formulations (Marathon 1% G; Merit 2.5 G), wettable powders (Marathon WP), or liquid formulations (Marathon II). While some imidacloprid formulations are labelled for soil broadcast applications, broadcast applications of imidacloprid (foliar or soil) will not be used in Forest Service programs and are not further considered.

2.3.3. Bark Applications

Some neonicotinoids such as dinotefuran (SERA 2009a) are labeled for basal bark applications. Current standard labels for imidacloprid formulations do not indicate that bark applications are permitted but this application method is being evaluated by the Forest Service and their cooperators (Cowles 2010; McCullough et al. 2011, 2013) under FIFRA 2(ee) recommendations. The FIFRA 2(ee) Recommendations reviewed in the preparation of the current risk assessment all specify the HWA as the target species but this application method may be extended to other species such as the emerald ash borer (McCullough et al. 2011). Bark applications of imidacloprid may be made as a mixture with dinotefuran. This approach may permit more rapid protection with dinotefuran being absorbed more quickly than imidacloprid but with imidacloprid providing longer-term protection (McCullough et al. 2013). As noted in Section 2.3.2, concentrations of imidacloprid in hemlock foliage may provide protection from the HWA for up to four years after soil applications (Benton et al. 2015). Studies of the duration of protection following bark applications, however, have not been identified.

Based on the FIFRA 2(ee) Recommendation for Mert 2F, the formulation is applied as a rate of about 3 to 6 mL per inch of trunk diameter (DBH). As with dinotefuran (SERA 2009a), the imidacloprid formulation will be mixed with an adjuvant such as 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.

Bark applications have the potential to substantially reduce offsite loses of imidacloprid relative to soil injection. The ability to quantify estimates of offsite losses associated with bark applications of imidacloprid is discussed further in Section 2.4.

2.3.4. Foliar Applications

Aerial, ground broadcast, and directed foliar (backpack) applications are standard application methods considered in most Forest Service risk assessments. Several of the formulations included in Table 2 are labeled for ground broadcast or directed foliar applications in which application rates are expressed in standard units of lb a.i./acre as discussed further in Section 2.4. Provado 1.6 is the only formulation of imidacloprid explicitly considered in the current risk assessment that is labeled for aerial applications.

As noted in Section 1.1, broadcast applications of imidacloprid will not be made in Forest Service programs. Foliar applications of imidacloprid are considered in the current risk assessment only to illustrate the reduced risks associated with more directed and focused application methods discussed in the previous sections. As discussed further in Section 2.5 (Use Statistics), many formulations of imidacloprid are labelled for agricultural uses for the control of insect pests. Although none of the Forest Service applications of imidacloprid will involve crop treatment, crop treatments may be conducted on some Forest Service lands by individuals or organizations permitted to use Forest Service lands for the cultivation of crops. All such agricultural applications are subject to U.S. EPA/OPP regulatory constraints (e.g., tolerance limits) and are not explicitly considered in Forest Service risk assessments.

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).

2.4.1. Tree Injection

As summarized in Table 2, the product labels for Imicide and IMA-jet do not express application rates in units of lb a.i./acre. Even with respect to application rates in units of g a.i./tree, the rates are highly variable depending on the size of the tree. In the absence of a specific labeled rate for imidacloprid applied by tree injection, the maximum labeled rate of 0.4 lb a.i./acre is limiting. The manner in which imidacloprid is applied will depend on the number and size of the trees in the area to be treated.

A key exposure factor for some accidental exposure scenarios is the concentration of the pesticide in the field solution. For most application methods, this concentration is calculated based on the concentration of the pesticide in the formulation and the volume of water or other solvent used to dilute the formulation. This approach, however, is not applicable to tree injection with imidacloprid because the formulations are loaded into the injection device without dilution. As summarized in Table 2, the formulations of imidacloprid labelled for tree injection contain imidacloprid at concentrations of about 53.5 mg a.i./mL (IMA-jet) and 110.7 mg a.i./mL

(Imicide). In the custom workbook for tree injection that accompanies this risk assessment (Attachment 1), the field concentrations are taken as 53.5 mg a.i./mL. The use of other formulations with different concentrations of imidacloprid in the formulation may be accommodated by changing the concentration of imidacloprid in the field solution in Worksheet A01 of Attachment 1.

2.4.2. Soil Injection

As discussed in Section 2.3, soil applications may involve either soil injection or soil drench. Application rates for soil drench are specified on the product labels for the imidacloprid formulations specifically labeled for soil drench (Table 2). Soil drench and soil injection are similar in that the intent of the application is to distribute the pesticide in the soil column. Soil drench is more intensive in terms of the amount of water required for the application and this may be limiting in forestry applications. As in the previous Forest Service risk assessment on imidacloprid (SERA 2005) as well as the Forest Service risk assessment on dinotefuran (SERA 2009a), only soil injections are explicitly considered in the current risk assessment. As with tree injection, labelled application rates are not expressed in units of lb a.i./acre and the maximum labelled rate of 0.4 lb a.i./acre for a single application is limiting.

Because soil injection involves placement of imidacloprid well below the soil surface, runoff and sediment losses, which are common mechanisms of offsite transport for soil surface or foliar applications, will be lower in soil injection applications relative to surface application (Section 3.2). Conversely and for the same reason, transport due to percolation is likely to be higher in soil injection applications. In other words, the lack of significant runoff and sediment losses would tend to increase losses due to percolation because more of the chemical will be available for percolation. Target soil concentrations for soil injection applications could be used to model the potential for soil loss but the concentrations are not specified on any product labels for soil injection. For the current risk assessment, soil injection is modeled by setting the average soil incorporation depth to 6 inches and assuming that the functional application rate for soil injection will not exceed the maximum labeled rate for a single application of 0.4 lb a.i./acre.

The product labels for imidacloprid formulations labeled for soil injection do not specify mixing rates for the preparation of field solutions. Instead, the product labels contain the following statement taken from the label for Marathon II or very similar language: "*Mix required dosage in sufficient water to inject an equal amount of solution in each hole*". In general, greater amounts of water are used in dry soils and less amounts of water in moist soils. Field solutions as dilute as about 2.5 mg a.i./mL have been reported in the literature – i.e., 1.5 g a.i./20 oz of water (591.471 mL), 1,500 mg/591.47 ≈ 2.536 mg a.i./mL or about 0.021 lb a.i./gallon (Griffin 2010). The greatest concentration noted in the literature is somewhat over 50 mg a.i./mL – i.e., 1.5 g a.i./29.5 mL, 1,500 mg/29.5 mL ≈ 50.84746 mg a.i./mL or about 0.424 lb a.i./gallon (Knoepp et al. 2012). This range of concentrations for field solutions is similar to the range cited in the Forest Service risk assessment on dinotefuran – i.e., about 21 to 85 mg a.i./mL (SERA 2009a). As detailed in Worksheet A01 of the workbook for soil injections of imidacloprid (Attachment 2), the field solutions are approximated using application volumes of 4 gallons/acre with a range of 1 to 20 gallons/acre. These application volumes resulted in field solutions of 0.1 (0.02 to 0.4) lb a.i./gallon, which is equivalent to 12 (2.4 to 48) mg a.i./mL.

2.4.3. Bark Applications

As noted in Section 2.3.3, FIFRA 2(ee) Recommendations are available and in use for bark applications of imidacloprid to control the HWA for formulations including Merit 2F. As with dinotefuran (SERA 2009a), the application rates for bark application are identical to those for soil injection. For Merit 2F, these rates are 3-6 mL per inch DBH [0.72 to 1.4 g a.i./inch DBH]. While the FIFRA 2(ee) Recommendations for imidacloprid formulations do not specify a maximum application rate, the maximum labeled application rate of 0.4 lb a.i./acre (which explicitly applies to broadcast applications) is applicable to any application method including bark applications.

Application volumes for bark applications are not specified on the FIFRA 2(ee) Recommendations for imidacloprid formulations. In the Forest Service risk assessment dinotefuran (SERA 2009a), the field solutions for bark applications (≈27 mg a.i./mL) were about the same as those used for tree injection (30 mg a.i./mL). The literature on bark applications of imidacloprid is not extensive. McCullough et al. (2011) report using 95 ml/2.5 cm DBH in bark applications of imidacloprid at rate of 1.704 g a.i/2.5 cm DBH. This corresponds to a field solution of about 18 mg a.i./L [1,704 mg a.i. ÷ 95 mL ≈ 17.9368 mg a.i./mL]. In the absence of further information, the field solutions for tree injection of imidacloprid – i.e., 0.1 (0.02 to 0.4) lb a.i./gallon – are applied to bark applications. These concentrations are equivalent to about 12 (2.4 to 48) mg a.i./mL, encompassing the concentration of 18 mg a.i./mL used in McCullough et al. (2011). For an application rate of 0.4 lb/acre, these field solutions correspond to application volumes of 4 (1-20) gallons/acre, as detailed in Worksheet A01 of Attachment 3.

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 as well as imidacloprid 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. As discussed in the Forest Service risk assessment on dinotefuran (SERA 2009a), Onken (2009) suggests that a maximum of 10% of the dinotefuran applied to bark might be splashed onto the ground or vegetation adjacent to the treated tree. Cowles (2009) suggests that a value of 5% might be more typical but that a lower rate could be achieved under favorable conditions. This information is presumably relevant to bark applications of imidacloprid and this information is considered further in Section 3.2.3.1.2 (Summary of Assessments) and Section 3.2.3.7 (Oral Exposure from Contaminated Vegetation).

2.4.4. Foliar Applications

Most of the formulations labeled for foliar applications (i.e., Marathon 60 WP, Marathon II, and Merit 2F) involve ground foliar applications at maximum rates of 0.4 lb a.i./acre. Similarly, the Marathon 1%G formulation is labeled for soil broadcast applications, also at an application rate of 0.4 lb a.i./acre.

The liquid formulations all specify an application volume of at least 2 gallons of water per 1000 square feet, equivalent to about 87 gallons per acre. As discussed in previous sections,

application volumes (i.e., the number of gallons of pesticide solution applied per acre) have an impact on the estimates of potential risk. The extent to which a formulation of imidacloprid is diluted prior to application primarily influences dermal and direct spray scenarios, both of which depend on 'field dilution' (i.e., the concentration of imidacloprid in the applied spray). In all cases, the higher the concentration of pesticide (i.e., equivalent to the lower dilution of the herbicide), the greater is the risk. Most Forest Service risk assessments use a range of recommended application volumes.

As discussed above, the application volume for Marathon 60 WP, Marathon II, and Merit 2F, however, is specified on the product labels only as a minimum application volume of 87 gallons per acre. While foliar applications are not a focus of the current risk assessment, it seems reasonable that higher application volumes would be used for imidacloprid. In the absence of more detailed information on broadcast application volumes for imidacloprid, application volumes of up to 400 gallons per acre are considered by analogy to dinotefuran (SERA 2009a). Thus, the application volumes for broadcast applications of imidacloprid are taken as 200 (87-400) gallons per acre, with the central estimate representing the approximate geometric mean of the range [$(87 \times 400)^{0.5} \approx 186$]. As detailed in Worksheet A01 of Attachment 4 (directed foliar applications), these dilution rates are equivalent to 0.24 (0.12-0.55) mg a.i./mL, substantially below the field concentrations for soil injection and bark applications – i.e., 12 (2.4 to 48) mg a.i./mL.

2.4.5. Relationship of Workbooks to Application Methods and Rates

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

This risk assessment is accompanied by four EXCEL workbooks:

- Attachment 1: Tree injection
- Attachment 2: Soil injection/drench
- Attachment 3: Bark Applications
- Attachment 4: Foliar Broadcast applications

As discussed in Section 2.3, most Forest Service risk assessments will involve tree injection, soil injection, or bark application. As also discussed in Section 2.3, broadcast applications will not be made in Forest Service programs. Attachment 4, which covers broadcast applications, is provided solely to contrast risks from focused applications to those associated with broadcast applications.

2.5. Use Statistics

Forest Service risk assessments attempt to characterize the use of a pesticide in Forest Service programs relative to the use of the pesticide in agricultural applications. Forest Service pesticide use reports up to the year 2004 are available on the Forest Service web site (http://www.fs.fed.us/foresthealth/pesticide/reports.shtml). While this dated information is not clearly relevant to the current use of pesticides by the Forest Service, recorded uses of imidacloprid are limited to Region 5 (Pacific Southwest) and Region 8 (Southern). For Region 5, three applications are

reported involving small amounts of the pesticide (i.e., a total of 0.0211 pounds) with one application made in 2001, 2003 and 2004. If these reports are accurate, all of these applications probably involved research projects and are not representative of the wider use of imidacloprid in forestry applications. For Region 8, five applications are reported all of which were made in 2004. Two of the applications report application rates in units of lb/acre, with one reported as 0.072 lb a.i./acre (Forest 4, 0.36 lb a.i. applied to 5 acres) and the other as 0.5 lb a.i./acre (Forest 11, 30 lbs a.i. applied to 60 acres.). Two other applications are reported as lbs/tree—i.e., 0.167 lbs/tree (Forest 11, 14.2 lbs treating 848 trees) and about 0.028 lbs/tree (Forest 12, 2.93 lbs/105 trees). The fifth application in Forest 11 is reported simply as 6.38 lbs applied in 8 "treatment stations". Note that the numeric designation of different forests within each Forest Service region (e.g., Forest 4 in Region 8) is a convention used in the Forest Service reporting documents. Bakke (2014) has indicated that very small amounts of imidacloprid (≈0.1 lb/year) may be used in nurseries in Forest Service Region 5 (California and Hawaii). Kyle (2015) has indicated that applications of imidacloprid have been made in Forest Service Region 9 (Eastern Region) by various application methods discussed in Section 2.3 but annual use rates (i.e., lbs a.i./year) are not specified.

Information on the agricultural use of pesticides is compiled by the U.S. Geological Survey (USGS 2014). The estimated agricultural use of imidacloprid in 2011 based on USGS (2014) statistics ranges from about 1,700,000 lbs (Figure 1) to somewhat over 1,800,000 lbs (Figure 2). The greatest use of imidacloprid is in the north central to central United States running from North Dakota to northern Texas and eastwards to Ohio and Florida. Based on use data by crop (also summarized in Figures 1 and 2), imidacloprid is currently used primarily on soybeans and cotton. While Douglas and Tooker (2015) note that a primary use of neonicotinoids involves the treatment of corn, this does not appear to be case with imidacloprid. As illustrated in Figure 1 and Figure 2, the use of imidacloprid on corn has declined since 2008. As also illustrated in Figures 1 and 2, the use of imidacloprid in the United States was under 500,000 lbs/year prior to 2004 but has increased substantially starting in 2009.

Detailed pesticide use statistics are compiled by the state of California. The use statistics from California for 2013, the most recent year for which statistics are available, indicate that a total of 376,517.32 lbs of imidacloprid was used in California (CDPR 2015, p. 438). The uses relevant to Forest Service programs appear to involve applications to forest timberland (4.12 lbs), regulatory pest control (764.23 lbs), and rights-of-way maintenance (217.82 lbs). The total of these uses (986.17 lbs) accounts for only about 0.26% of the total imidacloprid use in California in 2013 [986.17 lbs ÷ 376,517.32 ≈ 0.0026192]. Between 2009 and 2013, imidacloprid is the insecticide applied to the largest number of acres in California and the acreage treated in California has risen from about 0.04 million acres (2009) to somewhat over 0.16 million acres (2013) (CDPR 2015, Figure 18, p. 82).

Based on the use statistics from California, agricultural uses of imidacloprid are much greater than uses related to forestry. This is a common pattern in pesticides which reflects the larger areas of crop cultivation relative to forestry—i.e., about 613 million acres for agriculture (http://www.epa.gov/agriculture/ag101/landuse.html) relative to 193 million acres of forests managed by the Forest Service (http://www.fs.fed.us/documents/USFS_An_Overview_0106MJS.pdf) and the more intensive use of pesticides in agriculture relative to forestry.

1

3. HUMAN HEALTH

3.1. HAZARD IDENTIFICATION

3.1.1. Overview

Imidacloprid is a neonicotinoid insecticide, a member of a class of insecticides that act by binding or partial binding to specific areas of the nicotinic acetylcholine receptor (nAChR). This mechanism of action is distinct from other pesticides which inhibit acetylcholinesterase (AChE). Imidacloprid will bind to nAChR in mammals, insects, and other species; however, the affinity for imidacloprid to insect nAChR is much greater than the affinity to mammalian nAChR. This difference is the basis for the differential toxicity and insecticidal efficacy of imidacloprid. While imidacloprid is not an inhibitor of AChE, several recent studies from the Indian literature indicate that imidacloprid will lead to decreases in AChE activities in blood, plasma, and brain tissue following *in vivo* dosing of rats. While the decrease in the activity of plasma AChE may be secondary to liver damage, the mechanism for the reduction in red blood cell and brain AChE activity is unclear.

While neurotoxicity is a sensitive endpoint in acute exposures of mammals to imidacloprid, neurotoxicity is not the most sensitive endpoint in longer-term exposures. In other words, neurotoxicity is not generally noted in subchronic or chronic toxicity studies. The most sensitive effects (i.e., the effect occurring at the lowest doses) in chronic studies involve damage to the thyroid with decreases in thyroid hormones—i.e., a disruption in endocrine function. In addition, at higher doses, imidacloprid will cause general damage in many tissues which appears to be associated with oxidative stress. Imidacloprid does not induce birth defects at doses that are not maternally toxic. Nonetheless, imidacloprid may impair normal reproduction and cause adverse testicular effects at high doses. The chronic toxicity data on imidacloprid are adequate to assert that imidacloprid does not cause cancer. The U.S. EPA has classified imidacloprid as Group E for carcinogenicity—i.e., evidence of non-carcinogenicity for humans.

3.1.2. Mechanism of Action

The mechanism of action of imidacloprid has been extensively studied in insects and mammals (Bal et al. 2010; Tomizawa and Casida 2003, 2004, 2005; Marrs and Maynard 2013; Meijer et al. 2014; Yao et al. 2009). Imidacloprid is a neonicotinoid insecticide which produces neurotoxicity through binding or partial binding to specific sub-sites or protein subunits of the nicotinic acetylcholine receptor (nAChR), which in turn activates nAChR activity—i.e., imidacloprid is an nAChR agonist.

Acetylcholine is an important neurotransmitter in both insects and mammals, which is released at the nerve synapse in response to a membrane depolarization, 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 through binding to nAChRs are called nAChR agonists. Imidacloprid is a nAChR agonist that mimics the action of nicotine in the nervous system, binding at or near the site on the nAChR where nicotine binds (Tomizawa and Casida 2003, 2004, 2005). Although imidacloprid activates nAChRs, it is important to note that it does so in a manner fundamentally different from nicotine. This difference is important because, unlike nicotine, imidacloprid is more toxic to insects than to mammals (Matsuda et al. 2009; Yao et al. 2009). This mechanism of action, although it may be prevalent in mammals, may not be prevalent in all vertebrates. As discussed in Section 4.1.3.2, the study by Seifert and Stollberg (2005) suggests that imidacloprid may be a nAChR antagonist in cell cultures of *Xenopus laevis* embryonic frog muscle.

In studies designed to investigate the selective toxicity of imidacloprid to invertebrates, early investigators observed that radio-labeled imidacloprid binds to membranes of the head and brain in certain insects (e.g., house flies, cockroach, honey bee, cricket) but not to brain membranes of humans, dogs, mice, or chickens, suggesting that imidacloprid receptors are distributed differently among insects and mammals (Liu and Casida1993). Subsequent investigators determined that the structure of nAChRs in mammals is fundamentally different from the structure of nAChRs in insects (Buckingham et al. 1997; Chao et al. 1997; Liu and Casida 1993; Liu et al. 2010; Nagata et al. 1997, 1998; Matsuda et al. 2000, 2009; Nishiwaki et al. 2003; Tomizawa et al. 2001; Tomizawa and Casida 2003, 2004, 2005). Both imidacloprid and some of its metabolites show selective binding to nAChRs, with different affinities, depending on the structure of the metabolite and the nAChR subtype (Chao and Casida 1997; Yamamoto et al. 1998; Tomizawa et al. 2000, 2001; Tomizawa and Casida 1999, 2000, 2001; Shimomura et al. 2002, 2003, 2004; Zhang et al. 2002). In general, imidacloprid analogs or metabolites that bind with high affinity to insect nAChR do so with low affinity to mammalian nAChR (Bal et al. 2010).

There is a correlation between the toxicity of imidacloprid/imidacloprid metabolites and the binding of a number of imidacloprid/imidacloprid metabolites to nAChR sub-sites (i.e., low toxicity and low-affinity binding in mammals, versus high toxicity and high-affinity binding in insects) (Tomizawa and Casida 2003, 2004, 2005). Taken together, the studies conducted with imidacloprid and its metabolites suggest that the guanidine or desnitro- metabolites may be toxic metabolites in mammals but detoxification products in insects, while the reverse is true for the nitrosoimine and olefin metabolites (Schulz-Jander and Casida 2002; Schulz-Jander et al. 2002). Desnitro-imidacloprid was more toxic (lower i.p. LD_{50}) in mice and showed greater affinity for nAChR (lower IC_{50}) in mouse brain than imidacloprid (Chao and Casida1997). In spite of high-affinity binding to nAChR in excess of the binding exhibited by imidacloprid, however, the olefin metabolite was of low toxicity, probably due to detoxification.

Acetylcholinesterase (AChE) activity was decreased in both the brain and red bloods cells in rats after acute (Kapoor et al. 2014) and subchronic (Bhardwaj et al. 2010; Vohra et al. 2014) exposure to 20 mg/kg bw/day of imidacloprid. The inhibition of nAChR and the inhibition of AChE are distinct and different mechanisms of action (e.g., Ashokan et al. 2012). As noted by Bhardwaj et al. (2010), the decrease in AChE activity is an unusual observation in that imidacloprid is not an inhibitor of AChE. At somewhat higher doses in rats (45 and 90 mg/kg

bw/day), decreases in AChE activity were observed in plasma, red blood cells, and brain tissue (Lonare et al. 2014). Lonare et al. (2014) note that the decrease in plasma AChE is probably secondary to liver damage since plasma AChE is synthesized in the liver. Lonare et al. (2014) do not address the decreases in red blood cells and brain AChE, for which there is no apparent rationale. Moreover, there are no reports of decreased AChE activity in mammals associated with imidacloprid exposure in the available literature. The studies by Kapoor et al. (2014) and Bhardwaj et al. (2010) were conducted at the Indian Institute of Toxicology Research in Lucknow, India using technical grade imidacloprid. The study by Lonare et al. (2014) was conducted at the Indian Veterinary Research Institute in Bareilly, India using technical grade imidacloprid from a Mumbai chemical company. The study by Vohra et al. (2014) is from a different group of investigators (Punjab Agricultural University in Punjab, India) using a Confidor (17.8%) formulation of imidacloprid. Conversely, a developmental study in rats reports an increase in AChE activity in the brain tissue of offspring of female rats given a single intraperitoneal injection of 377 mg/kg bw imidacloprid on day 9 of gestation (Abou-Donia et al. 2008). As discussed in Section 4.1.2.4.1.2.1, increases in AChE activity were observed also in honeybees following exposure to imidacloprid (Boily et al. 2013). None of the toxicity studies submitted by U.S. registrants and reviewed by the U.S. EPA/OPP/HED (2008a, 2010a) or CalEPA (2013) reports AChE activity as an effect of exposure to technical grade imidacloprid or U.S. formulations of imidacloprid.

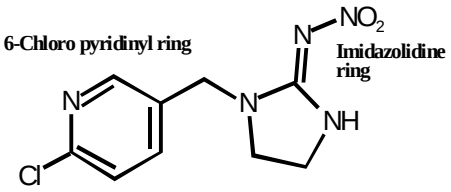
Little information is available on mechanisms of action for imidacloprid other than neurotoxicity. Based on *in vitro* studies using fat cells, Park et al. (2013) note that imidacloprid may impact normal adipocyte development and increase lipid accumulation. While a few *in vivo* subchronic toxicity studies in rats and mice report increases in both food consumption and body weight (Bal et al. 2012a ; Eiben 1988a,b, 1989), this pattern is not consistent with the majority of the subchronic and chronic studies indicating either weight loss or no effect on body weight (Section 3.1.5).

The effects of many pesticides and other chemicals include general signs of oxidative stress typically characterized by an increase in free radical production and other reactive oxygen species leading to increased lipid peroxidation, generalized tissue damage, cell death, and depletion of endogenous antioxidants such as glutathione (Abdollahi et al. 2004; Agrawal and Sharma 2010). As noted in several of the following sections, signs of general oxidative stress are reported in several toxicity studies on imidacloprid (e.g., Bal et al. 2012a; El-Gendy et al. 2010; Lonare et al. 2014). As discussed further in Section 3.1.16 (Toxicological Interactions), signs of oxidative stress caused by imidacloprid can be antagonized by antioxidants, a very common interaction in compounds which induce oxidative stress.

3.1.3. Pharmacokinetics and Metabolism

3.1.3.1. Metabolism

The chemical structure of imidacloprid and selected metabolites discussed in the EPA's most recent human health risk assessment (U.S. EPA/OPP/HED 2007a) are illustrated in Figure 3, parts of which are embedded in the following discussion for convenience. Imidacloprid consists of a pyridine ring and an imidazolidine linked by a methyl bridge (–CH_2–).



The pyridine ring contains a chlorine substituent (6-chloro) and the imidazolidine ring contains a nitroimine substituent (=N-NO_2) on the carbon between the two nitrogens. The metabolism of imidacloprid is mediated primarily by cytochrome P450 enzymes (Shi et al. 2009). As discussed further in Section 3.1.16 (toxicological interactions), cytochrome P450 is a group of structurally similar enzymes, typically referred to as isozymes, involved in the metabolism of many naturally occurring as well as synthetic chemicals.

The CYP2D6 isozyme is specific to the reduction of the nitro-group on the imidazolidine ring (i.e., =N-NO_2 → –N-NO → NH_2), and the CYP3A4 isozyme is involved in the 5-hyroxylation of the pyridine ring to form 5-hydroxyimidacloprid (Casida 2011), as illustrated in Figure 3. Nitro-reduction can also be mediated by an aldehyde oxidase, an enzyme distinct from the cytochrome P450 enzymes (Kick et al. 2005, 2006; Swenson and Casida 2013). Based on comparative metabolism studies in mice and spinach, the metabolic pathways of imidacloprid are similar in plants and animals, except that mammals are able to cleave the methyl bridge linking the pyridine and imidazolidine rings (Cassida 2011; Schulz-Jander et al. 2002; Schulz-Jander and Casida 2002). As discussed further in Section 4.1.2.4, different isozymes of P450 (i.e., CYP6AY1) are important in the metabolism of imidacloprid in some terrestrial invertebrates.

While imidacloprid is not a particularly large or complex molecule, several different metabolites may be formed. WHO (2001) proposes a partial metabolic pathway for rats with 15 metabolites, and Cassida (2011) identifies 12 metabolites in mice. It seems likely that additional metabolites of imidacloprid will be elaborated as further studies are conducted. As is true with many pesticides, the metabolites of imidacloprid are typically conjugated with endogenous compounds (e.g., glucuronides, amino acids, sulfates, glutathione) prior to excretion (Section 3.1.3.3).

Just as the full scientific names for imidacloprid (e.g., 1-(6-chloro-3-pyridylmethyl)-N-nitroimidazolidin-2-ylideneamine) are somewhat long and cumbersome, so are the full names of many of the metabolites of imidacloprid. Following the convention adopted in EPA risk assessments (e.g., U.S. EPA/OPP/HED 2007a), the current risk assessment uses abbreviated designations for some metabolites of imidacloprid, as specified in Figure 3. From a practical perspective, the most important metabolite is the nitrosimine (–N-NO) formed in the reduction of the nitro-group by the CYP2D6. This metabolite is commonly referred to as WAK 3839. As discussed further in Section 3.1.4 (acute toxicity) and Section 3.1.5 (subchronic or chronic toxicity), WAK 3839 is the only metabolite of imidacloprid for which *in vivo* toxicity studies are available.

The U.S. EPA typically requires intravenous and oral metabolism studies for pesticide registration, and a full set of studies conducted with rats and mice was submitted to EPA (Klein 1987a; Klein 1990; Klein and Karl 1990; Klein and Brauner 1991). These studies suggest that the metabolism of imidacloprid does not vary with route of administration, sex of animal, or frequency of administration at low doses (1 mg/kg body weight) and acute or sub-acute

exposures (1 to 14 days). At higher doses (20 mg/kg body weight), however, males appear to metabolize the parent compound more rapidly than females (Klein and Karl 1990). In addition, a metabolism study on WAK 3839, the nitrosimine metabolite of imidacloprid, noted no significant differences in the absorption, distribution, or excretion of this metabolite, relative to imidacloprid.

3.1.3.2. Absorption

3.1.3.2.1. Oral Absorption

Animal studies suggest that imidacloprid is rapidly and completely absorbed following oral administration. After oral administration of ^{14}C-methylene labeled imidacloprid in rats, 95% of the administered dose was absorbed, with an estimated half-life of 35 minutes. The absorbed radioactivity was distributed rapidly throughout the body, with an approximate volume of distribution from the central compartment of 84% of the body volume. The maximum concentration of radioactivity was reached in the plasma within 2.5 hours. The kidney and liver had the highest concentrations of radiation, while the brain had the lowest concentrations. The distribution pattern of radioactivity throughout the body was independent of dose (Klein 1987b).

Similar results were obtained with ^{14}C-imidacloprid labeled at the 4- and 5-carbon of the imidazolidine ring (Klein and Brauner 1991). Following oral administration, greater than 90% of the administered radiation was estimated (from renal excretion data) to have been absorbed, with maximum concentrations reaching the plasma between 1 hour (1 mg/kg body weight dose) and 4 hours (150 mg/kg body weight). After 48 hours, the highest concentration of radioactivity was detected in the liver, with residual radiation in the total body at 1%. There were no differences in the pattern or distribution of radioactivity in comparison to the Klein (1987b) study.

In a separate study, Klein (1987a) used autoradiography to determine the distribution of ^{14}C-methylene labeled imidacloprid in male rats following oral and intravenous administration (20 mg/kg body weight). This study determined that imidacloprid distributes rapidly to all tissues with the exception of the fatty tissues, central nervous system, and the mineral portion of bones, following either oral (1 hour) or intravenous (5 minutes) administration. With increased time following administration, radiation was also seen in the endocrine glands (thyroid, adrenals), the skin, and the walls of the aorta, indicating distribution and concentration of imidacloprid in these organs/tissues. Only small amounts of imidacloprid were found in the fatty tissues or central nervous system throughout the duration of the study. Concentrations decreased in most organs and tissues with increasing time following exposure. The pattern of distribution changed very little throughout the course of the study.

In addition to the studies in experimental mammals, suicide case studies (Wu et al. 2001; Proenca et al. 2005) demonstrate that oral intake of imidacloprid formulations results in absorption and distribution to the blood, kidneys, liver, and lung (see Section 3.1.4 for details).

3.1.3.2.2. First-Order Dermal Absorption

No data on the dermal absorption of imidacloprid are cited in U.S. EPA risk assessments on imidacloprid. As summarized in U.S. EPA/OPP/HED (2007a, p. 19), a dermal absorption factor of 7.2% (rounded to 7%) is used based on the ratio of the oral LOAEL of 72 mg/kg bw/day from

a developmental study in rabbits (Becker and Biedermann 1992 as discussed further in Section 3.1.9.1) to a subchronic dermal NOAEL in rabbits (Flucke 1990 as discussed further in Section 3.1.12) [72 mg/kg bw/day ÷ 1000 mg/kg bw/day = 0.072 = 7.2%]. This factor is used for exposures over the course of a work day (8 hours) and corresponds to a first-order dermal absorption rate of about 0.01 $hour^{-1}$ [k_a = -ln(1-0.072) ÷ 8 hours ≈ 0.0093404 $hour^{-1}$].

In the absence of experimental data, Forest Service risk assessments use an algorithm based on the molecular weight and octanol water partition coefficient (K_{ow}) to approximate a first-order dermal absorption rate coefficient—i.e., Eq. 23, Section 3.1.3.2.2 in SERA (2014a). As detailed in Worksheet B03b of the WorksheetMaker workbooks that accompany this risk assessment, the estimated first-order dermal absorption rate coefficient for imidacloprid based on this algorithm is about 0.0015 $hour^{-1}$ with a 95% confidence interval of 0.00067 to 0.0036 $hour^{-1}$ based on a molecular weight of 255.7 and K_{ow} of 3.7 (Table 1 values from U.S. EPA/OPP/HED 2007a). The central estimate of the k_a from the SERA (2014a) algorithm (0.0015 $hour^{-1}$) is lower than the U.S. EPA estimate based on toxicity studies by a factor of 6.2 [0.0093 ÷ 0.0015 = 6.2], and the upper bound from the SERA (2014a) algorithm (0.0036 $hour^{-1}$) is lower than the EPA estimate by a factor of about 2.6 [0.0093 ÷ 0.0036 ≈ 2.583].

Forest Service risk assessments are typically as conservative as EPA risk assessments, unless there is a compelling reason to be otherwise. There are two major and interrelated issues with the method used by U.S. EPA/OPP/HED (2007a, p. 19). The estimate of the 7.2% dermal absorption factor involves the comparison of an oral LOAEL to a dermal NOAEL. As discussed further in Section 3.1.12, a LOAEL is not defined in the dermal toxicity study by Flucke (1990). As also discussed in Section 3.1.12, the acute dermal studies on imidacloprid also fail to define a LOAEL at doses of up to 5000 mg/kg bw/day (Krotlinger 1989, MRID 42055332). While the EPA estimate of 7.2% may be viewed as conservative in that the dermal absorption rate coefficient is not likely to be underestimated, the EPA absorption factor may overestimate, perhaps grossly so, the dermal absorption of imidacloprid. Imidacloprid is used in veterinary applications for the control of fleas. While quantitative estimates of dermal absorption rates from these studies are not available, a microautoradiography study by Chopade et al. (2010) demonstrates that ^{14}C labelled imidacloprid remains largely in the stratum corneum with little indication of systemic absorption.

Given the above concerns, the current Forest Service risk assessment uses the estimated first-order dermal absorption rate coefficients of 0.0015 (0.00067 to 0.0036) $hour^{-1}$ for exposure assessments involving first-order dermal absorption.

3.1.3.2.3. Zero-Order Dermal Absorption

As detailed in SERA (2014, Section 3.1.3.2.1), dermal exposure scenarios involving immersion or prolonged contact with chemical solutions use Fick's first law and require an estimate of the permeability coefficient, K_p, expressed in cm/hour. Using the method recommended by U.S. EPA/ORD (1992, 2007), the estimated dermal permeability coefficient for imidacloprid is 0.00013 cm/hour with a 95% confidence interval of 0.000071 – 0.00023 cm/hour. Riviere et al. (2014) provide *in vitro* estimates of the Kp for imidacloprid using pig and dog skin preparations. For aqueous solutions, the estimated Kp values are about 0.000023 cm/h for pig skin (log Kp = -4.64 from Table 7 of publication) and 0.000029 cm/h for dog skin preparations (log Kp = -4.54 from Table 7 of publication). These estimates are about 5 times greater than the central

estimate using the EPA method. While the data from Riviere et al. (2014) suggest that the algorithm from U.S. EPA/ORD (1992, 2007) may be somewhat conservative (i.e., overestimates the Kp for humans), the magnitude of the potential overestimation is not substantial. Also, as discussed further in Section 3.4, none of the exposure assessments involving zero-order dermal absorption leads to hazard quotients that exceed the level of concern.

In the current risk assessment, the estimates based on U.S. EPA/ORD (1992, 2007) are used in all exposure assessments based on Fick's first law. The application of the EPA algorithm to imidacloprid is detailed in Worksheet B03a of the WorksheetMaker workbooks that accompany this risk assessment.

3.1.3.3. Excretion

Studies with mammals suggest that imidacloprid is rapidly and completely eliminated in the urine and feces. Following oral or intravenous administration of ^{14}C-methylene labeled imidacloprid in rats (Klein 1987b), imidacloprid was rapidly absorbed and distributed throughout the body. The elimination of radioactivity from the plasma was described by two exponential components, with half-lives of 3 hours and 26-118 hours. More than 90% of the radioactivity was eliminated in the urine and feces in the first 24 hours following exposure. Approximately 96% of the administered dose was eliminated, of which 75% was found in the urine and 21% in the feces, within 48 hours of exposure. Less than 0.5 and 0.06% of the residual radioactivity were detected in the carcass and gastrointestinal tract, respectively (Klein 1987b).

The results of a metabolism study conducted by Klein and Karl (1990) agree well with the above results. In the Klein and Karl (1990) study, 90-98% of the administered radioactivity was recovered in the urine and feces of rats within 24 hours of administration, regardless of the route of administration (oral versus intravenous), dose (1 mg/kg body weight versus 20 mg/kg body weight), or frequency of administration (single or repeated 14-day administration). Less than 1% of the administered radioactivity was recovered in the carcass. Results of another study in rats (Klein and Brauner 1991) using ^{14}C-imidacloprid labeled at the 4- and 5- carbon of the imidazolidine ring were in agreement with the study by Klein and Karl (1990), with approximately 90% of the administered radiation excreted in the urine within 48 hours.

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.

For the purpose of estimating body burden, studies involving whole body excretion half-lives are more relevant than plasma half-lives. As a conservative approach, the lower bound whole body excretion of 90% from Klein and Karl (1990) is used to estimate a first-order excretion rate (k_e)

of about 2.3 day^{-1} [k = 1/ln(1-0.9) = 2.30259 day^{-1}]. 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 1.11.

3.1.4. Acute Oral Toxicity

3.1.4.1. Mammals (other than humans)

Standard acute oral toxicity studies are typically used to determine LD_{50} values—i.e., the treatment dose estimated to be lethal to 50% of the animals. These standard studies involve a single gavage dose followed by a 14-day observation period. This section is limited to a discussion of standard toxicity studies. More specialized acute toxicity studies for neurotoxicity are discussed in Section 3.1.6.

LD_{50} values are not used directly to derive toxicity values as part of the dose-response assessment in Forest Service risk assessments. Even so, comparing the LD_{50} values for the active ingredient to the LD_{50} values for the formulations or metabolites of the active ingredient may be useful in assessing the potential impact of inerts or metabolites on potential risks. LD_{50} values as well as other measures of acute toxicity discussed in the following sections of the risk assessment are used by the U.S. EPA/OPP to categorize potential risks. U.S. EPA/OPP uses a ranking system for response ranging from Category I (most severe response) to Category IV (least severe response). Details of the EPA classification system are detailed in SERA (2014a, Table 4) as well as the U.S. EPA/OPP (2010b) label review manual.

The acute oral LD_{50} values for imidacloprid are summarized in Appendix 1, Table A1-1. Acute oral toxicity studies are available on technical grade imidacloprid, several imidacloprid formulations, and WAK 3839, the nitrosoimine metabolite of imidacloprid (Figure 3). The gavage study in rats (Bomann 1989b, MRID 42055331) yielded a definitive LD_{50} of 424 mg/kg bw in male rats and an approximate LD_{50} of 450 - 475 mg/kg bw in female rats. Based on this study, the U.S. EPA/OPP/HED (2007a, Table A.1) classified technical grade imidacloprid as Category II, the second most hazardous ranking. A standard study in mice yielded a somewhat lower LD_{50} of 131 mg/kg bw in males and 168 mg/kg bw in females (Bomann 1989b MRID 42256324). Based on the EPA classification system (cited above), these LD_{50} values would also result in a Category 2 designation—i.e., LD_{50} values of >50 mg/kg bw to 500 mg/kg bw. An open literature publication (El-Gendy et al. 2010) using only a 24-hour post-dosing observation period reports an LD_{50} in mice of about 150 mg/kg bw, similar to the values reported by Bomann 1989b (MRID 42256324) the standard registrant toxicity study in mice. The major signs of toxicity in the two standard registrant studies are similar and include generalized signs of neurotoxicity (ataxia, trembling, and labored breathing). The NOAELs for mortality are only modestly below the LD_{50} values in rats (a factor of about 1.1) and mice (a factor of about 2). The NOAELs for overt signs of toxicity are lower than the LD_{50} values by about a factor of about 8 in rats [≈420 ÷ 50 mg/kg bw ≈ 8.4] and 15 in mice [≈150 ÷ 10 mg/kg bw ≈ 15].

Also summarized in Appendix 1, Table A1-1, are standard acute toxicity studies in rats. For the most part, these studies indicate that the formulations are less toxic than technical grade imidacloprid when toxicity values are expressed in terms of mg a.i./kg bw. The only notable exception is BAY T-7391 10% Pour On formulation, for which the LD_{50} is in rats is somewhat less than 200 mg a.i./kg bw. As summarized in CalEPA (2013, p. 20), BAY T-7391 appears to

be a veterinary formulation of imidacloprid. A number of additional studies supporting the veterinary use of imidacloprid are also summarized in CalEPA (2013); however, these studies are not directly relevant to the assessment of imidacloprid formulations covered in the current risk assessment (i.e., Table 3). As with the open literature publication by See et al. (2009), veterinary formulations may contain other active ingredients (e.g., moxidectin in the publication by See et al., 2009); therefore clear inferences concerning the toxicity of imidacloprid itself cannot be made.

Table A1-1 in Appendix 1 also summarizes several studies on the nitrosoimine metabolite of imidacloprid—i.e., WAK 3839 as illustrated in Figure 3. These studies indicate that this metabolite is less toxic than imidacloprid. The definitive LD_{50} values for rats from Ohta (1991) are about 2000 mg/kg bw for males and 3500 mg/kg bw for females. These LD_{50} values are below the definitive LD_{50} values for technical grade imidacloprid in rats (i.e., about 450 mg/kg bw) by factors of about 4 - 8.

3.1.4.2. Poisoning Reports Involving Humans

Reports of human poisonings are summarized in Appendix 1, Table A1-2. Most reports (i.e., 14 cases in 13 publications) involve the suicidal ingestion of imidacloprid formulations. Of the reports summarized in Appendix 1, Table A1-2, some provide an estimate of the amount of the formulation ingested and the percent a.i. in the formulation, while several others do not include that information. With the exception of two studies (Fuke et al. 2014; Shadnia and Moghaddam 2008), body weights of the individuals ingesting the imidacloprid formulations are not reported. In Table A1-2, most doses are estimated assuming a 70 kg body weight for males and a 60 kg bw for females. For the two studies that do provide body weights, both are for males and the body weights are reported as 56 kg (Fuke et al. 2014) and 85 kg (Shadnia and Moghaddam 2008), for an average body weight of 70.5 kg.

As discussed in Section 3.1.4.1, the LD_{50} values in rats are about 450 mg/kg bw of technical grade imidacloprid with a NOAEL for mortality of 400 mg/kg bw. For mice, the toxicity values are somewhat lower—i.e., LD_{50} values of about 150 mg/kg bw with a NOAEL for mortality of about 70 mg/kg bw. Based on the reports of human poisoning, non-fatal doses typically range from about 75 to 140 mg/kg bw and fatal doses typically range from about 180 to over 1000 mg/kg bw. One exceptionally high nonfatal case involves an estimated consumption of 750 mg a.i./kg bw (Viradiya and Mishra 2011). While this estimate is uncertain because the body weight of the individual is not reported, Viradiya and Mishra (2011) report the amount of formulation consumed as well as the % a.i. in the formulation. As with any suicide attempt, survival of an otherwise fatal dose can be influenced by the quality of supportive medical care. Moreover, Viradiya and Mishra (2011) report that the individual vomited after consuming the formulation. Thus, the functional dose of imidacloprid may have been less and perhaps much less than 750 mg a.i./kg bw. The minimum dose associated with a fatal ingestion is 179 mg/kg bw (Fuke et al. 2014). As noted above, Fuke et al. (2014) do report the body weight (reducing the uncertainty in the estimated dose) but also note that the amount consumed was no more than 50 mL of a 20% a.i. formulation. Thus, the of dose of 179 mg/kg bw may be overestimated.

Despite the uncertainties in the human data involving attempted or successful suicides, the available data do not suggest that humans are markedly more sensitive than experimental mammals to the acute toxicity of imidacloprid. The clearest case may be the report by David et

al. (2004) in which an estimated dose of about 76 mg/kg bw was nonlethal, absent any report of aggressive supportive therapy. As summarized in Appendix 1, Table A1-2, the only signs of toxicity involved an elevated temperature and increased heartbeat. This estimated dose is close to the reported NOAEL 50 mg/kg bw for toxicity in rats (Bomann 1989a) and the NOAEL of 71 mg/kg bw for mortality in mice (Bomann 1989b).

It should be noted that none of the reported cases of suicidal ingestion of imidacloprid occurred in the United States. This is relevant in terms of the formulations. As discussed by Phua et al. (2009) in a more general review of human suicides involving neonicotinoids, many of the formulations used in suicide attempts contain N-methyl-2-pyrrolidone as a solvent. As with many solvents, N-methyl-2-pyrrolidone may cause corrosion of mucus membranes. While somewhat speculative, this effect could lead to secondary infections and elevated temperatures noted in some poisoning reports. While N-methyl-2-pyrrolidone is used as an "*inert*" is some pesticide formulations (http://iaspub.epa.gov/apex/pesticides/f?p=INERTFINDER:3:0::NO::P3_ID:7111), this inert is not listed as an inert on the MSDS for the formulations explicitly covered in the current risk assessment (Table 2).

Several of the poisoning reports (Lin et al. 2013; Shadnia and Moghaddam 2008; Viradiya and Mishra 2011; Chwaluk 2010) also note an increase in white blood cell counts which could be secondary to infection. These observations are consistent with a significant increase in leucocyte counts in rats (Mohany et al. 2012) and mice (Badgujar et al. 2013) following subchronic dosing. As discussed further in Section 3.1.5 and summarized in Appendix 1, Table A1-3, the rat study conducted by Mohany et al. (2012) involved a foreign formulation of imidacloprid (a 20% EC Confidor formulation from Egypt), whereas the mouse study conducted by Badgujar et al. (2013) used technical grade imidacloprid from Indofil Chemicals Company (Mumbai, India).

In addition to the above reports from the open literature, U.S. EPA/OPP/HED compiled a 44-page tabular list of incidents of adverse effects in humans associated with exposures to a number of imidacloprid formulations (U.S. EPA/OPP/HED 2008a). Most incidents involve skin or eye irritation. More unusual endpoints include blood clots in the lungs, respiratory difficulties or irritation, seizures, lethargy, chest pain, increased heart rate, and fever. Estimates of exposure are not given and the EPA report does not comment on the probability that the reported effects could be attributed to imidacloprid.

3.1.5. Subchronic or Chronic Systemic Toxic Effects

The subchronic and chronic toxicity studies on imidacloprid are summarized in Appendix 1, Table A1-3. These include numerous standard registrant-submitted subchronic and chronic studies required by the EPA for pesticide registration. All of these studies involve technical grade imidacloprid and are designated in Table A1-3 by both study author(s) and MRID number. In addition, several subchronic studies in rats are published in the open literature, primarily from India. These studies used both technical grade imidacloprid (Badgujar et al. 2013; Bhardwaj et al. 2010; Kapoor et al. 2010, 2011) as well as Confidor formulations of imidacloprid (Arfat et al. 2014; Mohany et al. 2012; Toor et al. 2013; Vohra et al. 2014). In addition to these studies conducted with technical grade imidacloprid and imidacloprid formulations, there is one subchronic study in rats conducted with the WAK 3839 nitrosoimine metabolite of imidacloprid (Krotlinger 1992).

Studies suggest that oral ingestion of imidacloprid can cause growth retardation and adverse effects on the liver, kidney, thyroid, testes, heart, thymus, bone marrow, pancreas and nervous system. As noted in Section 3.1.2 (mechanisms) and discussed further in Section 3.16, imidacloprid is clearly neurotoxic; however, neurotoxicity is not the most sensitive effect (i.e., the effect occurring at the lowest dose) in subchronic and chronic studies. The most sensitive effect in chronic studies appears to be effects on the thyroid which were observed in male rats exposed to a dietary concentration of 100 ppm, equivalent to 16.9 mg/kg bw/day for 24 months (Eiben and Kaliner 1991). No effects associated with neurotoxicity were noted at this dose level. As discussed further in Section 3.3, the study by Eiben and Kaliner (1991) is used by the U.S. EPA to derive the chronic RfD for imidacloprid.

Subchronic registrant-submitted studies involve exposures to cows, dogs, mice, and rats. The lowest reported NOAELs for dogs and mice span a relatively narrow range from about 31 mg/kg bw/day for dogs (Bloch 1987) to 87 mg/kg bw/day for mice (Eiben 1988b). The NOAEL for cows is intermediate at 50 mg/kg bw/day (Heukamp 1992a). The cow study (Heukamp 1992a) used only a single dose of 5 mg/kg bw/day for up to 10 days and is essentially a residue assay that provides only marginal information on effects—i.e., no gross signs of toxicity or changes in body weight. Rats appear to be the most sensitive species with a NOAEL of 14 mg/kg bw/day for male rats in a subchronic study (Eiben 1989) and a NOAEL of 5.7 mg/kg bw/day in a chronic study (Eiben and Kaliner 1991).

Subchronic toxicity studies with technical grade imidacloprid from the Indian literature (Bhardwaj et al. 2010; Kapoor et al. 2010, 2011) indicate a NOAEL of 10 mg/kg bw/day, reasonably consistent with the NOAEL of 14 mg/kg bw/day from the study by Eiben (1989). The NOAEL of 10 mg/kg bw/day for effects on the liver and kidney is also noted in the 15 day feeding study in mice using a Confidor formulation (Arfat et al. 2014). As detailed in Appendix 1, Table A1-3, these studies may consist of a single study in which data from different endpoints were presented in separate publications. As noted in Section 3.2, the most striking and unusual feature of these studies is the report of AChE inhibition at a dose of 20 mg/kg bw/day in the paper by Bhardwaj et al. (2010). This report is supported by the subchronic study with a Confidor formulation (17.8% a.i.) at doses of both 10 and 20 mg a.i./kg bw/day (Vohra et al. 2014). The Badgujar et al. (2013) study, also from the Indian literature, focuses on immune toxicity and is discussed further in Section 3.1.7.

Vohra et al. (2014) report a decrease in heart weight (8%) at a dose of 20 mg a.i./kg bw/day. This effect is consistent with the observation of an increased incidence of death in mice during blood withdrawal (reported by the investigator as *heart attack*), following subchronic exposure to a high dietary concentration (3000 ppm) of technical grade imidacloprid (Eiben 1988b, MRID 42256337). Watta-Gebert (1991a,b) also observed that male mice exposed to 2000 ppm imidacloprid in the diet died more frequently from *heart attack* (not otherwise specified) during manipulation (blood withdrawal, anesthesia, tattooing etc.) than controls. The basis for any direct cardiotoxicity is unclear. In the metabolism study on imidacloprid, Klein et al. (1987a) found that imidacloprid distributes to the walls of the aorta but no pathology is discussed. While potential cardiotoxicity is an obvious endpoint of concern, it is unclear if these effects are direct toxic effects on heart tissue or are secondary toxic effects.

One subchronic dietary study was conducted on rats with the nitrosoimine metabolite (WAK 3839) of imidacloprid (Krotlinger 1992). The effects observed in this study (e.g., changes in blood counts) are different from those observed following imidacloprid administration in any species, suggesting that the nitrosoimine metabolite is not responsible for the toxicity observed in studies conducted with imidacloprid. The NOAEL for WAK 3839 is 13 mg/kg bw/day, similar to the NOAEL for imidacloprid.

3.1.6. Effects on Nervous System

Imidacloprid is clearly neurotoxic, and the mechanism of action (i.e., activation of nicotinic acetylcholine receptors) is generally well understood (Section 3.1.2). As reviewed by Bal et al. (2010), imidacloprid binds with lower affinity in mammals (i.e., EC_{50} of 70 mM or about 17,900 mg/L) than in insects (EC_{50} of 0.86 - 1 mM or about 220 - 256 mg/L).

For neurotoxins, the EPA requires specialized tests for neurotoxicity. As summarized in Appendix 1, Table A1-10, the registrant-submitted studies include two acute neurotoxicity studies (Sheets 1994a,b, MRID 43170301), one subchronic neurotoxicity study (Sheets and Hamilton 1994, MRID 43286401), and one developmental neurotoxicity study (Sheets 2001, MRID 45537501). In addition, Abou-Donia et al. (2008) conducted a developmental neurotoxicity study involving intraperitoneal injection of imidacloprid. Both of these developmental studies are summarized in Appendix 1, Table A1-4.

The two acute neurotoxicity studies by Sheets (1994a,b, MRID 43170301) are essentially one divided study involving single dose gavage administration. The initial doses of 42, 151, and 307 mg/kg bw (Sheets 1994a) failed to yield a NOAEL, and a lower dose (20 mg/kg bw) was added which did yield a NOAEL. The LOAEL of 42 mg/kg bw was associated with symptoms of cholinergic toxicity (signs of motor and locomotor deficits such as sedation, apathy, staggering gait, trembling, and labored or accelerated breathing). The higher doses of 151 and 307 mg/kg bw resulted in more severe neurological effects as well as mortality. As discussed in Section 3.1.4.1, gavage doses ranging from 150 to 300 mg/kg bw are typically associated with mortality in rats. As discussed further in Section 3.3 (dose-response assessment), the U.S. EPA/OPP uses the LOAEL of 42 mg/kg bw as the basis for the acute RfD with an uncertainty factor of 300, which is equivalent to approximating an acute NOAEL of 14 mg/kg bw [42 mg/kg bw ÷ 3 = 14 mg/kg bw].

A 13-week neurotoxicity screening study (Appendix 2) found no evidence of motor/locomotor impairment in a series of tests conducted on rats fed up to 3027 mg/kg diet technical grade imidacloprid in the diet (Sheets and Hamilton 1994). Although there were no gross or microscopic lesions in the nerve or muscle tissue among these rats, deficits in the neurobehavioral functional observational battery were observed in males fed the highest dose (3027 ppm, equivalent to 196 mg imidacloprid/kg body weight/day). The NOAEL for neurobehavioral effects in this study is 69.1 mg/kg body weight/day (963 ppm). This subchronic NOAEL is somewhat higher than the estimated acute NOAEL of 14 mg/kg bw discussed above, which may be due to the less stressful and more gradual intake of a dietary study, relative to a gavage study.

In the developmental neurotoxicity study (Sheets 2001, MRID 45537501), rats were fed 0, 100, 200, 250 or 750 ppm technical grade imidacloprid in the diet from gestation day 0 through

lactation day 21. The only effect on maternal rats was a 14% reduction in food consumption at the highest dietary concentration. There were no effects on reproductive variables. Following an extensive battery of tests, the only neurological effect observed in the F_1 offspring was reduced activity in the figure-eight maze on post-natal days 17 (both sexes) and 21 (females only) relative to controls, among rats whose mothers were exposed to the highest dose (750 ppm). This LOAEL is equivalent to maternal doses of 54.7 - 58.4 mg/kg bw/day (during gestation) and 80.4 - 155.0 mg/kg bw/day (during lactation). There were no effects on the brain or histopathological changes in the brain, neural tissues, or skeletal muscle. The NOAEL for neurological effects in this study is 250 ppm (equivalent to maternal doses of 19.4 - 19.7 mg/kg body weight/day during gestation; and 30.0 - 45.4 mg/kg body weight/day during lactation). Lonare et al. (2014) noted signs of neurotoxicity in rats at gavage doses of 45 and 90 mg/kg bw/day. Again, these subchronic dietary NOAELs are somewhat higher than the estimated acute gavage NOAEL of 14 mg/kg bw. As noted above, this difference may be attributable to the less stressful and more gradual intake of a dietary study, relative to a gavage study.

As also summarized in Appendix 1, Table A1-4, single intraperitoneal injections of imidacloprid at a dose of 337 mg/kg bw to pregnant rats on Day 9 of gestation resulted in neurological impairment of offspring assayed at Day 30 after birth (Abou-Donia et al. 2008). Given the high dose and route of administration, the dose of 337 mg/kg bw is consistent with the subchronic dietary LOAEL (i.e., 80.4 to 155.0 mg/kg bw/day during lactation) from the subchronic dietary study by Sheets (2001, MRID 45537501).

None of the registrant submitted-studies conducted with rats found imidacloprid-related histopathological changes in the brain. Nonetheless, in a supplementary 24-month carcinogenicity study conducted with mice, Watta-Gebert (1991b) observed an increased incidence of mineralization of the thalamus in the brains of mice fed 2000 ppm technical grade imidacloprid in the diet. This dietary concentration was equivalent to mean doses of 413.5 and 423.9 mg imidacloprid/kg body weight/day for males and females, respectively. In addition, the intraperitoneal study by Abou-Donia et al. (2008) notes an increase in glial fibrillary acidic protein immunostaining of brain tissue in offspring following a maternal dose of 337 mg/kg bw. Using cell cultures of cerebellar neurons from neonatal rats, Kimura-Kuroda et al. (2012) noted altered function (increased calcium ion influxes and the proportion of excited neurons) at concentrations of 1 - 100 µM (see Figure 5 of publication)—i.e., concentrations of imidacloprid in cell cultures of about 0.26 to 26 mg/L.

3.1.7. Effects on Immune System

Subchronic or chronic animal bioassays typically involve morphological assessments of the major lymphoid tissues, including bone marrow, major lymph nodes, spleen and thymus (organ weights are sometimes measured as well), and blood leukocyte counts. These assessments can detect signs of inflammation or injury indicative of a direct toxic effect of the chemical on the lymphoid tissue. Changes in lymphoid tissue and blood, indicative of a possible immune system stimulation or suppression, can also be detected. Based on these types of inferences from the standard studies submitted to U.S. EPA, the most recent EPA human health risk assessment for imidacloprid does not express a marked concern for immunotoxicity:

> *The toxicology database for imidacloprid does not show any evidence of treatment-related effects on the immune system. The overall weight of evidence*

> *suggests that this chemical does not directly target the immune system. An immunotoxicity study is required as a part of new data requirements in the 40 CFR Part 158 for conventional pesticide registration; however, the Agency does not believe that conducting a functional immunotoxicity study will result in a lower POD* [point of departure] *than that currently used for overall risk assessment.*
>
> U.S. EPA/OPP/HED 2010a, pp. 16-17

As noted above, recent changes to pesticide regulations (40 CFR § 158) now require immunotoxicity assays as a condition for pesticide registration. It seems likely that an immunotoxicity study will be required during the upcoming registration review of imidacloprid. As noted in Section 1.1, the registration review will be completed in 2016.

As noted in Section 3.1.5 and discussed further in Section 3.3, effects on the thymus are used as the basis for the chronic RfD for imidacloprid, and changes in the thymus are a indicator of potential effects on immune function. In addition, three subchronic studies from the open literature raise concern for the potential impact of imidacloprid on immune function (Badgujar et al. 2013; Gawade et al. 2013; Mohany et al. 2012). The studies by Badgujar et al. (2013) and Mohany et al. (2012) involve relatively standard 28-day subchronic exposures and are summarized in Appendix 1, Table A1-3. The study by Gawade et al. (2013) is a developmental study and is summarized in Appendix 1, Table A1-4. The observations on immune function from Gawade et al. (2013) are discussed in this section, and the observations relating to standard developmental effects are discussed in Section 3.1.9.1.

The subchronic study by Badgujar et al. (2013) involved gavage administration of technical grade imidacloprid to mice at doses of 0, 2.5, 5, or 10 mg/kg bw/day. No signs of neurotoxicity are reported, which is consistent with the standard subchronic studies on imidacloprid (Section 3.1.5). Signs of an impact on immune function were noted primarily at the high dose and consisted of a significant decrease in platelet count, a delayed delayed-type hypersensitivity response characterized by an increase in paw thickness, and increased in T-cell (a type of white blood cell) proliferation. In addition to these effects, decreases in spleen weights (not statistically significant) and changes in spleen morphology were noted.

The subchronic study in rats by Mohany et al. (2012) is somewhat problematic in that the study used only a single low dose (0.21 mg/kg bw/day) of an Egyptian formulation of Confidor (20% EC). The study does not clearly indicate if the dose is expressed as formulation or active ingredient. As with the study by Badgujar et al. (2013), Mohany et al. (2012) report a significant increase in white blood cells and a decrease in phagocytic activity. As discussed in 3.1.4.2, the increases in white blood cell counts is consistent with several of the open literature publications on the suicidal ingestion of imidacloprid—i.e., Lin et al. (2013); Shadnia and Moghaddam (2008); Viradiya and Mishra (2011); and Chwaluk (2010). Also, as with the study by Badgujar et al. (2013) as well as several standard subchronic and chronic studies, Mohany et al. (2012) report pathological changes in the spleen and thymus.

In the developmental study by Gawade et al. (2013) a dose of 90 mg/kg bw technical grade imidacloprid was associated with a diminished response to sheep red blood cells (a standard

assay for immune function), and lower doses (10 and 30 mg/kg bw/day) were associated with dose-dependent decrease in hemagglutination titers and lower levels of immunoglobulin. All of these endpoints are consistent with impaired immune function.

3.1.8. Effects on Endocrine System

Assessments of the direct effects of chemicals on endocrine function are most often based on mechanistic studies on estrogen, androgen, or thyroid hormone systems (i.e., assessments on hormone synthesis, hormone receptor binding, or post-receptor processing). As discussed in U.S. EPA/OPP/HED (2010a, p. 19), U.S. EPA/OPP developed a battery of screening assays for endocrine disruption, and imidacloprid was selected for testing. The results of these Tier 1 screening studies are available and based on these results the EPA concluded:

> *Based on weight of evidence considerations, mammalian or wildlife EDSP Tier 2 testing is not recommended for imidacloprid since there was no convincing evidence of potential interaction with the estrogen, androgen or thyroid pathways.*
> U.S. EPA/OPP 2015, p. 2

As discussed in Section 3.1.5, the thyroid is a target organ in chronic studies on imidacloprid. In addition, as discussed in Section 4.1.2.2 and the most recent EPA ecological risk assessment (U.S. EPA/OPP/EFED 2007a, p. 2), imidacloprid causes effects on avian reproduction. Imidacloprid is clearly toxic to the thyroid. In autoradiographic and metabolic studies conducted with rats, Klein et al (1987a, b) determined that radiation from orally administered ^{14}C-methylene labeled imidacloprid appears rapidly in thyroid and adrenal tissues. No pathological findings involving adrenal tissues were reported in the comprehensive acute, subchronic, and chronic exposure studies conducted on rats, mice, and dogs with imidacloprid and imidacloprid formulations. Nonetheless, degenerative changes in the thyroid were detected in dogs (follicular atrophy) fed 5000 ppm technical grade imidacloprid for 28 days (Bloch 1987); in rats (mineralization of colloid follicles) fed 300 or 900 ppm technical grade imidacloprid for 24 months (Eiben and Kaliner 1991), and in rats fed 1800 ppm technical grade imidacloprid for 24 months (Eiben 1991). While imidacloprid is clearly toxic to the thyroid, the results from U.S. EPA/OPP (2015) indicate that this toxicity is not mediated through or involved in an impact on endocrine function.

An *in vitro* cell culture assay indicates that imidacloprid may induce insulin resistance (Kim et al. 2013). As discussed by Kim et al. (2013), insulin resistance could be associated with increases in body weight. Based on the available *in vivo* subchronic and chronic toxicity studies (Appendix 1, Table A1-3), increased body weights have not been associated with exposure to imidacloprid.

One publication from the Indian literature reports significant body weight gain in mice after dietary exposures to imidacloprid associated with a decrease in thyroid hormones (Bhaskar and Mohanty 2014). The dose of the imidacloprid formulation (i.e., a 17.8% a.i. Indian formulation of imidacloprid: Tatamida) used in the study cannot be determined. Moreover, the authors cite an oral LD_{50} of 131 mg/kg bw for mice which is attributed to the review by Cox (2001); however, Cox (2001) does not cite this LD_{50}. As summarized in Appendix 1, Table A1-1, an LD_{50} of 131 mg/kg bw for mice is reported by Bomann (1989b). Bhaskar and Mohanty (2014)

indicate that the target dose was equivalent to 0.5% of LD_{50}, which would be about 6.55 mg/kg bw/day.

3.1.9. Reproductive and Developmental Effects

3.1.9.1. Developmental Studies

Developmental studies are used to assess the potential of a compound to cause malformations and signs of toxicity during fetal development. These studies typically entail gavage administration of the chemical compound 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 by the EPA for the registration of pesticides.

Specific protocols for developmental and reproduction studies are established by EPA (U.S. EPA/OPPTS 2000). As summarized in Appendix 1, Table A1-4, standard developmental studies in rabbits (Becker and Biedermann 1992) and rats (Becker et al. 1992; Sheets 2001) using technical grade imidacloprid were submitted to the EPA. As discussed in Section 3.1.6, Sheets (2001) is a developmental neurotoxicity study, and the neurological effects noted in this study are discussed in Section 3.1.6. None of the developmental studies reports adverse effects in offspring at doses not toxic to dams. There appear to be no substantial differences in the maternal NOAEL of 8 mg/kg bw/day for rabbits (Becker and Biedermann 1992), the maternal NOAEL of 10 mg/kg bw/day (Becker et al. 1992) and about 20 mg/kg bw/day for rats (Sheets (2001). Frank fetotoxic effects included post-implantation losses in rabbits at 72 mg/kg bw/day (Becker and Biedermann 1992) and minor skeletal abnormalities (i.e., wavy ribs) in rats at 100 mg/kg bw/day (Becker et al. 1992).

The open literature includes an intraperitoneal neurotoxicity study in rats (Abou-Donia et al. 2008) and a developmental immunotoxicity study in rats (Gawade et al. 2013). The observations on neurotoxicity from the study by Abou-Donia et al. (2008) are discussed in Section 3.1.6, and the immunological responses noted in the study by Gawade et al. (2013) are discussed in Section 3.1.7.

Abou-Donia et al. (2008) used a relatively high intraperitoneal dose (i.e., a single intraperitoneal injection of 337 mg/kg bw on Day 9 of gestation); yet no signs of toxicity or developmental effects were observed in offspring. As noted above, the developmental study in rats by Becker et al. (1992) notes skeletal anomalies at a dose of 100 mg/kg bw/day (gavage). Since Abou-Donia et al. (2008) did not assay for morphological abnormalities, the study is not inconsistent with the standard study by Becker et al. (1992, MRID 42256338).

The gavage study by Gawade et al. (2013) reports a NOAEL of 10 mg/kg bw/day with post-implantation losses at 30 and 90 mg/kg bw/day. Although the NOAEL is identical to the NOAEL reported by Becker et al. (1992), the study does not report resorptions at 30 and 100 mg/kg bw/day. Furthermore, as discussed above, the most severe response observed by Becker et al. (1992) is an increase in wavy ribs at 100 mg/kg bw/day. Thus, the adverse effects noted in the Gawade et al. (2013) study are consistent with the standard study in rabbits by Becker and Biedermann (1992, MRID 42256339) which notes resorptions and a spontaneous abortion at 72 mg/kg bw/day.

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 F_0) generation (i.e., the male and female animals used at the start of the study) to the test substance prior to mating, during mating, after mating, and through weaning of the offspring (F_1). In a 2-generation reproduction study, this procedure is repeated with male and female offspring from the F_1 generation to produce another set of offspring (F_2). 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. Typically, the EPA requires one acceptable multi-generation reproduction study for pesticide registration (U.S. EPA/OCSPP 2013).

For imidacloprid, a two-generation reproduction study conducted by Suter (1990) was submitted to the U.S. EPA. In this study, summarized in Appendix 1, Table A1-4, imidacloprid was not found to affect reproductive variables or cause birth defects, although, reduced mean body weight and body weight gain, relative to controls, were observed in the offspring of all generations at the highest dietary concentration tested (700 ppm). Also, at this concentration, parental animals had reduced body weights, relative to controls, in association with reduced food consumption. Based on measured food consumption, the NOAEL of 350 ppm is equivalent to a dose of 20 mg/kg bw/day, similar to other NOAELs for subchronic toxicity (Section 3.1.5) and developmental effects (Section 3.1.9.2).

Studies on the reproductive effects of imidacloprid in mammals were not identified in the open literature.

3.1.9.3. Target Organ Toxicity

Two subchronic studies conducted with technical grade imidacloprid suggest that repeated high-dose exposure may result in testicular degeneration in mammals. Tubular degeneration of the testes was observed in dogs fed 5000 ppm imidacloprid in the diet for 28 days (Bloch 1987, MRID 42256330). "Low-grade degenerative changes" in testicular tubuli were reported in a study of rats fed 3000 ppm imidacloprid in the diet for 98 days (Eiben 1988a, MRID 42256334). More recently, as summarized in Appendix 1, Table A1-4, two 90-day gavage studies from the Turkish literature (Bal et al. 2012a) report adverse testicular effects in rats at doses as low as 0.5 mg/kg bw/day. These results are inconsistent with the NOAEL of 20 mg/kg bw/day from the multigenerational reproductive study in rats conducted by Suter et al. (1990, MRID 42256340). As well, an *in vitro* study using a sperm chromatin dispersion assay notes no remarkable adverse effects on sperm at imidacloprid concentrations of 500 μM (≈127 mg/L) and 5 mM (≈1,280 mg/L) (Gu et al. 2013). The papers by Bal et al. (2012a), however, are detailed and clearly reported. The only obvious concern with these studies is that the source and purity of the imidacloprid used in the studies is not reported. Nonetheless, these studies are a concern to the risk assessment and are discussed further in the dose-response assessment (Section 3.3).

In addition, a subchronic gavage study in the open literature (i.e., Kapoor et al. 2011) reports decreased ovarian weights and changes in ovarian morphology in rats at a dose of 20 mg/kg bw/day with a NOAEL of 10 mg/kg bw/day. More detailed summaries of these three studies are given in Appendix 1, Table A1-3.

3.1.9.4. Epidemiology

Two recent epidemiology studies suggest potential associations of imidacloprid exposures with adverse effects on children—i.e., a potential association with autism (Keil et al. 2014) and a potential association with neural tube defects (Yang et al. 2014). Both studies involve populations living in California.

The study by Keil et al. (2014) concerns exposures of household pets to veterinary products containing imidacloprid (i.e., Advantage and K9 Advantix) and the associated exposures in pregnant women with the subsequent diagnosis of autism in their children. Levels of exposure were not quantified analytically in terms of potential dose. Instead, exposures were qualitatively assessed based on self-reporting as *consistent use* (defined as use of imidacloprid at least once per month during pregnancy) or *occasional use* (defined as use less than once each month during pregnancy). The results are expressed as "odds ratios" which may be viewed as the risk of the exposed population responding, relative to an unexposed population. The overall odds ratio is reported as 1.3 (95% confidence interval of 0.78 to 2.2), and the odds ratio for consistent users is reported as 2.0 (95% confidence interval of 1.0 to 3.9). Note that the overall odds ratio is not statistically increased (i.e., significantly greater than 1.0), and the odds ratio for consistent users is only marginally significant. As interpreted by the study authors, these results … *assuming perfect exposure classification, indicated an imprecise, weak positive association between ASD and prenatal imidacloprid exposure compared to typically developing controls* (Keil et al. 2014, p. 4). The authors discuss confounding factors, particularly recall bias, which could have inflated the estimated odds ratios. Furthermore, another epidemiology study by Nevison (2014) examined the temporal associations in the prevalence of autism in California, and, while the study does not specifically address imidacloprid or other neonicotinoids, the author notes that…*~75-80% of the tracked increase in autism since 1988 is due to an actual increase in the disorder rather than to changing diagnostic criteria* (Nevison 2014, p.1) and further notes that this increase parallels increases in the use of some agents such as polybrominated diphenyl ethers and glyphosate. As discussed in Section 2, neonicotinoids are relatively new pesticides, and imidacloprid was not used in the United States until 1994 (Gervais et al. 2010), after the increase in autism was first noted. While Keil et al. (2014) raises legitimate concerns, the authors note that this study is not conclusive and that …*the association could result from exposure misclassification alone*. Nonetheless, as noted by Keil et al. (2014), the results from this study may justify a more refined analysis with more objective measures of exposure to imidacloprid.

The study by Yang et al. (2014) examines the prevalence of neural tube defects in the San Joaquin Valley of California. The exposures were assessed qualitatively rather than quantitatively, as in the Keil et al. (2014) study, based on the self-reported proximity of individuals to agricultural applications. The self-reports were obtained during interviews conducted at an average of 10 months after birth for potentially exposed mothers and 8 months after birth for presumably unexposed (i.e., control) mothers. Unlike Keil et al. (2014), Yang et al. (2014) examined the prevalence of neural tube defects in association with numerous pesticides, including imidacloprid. For imidacloprid, the odds ratio is reported as 2.9 with a 95% confidence interval of 1.0 - 8.2. Like the lower bound odds ratio for consistent users in Keil et al. (2014), the lower bound of 1.0 for imidacloprid in Yang et al. (2014) suggests that the association of neural tube defects with imidacloprid exposure may be viewed as marginally significant. A problem with this interpretation, however, involves multiple comparisons. While Yang et al. (2014) adjusted confidence intervals for a number of potential confounders (e.g.,

race, education, body mass, and smoking), the study involves 461 chemicals, and the authors do not appear to have adjusted the significance levels used to account for multiple comparisons. Yang et al. (2014) note the following: *Because of sample size limitations and multiple comparisons, our positive findings should be interpreted with caution and need to be replicated in other populations* (Yang et al. 2014, p. 747). In the study abstract, the authors provide a much stronger caveat: *Given that such odds ratios might have arisen by chance because of the number of comparisons, our study showed a general lack of association between a range of agricultural pesticide exposures and risks of selected birth defects* (Yang et al. 2014). While both statements are correct, the latter statement seems to excessively diminish concern for the potential association of imidacloprid with neural tube defects. The results for imidacloprid from Yang et al. (2014) raise at least a modest concern that additional investigation is warranted.

3.1.10. Carcinogenicity and Mutagenicity

There are no human or animal studies which suggest that imidacloprid causes cancer. Technical grade imidacloprid was tested in comprehensive carcinogenicity studies with rats (Eiben and Kaliner 1991; Eiben 1991) and mice (Eiben 1988b; Watta-Gebert 1991a,b). These studies were conducted in accordance with EPA guidelines for testing, and are summarized in Appendix 1, Table A1-3. As discussed in Section 3.1.5, although signs of chronic toxicity were observed in these studies, neither changes in time-to-tumor development nor increases in the incidence of tumors among animals were observed.

These studies are reviewed in the most recent EPA human health risk assessment on imidacloprid, which provides the following conclusions concerning the potential carcinogenicity of imidacloprid:

> *There was no evidence of carcinogenic potential in either the rat chronic toxicity/carcinogenicity or mouse carcinogenicity studies, and there was no concern for mutagenicity across a host of genotoxicity assays. On 11/10/93, the RfD Peer Review Committee classified imidacloprid as a Group E chemical, "Evidence of non-carcinogenicity for humans," by all routes of exposure based upon lack of evidence of carcinogenicity in rats and mice.*
>
> U.S. EPA/OPP/HED 2010a, p. 15

As indicated in the excerpt above, EPA reviewed numerous standard mutagenicity studies on imidacloprid. These studies, identified by MRID numbers, are summarized in Appendix 1, Table A1-11, which also summarizes several mutagenicity studies published in the open literature on imidacloprid (Bianchi et al. 2015; Calderon-Sequra et al. 2012; Costa et al. 2009; Demsia et al. 2007; Feng et al. 2005). Unlike the studies submitted to EPA, several of the open literature studies note signs of chromosomal damage at high concentrations in the *in vitro* studies and in the one *in vivo* study. Nonetheless, the standard chronic studies for carcinogenicity are the most relevant to the assessment of potential human health effects, and these studies clearly indicate that carcinogenicity is not an endpoint of concern for imidacloprid.

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

As with acute oral toxicity, the U.S. EPA/OPP requires acute assays for skin irritation, sensitization, and eye irritation and uses a ranking system for responses ranging from Category I (most severe response) to Category IV (least severe response) for skin and eye irritation. Skin

sensitization is classified simply as occurring or not occurring. For each type of assay, the EPA developed standard protocols (U.S. EPA/OCSPP 2013).

3.1.11.1. Skin Irritation

A number of standard assays for skin irritation were conducted in response to EPA pesticide registration requirements for imidacloprid, and these studies are summarized in Appendix 1, Table A1-6. Based on the skin irritation study with technical grade imidacloprid (Pauluhn 1988c, MRID 42055335), U.S. EPA/OPP/HED (2010a, p. 48), classifies imidacloprid as Category IV, the least hazardous ranking. Some imidacloprid formulations, however, cause slight or mild skin irritation (i.e., Sheets and Phillips 1991c; Wakefield 1996b; Warren 1995d; Robbins, 1996b) suggesting that some of the ingredients in the formulations (other than imidacloprid) may be responsible for the observed irritation. The potential role of other ingredients in imidacloprid formulations is considered further in Section 3.1.14

3.1.11.2. Skin Sensitization

Studies on skin sensitization are also summarized in Appendix 1, Table A1-6. Skin sensitization studies are available on technical grade imidacloprid (Ohta 1988) as well as several formulations (Pritchard and Donald 2004e; Sheets 1990e; Sheets 1990j; Sheets and Phillips 1991d; Warren 1995e). All of these studies were submitted to EPA in support of the registration of imidacloprid, and the MRID numbers for each study are included in Appendix 1, Table A1-6. None of these studies report signs of skin sensitization. Based on the study using technical grade imidacloprid (Ohta 1988), the EPA determined that imidacloprid is not a skin sensitizer (U.S. EPA/OPP/HED (2010a, p. 48).

3.1.11.3. Ocular Effects

Studies on the irritant effects of imidacloprid and imidacloprid formulations are summarized in Appendix 1, Table A1-7. The study by Pauluhn (1988b, MRID 42055334) indicates that technical grade imidacloprid does not cause eye irritation (under standard test conditions); accordingly, the EPA classifies imidacloprid as Category IV for eye irritation (U.S. EPA/OPP/HED 2010a, p. 48). As with skin irritation, some imidacloprid formulations are mild to moderate eye irritants (Sheets 1990c,h; Astroff 1992; Sheets and Phillips 1990, 1991; Astroff and Phillips 1992; Warren 1995c; Robbins 1996a), indicating that components other than imidacloprid are probably responsible for the observed irritation. The potential role of other ingredients in imidacloprid formulations is considered further in Section 3.1.14.

3.1.12. Systemic Toxic Effects from Dermal Exposure

The acute dermal toxicity studies on imidacloprid and imidacloprid formulations are summarized in Appendix 1, Table A1-5. As with acute irritant effects to the skin and eyes (Section 3.1.11), the U.S. EPA/OPP requires acute dermal toxicity studies for both active ingredients and formulations and classifies the potential for acute dermal toxicity using a Category I (most hazardous) to Category IV (least hazardous) classification system (SERA 2014a, Table 4; U.S. EPA/OPP 2010b). Based on the acute dermal toxicity study for technical grade imidacloprid (Krotlinger 1989, MRID 42055332) which reports no effects at a dermal dose of 5000 mg/kg bw in rats, the EPA classifies imidacloprid as Category IV for acute dermal toxicity (U.S. EPA/OPP/HED 2010a). As also summarized in Appendix 1, Table A1-5, acute dermal toxicity studies are also available on several imidacloprid formulations. Most of these studies also indicate no signs of toxicity at formulation doses of 2000 mg/kg bw (Pritchard and Donald

2004b; Sheets 1990b; Warren 1995b). Minor signs of toxicity are reported in two studies—i.e., muscle fasciculation in one of five male and one of five female rats (Sheets 1990g) and alopecia in one of five female rats (Sheets and Gilmore 1991). These endpoints are not cited in the more extensive body of toxicity studies involving oral administration, and their association with imidacloprid seems tenuous.

Also summarized in Appendix 1, Table A1-5 is the one available subchronic toxicity study on technical grade imidacloprid in which no treatment-related effects were observed in rabbits following dermal doses of 1000 mg/kg bw/day, 5 days/week, for 3 weeks (Flucke 1990, MRID 42256329). As noted in Section 3.1.3.2.2, U.S. EPA/OPP/HED uses this study to estimate a dermal absorption factor for imidacloprid by comparison to an oral LOAEL of 72 mg/kg bw/day from the developmental study in rabbits by Becker and Biedermann (1992). The absorption factor of 7.2% is derived by dividing the oral LOAEL by the dermal NOAEL (U.S. EPA/OPP/HED 2007a, p. 19). As discussed in Section 3.1.3.2.2, this approach is questionable because the dermal NOAEL of 1000 mg/kg bw/day is free-standing. In other words, only a single dose was used in the subchronic dermal study by Flucke (1990), and a LOAEL for dermal toxicity was not defined.

3.1.13. Inhalation Exposure

Standard acute and longer-term inhalation studies required by the U.S. EPA/OPP in support of the registration of imidacloprid are summarized in Appendix 1, Table A1-1. Following standard EPA protocols, all of these studies involve exposure of rats for periods of 4 hours.

Acute inhalation toxicity studies are available on technical grade imidacloprid (Pauluhn 1988a,d) as well as several formulations of imidacloprid (Warren 1990a,b; Warren 1991; Warren and Berry 1995). For technical grade imidacloprid, no mortality was noted at concentrations of up to 5323 mg/m^3. Based on this study, the U.S. EPA/OPP/HED classifies imidacloprid as Category IV (the least hazardous ranking) for acute inhalation toxicity (U.S. EPA/OPP/HED 2010a, p. 48). Similarly, no mortality was noted with two formulations, a 2% a.i. granular formulation at a concentration of 5092 mg formulation/m^3 (Warren 1990a) and a 10% a.i. liquid formulation at a concentration of 2415 mg formulation/m^3 (Warren and Berry 1995). Mortality and other signs of toxicity were observed at high concentrations of two other formulations (Warren 1990b; Warren 1991). The most toxic formulation was a 75% wettable powder formulation which yielded a definitive LC_{50} of about 2700 mg/m^3 (Warren 1991).

While most poisoning reports in humans involve intentional suicidal ingestion, several reports of accidental poisoning associated with spraying imidacloprid formulations are available (Agarwal and Srinivas 2007; Agha et al. 2012; Chwaluk 2010; Kumar et al. 2014). Details of these reports are summarized at the end of Appendix 1, Table A1-2. As with the suicidal ingestions, none of the reports of human poisoning associated with spraying imidacloprid involved incidents occurring in the United States. Consequently, these reports do not appear to have involved formulations available or marketed in the United States. Given the low inhalation toxicity of technical grade imidacloprid and the somewhat greater toxicity of some imidacloprid formulations, it seems reasonable to suppose that some or all of the toxic effects seen in humans following spraying of imidacloprid formulations are probably attributable to the ingredients other than imidacloprid in the formulations.

In short-term inhalation studies in which rats were exposed to repeated doses of technical grade imidacloprid for periods of 5 to 28 days, the results were similar to those observed in oral exposure studies, with one additional symptom (Pauluhn 1988a,d, 1989). Imidacloprid-exposed rats in the Pauluhn studies had significantly reduced blood clotting times and increased urine pH relative to air-only exposed controls. The investigators stated that these changes were related to functional changes in the liver (induction of hepatic mixed function oxidases was the most sensitive endpoint in these studies), although neither of these conditions was observed in orally exposed rats whose livers were also adversely affected by imidacloprid exposure. The NOAEC for inhalation exposure in the 28 day study was 5.5 mg a.i./m^3.

3.1.14. Other Ingredients and Adjuvants

3.1.14.1. Other Ingredients

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*. For brevity, the following discussion uses the term *inert*, recognizing that *inerts* may be biologically active and potentially hazardous components.

U.S. EPA has classified 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/. In addition, the U.S. EPA/OPP (2014c) maintains a database, InertFinder, with information on approved inerts in pesticide formulations.

The identity of inerts in pesticide formulations is considered proprietary and is not disclosed to the general public. Nonetheless, all inerts are disclosed to and approved by the U.S. EPA/OPP as part of the registration of pesticide formulations. In addition, potentially hazardous inerts are disclosed in Material Safety Datasheets for pesticide formulations. As summarized in Table 2, the disclosed inerts in pesticide formulations of imidacloprid explicitly encompassed by the current risk assessment include crystalline silica (CAS No. 14808-60-7), glycerol (CAS No. 56-81-5, a.k.a. 1,2,3-propanetriol), and tetrahydrofurfuryl alcohol (CAS No. 97-99-2). Based on information in the EPA InertFinder database (U.S. EPA/OPP 2014c), crystalline silica is a pesticide inert exempt from tolerances. This determination essentially indicates that risks are considered minimal. Glycerol is classified as a List 4A inert (i.e., non-toxic). In addition, both glycerol and silica are listed by the FDA as approved food additives (http://www.fda.gov/food/ingredientspackaginglabeling/foodadditivesingredients/ucm091048.htm#ftnS). Tetrahydrofurfuryl alcohol is a commonly used commercial solvent. Like many solvents, the tetrahydrofurfuryl alcohol primarily affects the central nervous system (IPCS 2001; PENN Specialty Chemicals 2005).

Reports in the open literature (Jemec et al. 2007; Pestana et al. 2009b; Tisler et al. 2009) indicate that Confidor SL 200 contains 38.4% of dimethylsulfoxide and 37.5% of 1-methyl-2-pyrrolidone. This appears to be a European formulation, and Confidor formulations are not specifically designated for use by the Forest Service (Table 2).

One of the clearest methods to assess the potential toxicity of inerts involves tests with both the active ingredient and the formulation (i.e., the active ingredient with inerts). As discussed previously, the acute toxicity data on several formulations suggest that the formulations are more toxic than imidacloprid, in terms of acute oral toxicity (Section 3.1.4.1), acute dermal toxicity (Section 3.1.12), and acute inhalation toxicity (Section 3.1.13). In addition, several *in vitro* toxicity studies indicate that Confidor formulations of imidacloprid are more toxic than imidacloprid itself (Costa et al. 2009 using an Italian formulation; Mesnage et al. 2014 using a French formulation; Skandrani et al. 2006 using a French formulation). None of the studies with Confidor formulations are from the U.S. literature, and it is not clear that formulations outside of the United States contain the same inerts as formulations marketed within the United States. Moreover, as summarized in Table 2, Confidor formulations of imidacloprid are not explicitly encompassed by the current risk assessment.

While not directly relevant to human health, toxicity studies on amphibians suggest that the inerts in a Merit 75% a.i. powder formulation (probably Merit 75 WP) do not contribute to the toxicity of the formulation. This information is discussed in more detail in Section 4.1.3.2 (hazard identification for aquatic-phase amphibians).

Concerns with ingredients other than the active ingredient are a concern in many pesticide risk assessments, and concerns with inert ingredients in imidacloprid formulations cannot be completely dismissed. Nonetheless, as with virtually all pesticide risk assessments, the focus of the current risk assessment is on the active ingredient, because sufficient information on other ingredients in imidacloprid formulations does not support a quantitative consideration of the inerts. This limitation is also apparent in all of the available risk assessments from the U.S. EPA. As with the EPA risk assessments, concern for inerts is one of the many factors that justify the generally conservative assumptions used in both the exposure assessment (e.g., the most exposed individual as discussed in Section 3.2.3.1.1) and the dose-response assessment (Section 3.3).

3.1.14.2. Adjuvants

Adjuvants may be used in some applications of imidacloprid formulations. As noted in Section 2.3.3, bark applications of imidacloprid may involve adjuvants such as Pentra-Bark to enhance the absorption of imidacloprid 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 quantitatively in the Forest Service risk assessment on glyphosate (SERA 2010a).

No information is available on the hazards which might be associated with the use of Pentra-Bark or other adjuvants with imidacloprid. 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 imidacloprid cannot be assessed based on the available information.

3.1.15. Impurities and Metabolites

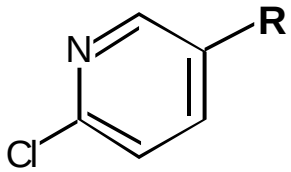
3.1.15.1. Metabolites

As discussed in Section 3.1.3.1 and illustrated in Figure 3, imidacloprid is metabolized extensively in mammals. As reviewed by Casida (2011, Figure 5), the metabolites found in plants are also found in mammals, with mammals producing some metabolites that are not found in plants. In this respect, the risks posed by imidacloprid metabolites should be encompassed by the *in vivo* toxicity studies on imidacloprid. While bacteria also degraded imidacloprid, cleavage of the 6-chloropyridinyl ring by microorganisms (discussed further below) has not been reported (Pandey 2009).

Tomizawa and Casida (1989, Table 1, p. 117 of paper) indicate that several imidacloprid metabolites, including WAK 3839, are more toxic than imidacloprid to mice following intraperitoneal injection. Specific LD_{50} values, however, are not given. As summarized in Appendix 1, Table A1-9, the intraperitoneal LD_{50} of imidacloprid in rats is about 160 - 190 mg/kg bw (Krotlinger 1990; MRID 42256326), and the reported LD_{50} value for WAK 3839 in mice is about 30 - 60 mg/kg bw (Nakazato 1988a, MRID 42256325). As discussed in Section 3.1.3, however, mice appear to be more sensitive than rats following acute oral dosing with imidacloprid.

Information on the toxicity of imidacloprid metabolites from more relevant routes of exposure is limited to the nitrosoimine metabolite, WAK 3839. Based on acute oral toxicity studies in rats (Appendix 1, Table A1-1), the only definitive LD_{50} values for WAK 3839—i.e., 1980 (M) and 3500 (F) mg/kg bw from Nakazato 1988a, MRID 42256325—are substantially higher than the definitive LD_{50} values of imidacloprid in rats—i.e., 424 (M) and 450 - 475 (F) mg/kg bw from Bomann 1989a, MRID 42055331. Similarly, the definitive LD_{50} values for WAK3839 in mice—i.e., 200 - 300 mg/kg bw from Nakazato 1988a, MRID 42256325—are higher than the definitive LD_{50} values for imidacloprid in mice—i.e., about 130 - 150 mg/kg bw from Bomann 1989b, MRID 42256324 and El-Gendy et al. 2010. In terms of subchronic oral toxicity, the NOAEL of 13 mg/kg bw/day for WAK 3839 (Krotlinger 1992, MRID 42256362) is comparable to several subchronic and chronic toxicity studies in mammals which generally indicate NOAELs of about 10 - 20 mg/kg bw/day (Section 3.1.5). As with imidacloprid, WAK 3839 does not appear to be clastogenic—i.e., there is no indication mutagenicity or chromosomal damage (Appendix 1, Table A1-11).

The U.S. EPA/OPP/HED (2010a) takes the position that metabolites of concern for imidacloprid include all metabolites containing the 6-chloropyridinyl ring.



This determination would classify all of the compounds in Figure 3, except for 6-hydroxynicotinic acid, as metabolites of concern, which may be viewed as a somewhat conservative or protective assumption in that the available data on WAK 3839 indicates that this metabolite is at least somewhat less toxic than imidacloprid. On the other hand, the minimal toxicity data on the other metabolites suggest that the EPA assumption is prudent. The practical impact of the EPA assumption is that conservative values relating to environmental fate are used in the exposure assessments for imidacloprid. This approach essentially treats the major metabolites of imidacloprid as if they were the parent compound. This approach is discussed further in Section 3.2 (exposure assessments).

3.1.15.2. Impurities

There is no information in the published literature concerning the manufacturing impurities in imidacloprid. Nonetheless, virtually no chemical synthesis yields a totally pure product. Technical grade imidacloprid, like other technical grade products, contains some impurities. These impurities are disclosed to U.S. EPA but are not made publically available. Because specific information concerning impurities may provide insight into the manufacturing process used to synthesize imidacloprid, it is considered proprietary, is protected under FIFRA (Section 10), and was not available for the preparation of the current Forest Service risk assessment.

As with most pesticides, concern for impurities in technical grade imidacloprid is reduced because most of the existing toxicity studies were conducted with the technical grade product or formulated products. Thus, toxic impurities present in the technical grade product are likely to be encompassed by the available toxicity studies.

3.1.16. Toxicological Interactions

As discussed in Section 3.2, imidacloprid will induce signs of generalized toxicity associated with oxidative stress. These effects can generally be ameliorated by antioxidants. Acute toxicity studies with imidacloprid in mammals demonstrate this antagonism of toxicity with three antioxidants—i.e., vitamin C (El-Gendy et al. 2010), curcumin (Lonare et al. 2014), and thymoquinone (Mohany et al. 2012). It is only modestly speculative to suggest that many antioxidants would reduce the toxicity of imidacloprid to mammals as well as other species.

As discussed in Section 3.1.3.1 (metabolism), imidacloprid is metabolized by at least two cytochrome P450 isozymes—i.e., CYP2D6 (nitro-reduction) and CYP3A4 (hydroxylation). Piperonyl butoxide is a well-known competitive inhibitor of cytochrome P450, and studies in insects clearly demonstrate that piperonyl butoxide will enhance the toxicity of imidacloprid by inhibiting detoxification by cytochrome P450 (e.g., Bingham et al. 2008; Zewen et al. 2003). While mammals are much less sensitive than insects to imidacloprid, metabolism of imidacloprid appears to be predominantly a detoxification process. Albeit speculative, it seems likely that piperonyl butoxide as well as other inhibitors of cytochrome P450 systems will enhance the toxicity of imidacloprid to mammals, including humans. Experimental data in mammals supporting this supposition, however, were not identified in the literature on imidacloprid.

3.2. EXPOSURE ASSESSMENT

3.2.1. Overview

As discussed in Section 2.4.5, the exposure assessments for this risk assessment are detailed in five sets of worksheets:

- Attachment 1: Tree injection
- Attachment 2: Soil injection/drench (clay or loam soils)
- Attachment 3: Bark Applications (clay or loam soils)
- Attachment 4: Foliar Broadcast applications (clay or loam soils)
- Attachment 5: Applications (any method other than tree injection) to sandy soils.

For tree injection, quantitative estimates of worker exposures are based on an EPA assessment of workers injecting emamectin benzoate. Except for an accidental spill into a small pond, no quantitative exposure assessments for members of the general public are given for tree injection of imidacloprid because this application method is extremely specific to the targeted species and the plant to be protected. Accordingly, it is unlikely that tree injections of imidacloprid will result in substantial levels of exposure to members of the general public. Furthermore, there are no methods and no information sufficient to quantify the exposures, except to suggest that they will be less than those associated with other application methods.

As with tree injection, standard methods for estimating worker exposures in Forest Service risk assessments do not accommodate soil injection. In the current risk assessment, the exposure assessment for workers is based on the approach taken by EPA (i.e., the PHED database). This method appears to be reasonable by comparison to a worker exposure study involving mechanical soil injection. For soil injection, exposures to members of the general public can be estimated quantitatively for exposure scenarios involving the consumption of contaminated surface water following both an accidental spill as well as expected concentrations of imidacloprid in surface water following soil injection. Exposure scenarios involving direct spray are not relevant to soil injection, and incidental exposures associated with contaminated vegetation are likely to be very low but cannot be estimated quantitatively.

A complete set of exposure scenarios are developed for bark applications. As noted in Section 2.4.3, bark applications are assumed to involve an application efficiency of about 90% with 10% of the pesticide nominally applied to bark being lost to soil and/or vegetation in the vicinity of the tree being treated. In this respect, bark applications may be viewed as foliar applications at 10% of the nominal application rate. For workers, worker exposure rates for bark applications are taken from the recent update of methods used to estimate occupational exposures in Forest Service risk assessments (SERA 2014b).

As discussed in Section 2.4.4, the Forest Service will not apply imidacloprid by broadcast methods and will not apply imidacloprid to predominantly sandy soils. The workbooks for foliar broadcast and applications to sandy soils are included in the current risk assessment simply to illustrate the consequences of using such application methods in contrast to the more focused application methods that will be used in Forest Service programs.

3.2.2. Workers

Two types of exposure assessments are considered for workers: general exposure and accidental/incidental exposure. The term *general exposure* 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. All exposure assessments (i.e., those for workers as well as members of the general public and ecological receptors) are based on the maximum application rate of 0.4 lb a.i./acre (Section 2.4). For most exposure scenarios, exposure and consequent risk will scale linearly with the application rate. The consequences of using lower application rates or only a single application in one season are considered as needed in the risk characterization (Section 3.4).

3.2.2.1. General Exposures

General exposures for workers are all calculated as the amount a.i. handled by a worker in single day multiplied by a worker exposure rate (in units of mg/kg bw per lb a.i. handled). For bark applications as well as foliar broadcast applications, relatively well documented worker exposure rates are available (SERA 2014b). Worker exposure rates are not well documented for tree injection and soil injection. For these application methods, worker exposure rates are derived from approaches taken in EPA risk assessments.

3.2.2.1.1. Tree Injection

The previous Forest Service risk assessment on imidacloprid (SERA 2005) did not quantitatively address worker exposures during tree injection. Standard exposure rates for tree injection have not been developed for Forest Service risk assessments (SERA 2014b), and U.S. EPA/OPP human health risk assessments on imidacloprid do not address tree injection (i.e., U.S. EPA/OPP/HED 2007a, 2008a, 2010a). Nonetheless, U.S. EPA/OPP addresses worker exposures associated with tree injection in their risk assessments on emamectin benzoate (U.S. EPA/OPP 2008a,b), an insecticide that is applied only by tree injection. The EPA approach is used in the recent Forest Service risk assessment on emamectin benzoate (SERA 2010b) and is adopted in the current risk assessment to assess worker exposures in tree injections of imidacloprid.

In its worker exposure assessment for emamectin benzoate (U.S. EPA/OPP 2008a,b), the EPA assumes that a worker could perform up to 160 injections—i.e., individual holes in a tree—during an 8-hour workday and that each injection would consist of 36 mL of the formulation, equivalent to 0.0034 lb a.i (see U.S. EPA/OPP 2008a, pp. 35-36) . For the current risk assessment on imidacloprid, the injection volume is taken as 8 mL/injection site. This value is based on the product label for IMA-jet which gives an example for a 12" DBH tree that would require six injection sites for a total dose of 48 mL/tree, which is equivalent to 8 mL/injection site [48 mL/tree ÷ 6 injection sites]. Taking a specific gravity for IMA-jet of 1.07 g/mL and the 5% a.i. (w/w) concentration of imidacloprid in IMA-jet, each injection would consist of 428 mg a.i. [1,070 mg formulation/mL x $0.05_{\text{a.i./formulation}}$ x 8 mL/injection site ≈ 428 mg a.i.]. Taking the constant of 453,592 mg/lb, each injection would consist of about 0.000944 lb a.i./injection [428 mg a.i./injection ÷ 453,592 mg/lb ≈ 0.000943579 lb a.i./injection].

The value of 160 injections is clearly characterized by EPA as an upper bound: …*a professional applicator could perform up to 160 injections in an 8-hr workday* (U.S. EPA/OPP 2008a, p. 35). As in the Forest Service risk assessment of emamectin benzoate, the number of injections that a

worker might perform in a single day is taken as 80 (40-160). The central estimate and lower bound are intended to reflect circumstances (e.g., rough terrain) that might be encountered in forestry applications while maintaining the upper bound of 160 injections from U.S. EPA/OPP (2008a). As detailed in Worksheet A01 of Attachment 1 (workbook for tree injections), the amount handled by a worker would be about 0.0755 (0.038-0.151) lb a.i./day.

In addition to the amount handled, the worker exposure estimate requires an exposure rate. U.S. EPA/OPP (2008a,d) derives rates based on the Pesticide Handler Exposure Database (PHED), Version 1.1. As discussed in SERA (2014b, Section 3.2.2.1), PHED is a deposition-based approach to estimating worker exposure. In this type of model, the exposure dose is estimated from air concentrations and skin deposition monitoring data. Using these estimates, the absorbed dose can be calculated if estimates are available on absorption rates for inhalation and dermal exposure. As summarized in Table 3 of the current Forest Service risk assessment, PHED does not contain exposure rates for tree injections. As indicated in bold typeface in Table 3, the exposure rates selected by the EPA are based on PHED Scenario 3—i.e., all liquids, open mixing and loading. As discussed by U.S. EPA/OPP (2008a, p. 35), this approach is taken …*to assess loading into a tree injection device, application is a closed system; therefore, additional exposure is expected to be negligible*.

As indicated in Table 3 of the current Forest Service risk assessment and Table 9.1 of U.S. EPA/OPP (2008a), the EPA used two dermal exposure rates, 2.9 mg/lb a.i. handled (no gloves) and 0.023 mg a.i./lb a.i. handled (with gloves). Loading imidacloprid without gloves is considered a misapplication. The product label for Imicide clearly indicates that gloves are required, and it is likely that Forest Service personnel would wear chemical resistant gloves in any application of imidacloprid. Consequently, the derivation of worker exposure rate is based on the dermal factor of 0.023 mg a.i./lb a.i. handled (with gloves).

All of the above rates are deposition-based rates and are not chemical specific. To consider a specific chemical, assumptions are needed concerning both inhalation absorption and dermal absorption. For inhalation exposures, the assumption is made that 100% of the pesticide is absorbed. This assumption is used in U.S. EPA/OPP (2008a) and is a standard assumption for inhalation exposures in EPA's use of PHED. The proportion of the dermal dose that is absorbed is based on the first-order dermal absorption rates given in Section 3.1.3.2.2—i.e., 0.0015 (0.00067 to 0.0036) $hour^{-1}$ and a functional exposure period of 8 hours—i.e., the proportion absorbed is calculated as $1-e^{-kt}$.

Details of the implementation of worker exposure rates based on PHED are given in Worksheet C01-Sup of Attachment 1 (tree injection). The derived worker exposure rates for tree injection, rounded to one significant place, are 0.00004 (0.00003 to 0.00006) mg a.i./kg bw/day per lb a.i. handled. These rates are linked to Worksheet A01, and the rates from Worksheet A01 are used in Worksheet C01 of Attachment 2 to estimate absorbed doses in workers involved in tree injections of imidacloprid.

3.2.2.1.2. Soil Injection

As with tree injection, no standard worker exposure rates or treatment rates have been developed for soil injection. The most recent human health risk assessment from EPA (U.S. EPA/OPP/HED 2010a) does not address soil injection, and the prior EPA risk assessment notes

that soil injections are used in forestry but does not develop exposure assessments for applicators (U.S. EPA/OPP/HED 2008a, Table 9, p. 24). Unlike the case with tree injection (Section 3.2.2.1.1), the EPA risk assessments do not discuss the number of injections that a worker might make per day and do provide other methods for estimating the amount of imidacloprid that a worker involved in tree injections might handle in the course of a single day. The U.S. EPA does use a standard set of assumptions involving the number of acres that a worker might treat per day based on several different application methods; however, the methods do not include soil injection (Sandvig 2001).

In the previous Forest Service risk assessment on imidacloprid (SERA 2005), the assumption was made that a worker might treat 4.375 (1.5-8) acres/day. These are standard values used in Forest Service risk assessments for directed foliar applications (i.e., SERA 2014b, Table 2). In the absence of additional information, these treatment rates are maintained for the current Forest Service risk assessment in Worksheet C01 of Attachment 2 (the WorksheetMaker workbook for soil injections).

As detailed in Worksheet A01 of Attachment 2, the maximum application rate of 0.4 lb a.i./acre is used for the worker exposure assessment for soil injections. The maximum dose per tree is specified on the product labels as 1.4 g a.i./inch DBH. For an 18 inch DBH tree, the total dose per tree would be 25.2 g/tree [1.4 g a.i./inch DBH x 18 inch DBH = 25.2 g/tree] which is equivalent to about 0.055 lb a.i.[25.2 g ÷ 453.59 g/lb ≈ 0.0555 lb a.i.]. Thus, for an application rate of 0.4 lb a.i./acre and taking an average DBH of 18 inches for the size of the tree, a worker would treat an average of about seven trees per acre [0.4 lb a.i./acre ÷ 0.055 lb a.i./tree ≈ 7.26 trees per acre]. In the interest of clarity, it is noted that treating seven trees per acre while covering 4.375 (1.5-8) acres/day, the worker would treat about 31 (10 to 56) trees per day [7 trees/acre x 4.375 (1.5-8) acres = 30.625 (10.5 to 56) trees/day]. The extent to which this treatment rate reflects Forest Service experience in soil injections is unclear.

In the previous Forest Service risk assessment (SERA 2005), worker exposure rates—i.e., mg/kg bw per lb applied) were based on worker exposure rates for backpack applications. In the more recent revisions to worker exposure rates (SERA 2014b), worker exposure rates for soil injection are not derived; however, a study involving sweep injection boom applications is reviewed in which very low worker exposure rates are derived—i.e., the study by Lunchick et al. (2005) discussed in Section 3.3.1.5 of SERA (2014b) with worker exposure rates of 0.000007 (0.0000002 – 0.0002) mg/kg bw/day per lb a.i. applied mg/kg bw per lb applied. While mechanical soil injection is not directly comparable to manual soil injections, the study by Lunchick et al. (2005) raises concern that the use of worker exposure rates for backpack applications may grossly overestimate worker exposures in soil injection applications.
As summarized in Table 2, Scenario 37, PHED exposure rates have been estimated for liquid, open pour, termiticide injection. The exposure rates are given as 0.36 mg/lb handled for dermal exposure and 0.0022 mg/lb for inhalation exposure. For a 70 kg man, the dermal exposure is equivalent to about 0.00514 mg/kg bw per lb handled [0.36 mg/lb handled ÷ 70 kg bw = 0.005142857 mg/kg bw per lb handled], and the inhalation exposure is equivalent to about 0.000031 mg/kg bw per lb handled [0.0022 mg/lb ÷ 70 kg bw ≈ 0.00003143 mg/kg bw per lb handled]. As with the calculations for tree injection (3.2.2.1.1), the proportion of the dermal dose that is absorbed is calculated as $1\text{-}e^{-kt}$, using the first order dermal absorption rates given in

Section 3.1.3.2.2. Also as in the calculations for tree injection, inhalation absorption is assumed to be 100%. Based on this approach, the worker exposure rates in terms of absorbed dose can be calculated as 0.00005 (0.00004 – 0.0007) mg/kg bw/day. Details of these calculations of the worker exposure rates are given in Worksheet C01-Sup. Note that the central estimate of the worker exposure rate is higher than the rate from the study by Lunchick et al. (2005) by about a factor of 7 [0.00005 ÷ 0.000007 ≈ 7.14]. While this approach does not validate the estimate from PHED, a higher estimate for manual soil injection relative to mechanical soil injection does appear to be sensible.

In the absence of more relevant data, the exposure rates derived from PHED are used, as given in Worksheet C01-Sup of Attachment 2. These rates are rounded to one significant place and linked to Worksheet A01. These rates from Worksheet A01 are used in Worksheet C01 of Attachment 2 to estimate absorbed doses in workers involved in soil injections of imidacloprid.

3.2.2.1.3. Bark Application

Worker exposure rates for bark applications are derived in SERA (2014b). These rates are based on a study by Middendorf (1992) of workers applying the butoxyethyl ester triclopyr in a basal bark application. As summarized in Table 14 (p. 82) of SERA (2014b), the worker exposure rate from this study is 0.001 mg/kg bw/day per lb handled with a 95% prediction interval of 0.0001 - 0.02 mg/kg bw/day per lb handled. As discussed in SERA (2014b, Section 4.2.1), chemical-specific worker exposure rates are derived by adjusting for differences in the first-order dermal absorption rate coefficient for triclopyr (the reference chemical) and the chemical of concern (in this case imidacloprid). This adjustment is detailed in Table 4 of the current risk assessment. In Worksheet C01 of Attachment 3 (the WorksheetMaker workbook for bark applications), the exposure rates from Table 4 are rounded to one significant place (i.e., 0.0005 [0.00005-0.01] mg/kg bw/day per lb handled) and used to estimate worker exposures to imidacloprid during bark applications.

As with other worker exposure assessments, worker exposures are estimated on the maximum application rate (0.4 lb a.i./acre). The amount handled per day is estimated based on standard rates for directed foliar applications, as discussed in the worker exposure assessment for soil injection (Section 3.2.2.1.2) – i.e., 1.75 (0.6 to 3.2) lb a.i./day.

3.2.2.1.4. Foliar Application

Foliar application methods are used in agriculture but are not used in Forest Service programs, as discussed in Section 2.3.4. The current risk assessment addresses the risks associated with foliar applications in contrast to the much more focused applications used in forestry programs—i.e., tree and soil injections as well as bark applications. For this comparison, directed foliar applications are used as detailed in Attachment 4 (the WorksheetMaker workbook for directed foliar applications).

Worker exposure rates for directed foliar applications are derived in SERA (2014b). In Table 14 of SERA (2014b), three reference chemicals with corresponding worker exposure rates are given for backpack applications—i.e., glyphosate (k_a = 0.00041 hour^{-1}), 2,4-D (k_a = 0.00066 hour^{-1}), and triclopyr BEE (k_a = 0.0031 hour^{-1}). As discussed in Section 3.1.3.2.2 of the current risk assessment, the central estimate of the first-order dermal absorption rate coefficient for imidacloprid is 0.0015 hour^{-1}. To minimize extrapolation, triclopyr BEE is used as the reference

chemical for imidacloprid. As indicated in Table 14 of SERA (2014b), the worker exposure rates for backpack applications of triclopyr BEE are 0.01 (0.002-0.06) mg/kg bw per lb —i.e., central estimate and 95% prediction interval. The adjustment for the differences in dermal absorption is detailed in Table 5 of the current risk assessment. In Worksheet A01 of Attachment 4 (the WorksheetMaker workbook for backpack applications), the exposure rates from Table 5 are rounded to one significant place (i.e., 0.005 [0.001-0.03] mg/kg bw/day per lb handled). These worker exposure rates are used in Worksheet C01 to estimate exposures in workers involved in directed foliar applications of imidacloprid. Estimates of the amount of pesticide handled by a worker in backpack applications are standard rates used in Forest Service risk assessments involving backpack applications (SERA 2014a, Table 6, p. 131).

As summarized in Worksheet E01 of Attachment 4 (Directed foliar applications), the estimated exposures for workers applying imidacloprid are 0.00875 (0.006 - 0.096) mg/kg bw/day. In a deposition-based worker exposure study involving hand-held sprayer, Choi et al. (2013, p. 10647) estimated absorbed doses for applicators in the range of 0.1 - 0.4 mg/day. Assuming a 70 kg body weight, these doses are equivalent to about 0.0014 - 0.0057 mg/kg bw/day. The exposure period in the study by Choi et al. (2013) lasted for only 1 hour. As might be expected, the estimated doses for workers in the study by Choi et al. (2013) are within the lower bounds of the doses estimated in the current risk assessment. More recently, Cao et al. (2015) estimated dermal deposition of about 0.014 and 0.48 mg in two workers involved in backpack applications to fields with only negligible levels (≈0.0005 and 0.002 mg) of potential inhalation exposures (Cao et al. 2015, Table 2). This study, however, involved only a 15 minute application period. Harris et al. (2010) assayed imidacloprid in the urine of lawn care workers applying imidacloprid and a variety of other pesticides. The studies by Cao et al. (2015) and Harris et al. (2010) do not characterize the amount of imidacloprid applied by the workers and cannot be used to assess the worker exposures in the current risk assessment.

3.2.2.2. Accidental Exposures

Generally, dermal exposure is the predominant route of exposure for pesticide applicators (Ecobichon 1998; van Hemmen 1992), and accidental dermal exposures are considered quantitatively in all Forest Service risk assessments. The two types of dermal exposures modeled in the risk assessments include direct contact with a pesticide solution and accidental spills of the pesticide onto the surface of the skin. In addition, 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 of the EXCEL workbooks that accompany this risk assessment—i.e., Attachments 1 through 4. Additionally, Worksheet E01 references other worksheets in which the calculations of each exposure assessment are detailed.

Exposure scenarios involving direct contact with solutions of imidacloprid are characterized either by immersion of the hands in a field solution for 1 minute or wearing pesticide contaminated gloves for 1 hour. The assumption that the hands or any other part of a worker's body will be immersed in a chemical solution for a prolonged period of time may seem unreasonable; however, it is possible that the gloves or other articles of clothing worn by a worker may become contaminated with a 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 the solution. In both cases, the chemical concentration in contact with the skin and the resulting dermal absorption rate are essentially 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 imidacloprid are provided in Section 3.1.3.2.2.

The amount of the pesticide absorbed per unit time depends directly on the concentration of the chemical in solution. This concentration is highly variable depending on the application method. As detailed in Worksheet A01 of Attachment 1 (tree injection), the formulation (IMA-jet, 5% a.i.) is not diluted and the concentration of imidacloprid in the formulation is 53.5 mg/mL. For soil injection and bark applications, the formulations are diluted and the concentration in the applied solution is estimated at somewhat less than 240 mg/mL (Worksheet A01 in Attachments 2 and 3). For foliar applications, the formulation (Marathon II, 21.4% a.i., 2 lb a.i./gallon) is applied at application volumes of 10 (5-20) gallons per acre and the concentrations in field solutions are estimated at 4.8 (2.4-9.6) mg/mL (Worksheet A01 of Attachment 4).

The details of the accidental dermal exposure scenarios for workers consist of spilling a chemical solution on to the lower legs as well as spilling a chemical solution on to the hands, at least some of which adheres to the skin. The absorbed dose is then calculated as the product of the amount of chemical on the skin surface (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 chemical concentration in the liquid), the first-order absorption rate coefficient, and the duration of exposure. The first-order dermal absorption rate coefficient (k_a) is derived in Section 3.1.3.2.1.

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 imidacloprid in Forest Service programs appears to be low for the application methods to be used by the Forest Service—i.e., tree and soil injection or bark application. As discussed further in Section 3.2.3.1.2 (Summary of Assessments), the only quantifiable exposures to members of the general public with regard to tree injection involve accidental spills into a small pond. With regard to soil injections, exposure scenarios are based on both the accidental spill scenario and estimates of the modelled and non-accidental contamination of surface water. Bark applications may lead to the contamination of surface water and the incidental contamination of surrounding vegetation. As discussed in Section 2.3.4, foliar application methods will not be used in Forest Service programs; nonetheless, they are considered in the current risk assessment to illustrate the differences between the focused applications used in Forest Service programs and the more general broadcast applications made in agricultural applications of imidacloprid.

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 (2014a, 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 other organizations. In the current risk assessment and other Forest Service risk assessments, the upper bounds on exposure estimates 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, this is strong indication that the pesticide cannot be used in a manner that will lead to acceptable risk.

3.2.3.1.2. Summary of Assessments

Table 6 provides an overview of the exposure scenarios for members of the general public. As indicated in Table 6, not all exposure scenarios are applicable to each of the application methods covered in the current risk assessment. This section discusses the rationales for omitting specific scenarios for tree injection and soil injection. Except for emphasis or clarification, this discussion is not repeated in the following sections on the exposure scenarios.

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. 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 imidacloprid. 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*).

For tree injections, the only exposure scenarios developed for members of the general public involve the accidental spill of imidacloprid into a small pond. This is an elaboration from previous Forest Service risk assessments involving tree injection—i.e., the previous risk assessment on imidacloprid (SERA 2005) as well as Forest Service risk assessments on

dinotefuran (SERA 2009a) and emamectin benzoate (SERA 2010b)—in which no exposure scenarios for members of the general public were developed. As detailed further in Section 3.2.3.4.1, this elaboration is based on EPA estimates of the number of injections a worker might make in 1 day, which are, in turn, used to estimate the amount of imidacloprid that a worker might handle in 1 day. These estimates are detailed in Section 3.2.2.1.1. The decision to develop only one exposure scenario for general public exposure to imidacloprid resulting from tree injection is not meant to rule out the possibility of other scenarios in which members of the general public may be exposed to imidacloprid following tree injection. For example, in the unlikely event that a member of the general public were in the vicinity of a tree injection application during an equipment malfunction, a splash of imidacloprid onto the skin, however improbable, is possible. Accidental exposures scenarios are covered for workers in Section 3.2.2.2 and are applicable, albeit less likely, to occur for members of the general public.

Another possible set of exposure scenarios would involve leaf fall from trees that are injected with imidacloprid. It is possible that members of the general public could come into contact with the contaminated leaves or other material from the tree either directly or secondarily through the contamination of soil or surface water. There is no basis, however, for asserting that these exposures would be substantial, relative to other application methods. Furthermore, the literature on imidacloprid does not include methods for estimating exposures for members of the general public secondary to leaf or needle fall in a treated tree. Finally, as discussed further in Section 3.4 (risk characterization), members of the general public do not appear to be at substantial risks following applications of imidacloprid by application methods other than foliar applications for which exposures are more likely in terms of both probability and magnitude. The potential impact of the contamination of surface water is a greater concern with aquatic invertebrates and this issue is discussed further in the risk characterization for aquatic invertebrates (Section 4.4.3.4).

Soil injection may be viewed as somewhat less focused than tree injection in that non-accidental contamination of surface water is both likely and quantifiable. As discussed further in Section 3.2.3.4.3, the model used to estimate surface water contamination accommodates soil injection. Consequently, as summarized in Table 6, exposure scenarios involving the contamination of surface water are developed for soil injection. This approach is identical to the approach taken in previous Forest Service risk assessments involving soil injection (i.e., SERA 2005, 2009a). As with tree injection, trees and other vegetation in the vicinity of a soil injection will absorb imidacloprid making exposures through the consumption of vegetation possible, but probably not substantial. In addition, accidental exposure scenarios involving a spill into a small water body are applicable to soil injection applications and must be taken into consideration in the current risk assessment.

As full set of exposure scenarios, identical to those used for broadcast applications, are developed for bark applications, as in the previous Forest Service risk assessments on dinotefuran (SERA 2009a) and carbaryl (2009b). In essence bark applications are treated as foliar applications in that application to the bark will not be 100% efficient. Some imidacloprid applied to the bark will splash or otherwise contaminate nontarget vegetation. As noted in Section 2.4.3, estimates of loss from a bark application to the surrounding area range from 5% (Cowles 2009) to 10% (Onken 2009). As with the Forest Service risk assessment on dinotefuran

(SERA 2009a), the current risk assessment on imidacloprid uses the 10% estimate for unintended loss. Thus, in Worksheet A01 of Attachment 3 (the WorksheetMaker workbook for bark applications), the application efficiency to the bark is assumed to be 90%.

The exposure scenarios for foliar application are identical to those for bark application—i.e., a full set of standard exposure scenarios used in all Forest Service risk assessments for foliar applications. The only difference is that the exposure assessments for foliar application are based on the assumption of 100% application efficiency. This is a standard approach taken in all Forest Service risk assessments involving foliar applications.

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). These exposure scenarios are considered in the workbooks for bark and foliar applications.

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 2014a). As with the accidental exposure scenarios for workers (Section 3.2.2.2), different application methods involve different concentrations of imidacloprid 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 (2014a), 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.

No data are available on dermal transfer rates for imidacloprid. This is not a severe limitation in this risk assessment. As detailed in Durkin et al. (1995), dermal transfer rates are reasonably consistent for numerous pesticides, and the methods and rates derived in Durkin et al. (1995) are used as defined in Worksheet D02.

Standart (1999) estimated the dislodgeable foliar residue of imidacloprid at 0.00018 - 0.0009 mg/cm^2 after a cumulative application of 0.3 lb a.i./acre. These estimates are based on data from other pesticides applied to cotton, apples, and grapes. Since 0.3 lb a.i./acre corresponds to an application rate of 0.003363 mg/cm^2, the dislodgeable residue as a proportion of the application rate was estimated by Standart (1999) as 0.054 [0.00018 mg/cm^2 / 0.003363 mg/cm^2] to 0.27 [0.0009 mg/cm^2 / 0.003363 mg/cm^2]. These values bracket the standard value of 0.1 used in most Forest Service risk assessments. For the current risk assessment, the standard value of 0.1 is used to estimate dislodgeable residue on turf (Worksheet D02). As discussed in Section 3.4, the hazard quotients associated with this exposure scenario are far below a level of concern, and this assumption has no impact on the current risk assessment.

The exposure scenario assumes a contact period of 1 hour and further assumes that the chemical is not effectively removed by washing for 24 hours. Other approximations used in this exposure scenario include estimates of body weight, skin surface area, and first-order dermal absorption rates, as discussed in Section 3.2.3.2 (Direct Spray).

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 a highly variable scenario in the sense that the concentration in the pond depends on the amount of the field solution spilled into the pond and the concentration of the pesticide in the field solution.

The accidental spill scenario is developed for all application methods. For tree injection (Attachment 1), the amount of the spill is equal to the amount of imidacloprid that a single worker would handle in 1 day. The amount that a worker would handle is based on the number of injections per day and the amount of imidacloprid contained in each injection, as discussed further in Section 3.2.2.1.1 (the worker exposure assessment for tree injection).

For other application methods, the amount spilled is calculated from concentrations of imidacloprid in the applied solution. These concentrations are calculated in Worksheet A01 of

the Attachments 2-4 and are discussed in Section 3.2.2.2. The calculations of the concentration of imidacloprid in the small pond are detailed in Worksheet B04b. Because this scenario is based on the assumption that exposure occurs shortly after the spill, no dissipation or degradation is considered.

For broadcast and directed foliar applications, Forest Service risk assessments typically assume a spill of 100 gallons with a range from 20 to 200 gallons of a field solution. As detailed in Worksheet A01 of Attachment 4 (directed foliar applications), the most concentrated field solution of imidacloprid in a field solution for directed foliar applications is about 0.0046 lb a.i./gallons. Thus, a spill of 200 gallons would be equivalent to approximately 0.92 lb a.i. or the amount required to treat about 2.3 acres [0.92 lb a.i. ÷ 0.4 lb/acre = 2.3 acres].

Substantially higher concentrations of imidacloprid—i.e., 0.1 (0.02- 0.4) lb a.i./gallon—are used in field solutions for soil injection (Section 2.4.2) and bark application (Section 2.4.3). Thus, spills of 100 (20 - 200) gallons would be equivalent to 10 (0.4 - 80) lbs a.i. [0.1 (0.02 - 0.4) lb a.i./gallon x 100 (20 - 200) gallons]. This would be equivalent to the amount of imidacloprid needed to treat 25 (1 - 200) acres [10 (0.4 - 80) lbs a.i. ÷ 0.4 lb a.i./acre]. Assuming an accidental spill involving an amount of imidacloprid that might be applied to 25 (1 - 200) acres in a soil injection or bark application is grossly more extreme than the standard Forest Service spill scenario for broadcast and directed foliar applications. As discussed in Section 3.2.2.1.2 (soil injection) and Section 3.2.2.1.3 (bark application) and detailed in the corresponding workbooks, workers applying imidacloprid by these application methods are estimated to handle up to 3.2 lb a.i./day. This amount is less than the upper bound for the amount of 80 lbs a.i. in a spill of 200 gallons by a factor of 25. To make the spill scenario for soil injection and bark application more comparable to the standard spill scenario used in broadcast applications, the spill volumes are reduced to 4 (0.8 - 8) gallons in Worksheet A01 of the EXCEL workbooks for soil injection (Attachment 2) and bark applications (Attachment 3).

The accidental spill scenario assumes that a young child consumes contaminated water shortly after an accidental spill into a small pond. Estimated doses to the child are given in Worksheet D05 of the workbooks.

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

This scenario involves the accidental direct spray or incidental spray drift to a small pond and a small stream. The exposure scenarios involving drift are less severe but more plausible than the accidental spill scenario described in the previous section. This scenario is applied only to directed foliar (backpack) applications (Attachment 4). Drift from backpack applications are always modeled using coarse droplet sizes, and the specific estimates of drift are given in Worksheet A04. The estimates of drift are taken from AgDrift. Calculations of the imidacloprid concentrations in surface water are given for a small pond (Worksheet B04c) and a small stream (Worksheet B04d). The specifics of these exposure scenarios are discussed in SERA (2014a, Section 3.2.3.4.2.).

3.2.3.4.3. GLEAMS Modeling

3.2.3.4.3.1. Inputs

Gleams-Driver is used to estimate expected peak and longer-term pesticide concentrations in surface water. Gleams-Driver serves as a preprocessor and postprocessor for GLEAMS (Knisel and Davis 2000). GLEAMS is a field scale model developed by the USDA/ARS and has been used for many years in Forest Service and other USDA risk assessments (SERA 2007a, 2011b).

Gleams-Driver offers the option of conducting exposure assessments using site-specific weather files from Cligen, a climate generator program developed and maintained by the USDA Agricultural Research Service (USDA/NSERL 2004). Gleams-Driver is used in the current risk assessment to model imidacloprid concentrations in a small stream and a small pond.

As summarized in Table 7, nine locations are used in the Gleams-Driver modeling. These locations are standard sites used in Forest Service risk assessments for Gleams-Driver simulations and are intended to represent combinations of precipitation (dry, average, and wet) and temperature (hot, temperate, and cool) (SERA 2007a).

The characteristics of the fields and bodies of water used in the simulations are summarized in Table 8. For each location, simulations were conducted using clay (high runoff, low leaching potential), loam (moderate runoff and leaching potential), and sand (low runoff, high leaching potential) soil textures. For each combination of location and soil, Gleams-Driver was used to simulate pesticide losses to surface water from 100 modeled applications at a unit application rate of 1 lb a.i./acre, and each of the simulations was followed for a period of about 1½ years post application. Note that an application rate of 1 lb a.i./acre is used as a convention in all Forest Service risk assessments in order to avoid rounding limitations in GLEAMS outputs. All exposure concentrations discussed in this risk assessment are based on an application rate of 0.4 lb a.i./acre.

Table 9 summarizes the chemical-specific values used in Gleams-Driver simulations. For the most part, the chemical properties used in the Gleams-Driver simulations are based on the parameters used by the Environmental Fate and Effects Division (EFED) of the U.S. EPA's Office of Pesticides Programs modeling of imidacloprid (U.S. EPA/OPP/EFED 2009a, 2014a). The inputs for GLEAMS-Driver are substantially different from the inputs used in the previous Forest Service risk assessment on imidacloprid (SERA 2005). As discussed in Section 3.1.15.1, The U.S. EPA/OPP/HED (2010a) takes the position that metabolites of concern for imidacloprid include all metabolites containing the 6-chloropyridinyl ring. Consequently, the EPA's PRZM/EXAMS modeling of imidacloprid (discussed further in 3.2.3.4.4) uses input values that appear to reflect not only the degradation of imidacloprid but also imidacloprid metabolites that contain the 6-chloropyridinyl ring. As also discussed in Section 3.1.15.1, the information available on the toxicity of imidacloprid metabolites is limited. While it is not clear that all imidacloprid metabolites containing the 6-chloropyridinyl ring are as toxic as imidacloprid, the current risk assessment defers to U.S. EPA/OPP/HED (2010a) because the available information does not provide a sufficient basis to develop an alternative method. In addition, Forest Service risk assessments will be at least as conservative as EPA risk assessments, unless there is a compelling reason to do otherwise.

The EPA modeling efforts are discussed below (Section 3.2.3.4.4). In the current risk assessment, most of the model input values are based on the environmental fate studies submitted to the U.S. EPA by registrants as well as standard values for GLEAMS modeling recommended by Knisel and Davis (2000). The notes to Table 9 indicate the specific sources of the chemical properties used in the GLEAMS modeling effort.

Details of the results for the Gleams-Driver runs are provided in Appendix 8 (soil injection) and Appendix 9 (foliar application). As discussed in Section 3.2.3.1.2, no surface water modelling is done for tree injections. Bark applications are treated similarly to foliar applications but with a functional application rate of only 10% of the foliar application rate. Consequently, separate GLEAMS-Driver runs for bark applications are unnecessary.

3.2.3.4.3.2. Results

Table 10 summarizes the modeled concentrations of imidacloprid in surface water in GLEAMS-Driver and the EPA models discussed in Section 3.2.3.4.4. The use of these estimates in developing the exposure assessments for the current risk assessment is discussed in Section 3.2.3.4.6.

The summary of the GLEAMS-Driver modeling for imidacloprid is atypical relative to most discussions of GLEAMS-Driver modeling in Forest Service risk assessments. As discussed in Section 2.4, the current risk assessment is consistent with the previous Forest Service risk assessment in that applications of imidacloprid to predominantly sandy soils are not considered explicitly as part of Forest Service programs. This limitation is based on the rapid leaching from sandy soils. Thus, the summary in Table 10 gives water contamination rates for soil injection and directed foliar applications for a composite of clay and loam soils. In these composites, the central estimate is the approximate average of the means for the simulations for clay and loam soils. The lower bound is the lowest of the nonzero 25th percentiles for clay and loam soils. The upper bound is the highest of the maximum values for clay and loam soils.

A reasonable expectation would be that water contamination rates for broadcast applications would be consistently higher than soil injection, because soil injection is a more focused application method, and soil injection should reduce runoff and sediment losses relative to broadcast application. As indicated in a comparison of the individual simulations for soil injection (Appendix 9) and broadcast application (Appendix 12), this expectation is not correct in all cases. Take as an example, the results for peak concentrations in a small pond (i.e., Table 7 in each of the two appendices). In locations with little or average rainfall, peak concentrations of imidacloprid in a small pond are consistently higher following broadcast applications, compared with soil injection for both clay and loam soil textures. These results are intuitive. In areas with high rates of rainfall, however, concentrations of imidacloprid in the small pond are higher following soil injection for loam but not clay soil textures. While not intuitive, this pattern is associated with the greater significance of leaching, the predominant loss mechanism in loamy soils, relative to runoff and sediment losses, the predominant mechanisms of loss in clay soils. Thus, in areas with loamy soils and high rates of rainfall, injecting imidacloprid into the soil may result in higher rates of contamination to surface water relative to applications of imidacloprid to vegetation. In addition to the role of leaching versus runoff, the simulations for foliar applications assume that about half of the imidacloprid is applied to vegetation and half to soil

(Table 9). Thus, vegetation will act as an at least temporary reservoir for imidacloprid, reducing the peak concentrations of imidacloprid in surface water following foliar application, relative to soil injection. As with all Forest Service risk assessments, the current risk assessment on imidacloprid should consider the specific water contamination rates given in the appendices for different rainfall, temperatures, and soil types rather than composite rates given in Table 10 and used in the WorksheetMaker workbooks that accompany this risk assessment.

3.2.3.4.4. Other Modeling Efforts

Other efforts to model imidacloprid concentrations in surface water are summarized in Table 10, which also summarizes the surface water modeling conducted for the current risk assessment (Section 3.2.3.4.3). To estimate concentrations of a pesticide in ambient water as part of a screening level risk assessment, the U.S. EPA typically uses Tier 1 screening models (e.g., GENEEC, FIRST, and SCIGROW). For more refined and extensive risk assessment, the U.S. EPA/OPP typically use PRZM/EXAMS, a more elaborate Tier 2 modeling system. The U.S. EPA/OPP typically models pesticide concentrations in water at the maximum labeled rate.

All of the concentrations given in Table 10 are expressed as Water Contamination Rates (WCRs)—i.e., the modeled concentration divided by the application rate. All of the concentrations discussed below are WCRs (µg/L per lb applied), comparisons below are discussed in units of µg/L in the interest of brevity.

The adjustments made to the EPA modeling are given in the footnotes to Table 10. These adjustments result in values expressed as µg/L per lb/acre, which are directly comparable to the modeling values from GLEAMS-Driver summarized in Table 10. All of the EPA modeling involves foliar applications focused on ponds or other lentic bodies of water. Thus, the comparisons to GLEAMS-Driver modeling are based on GLEAMS-Driver simulations for a pond following directed foliar applications.

The estimated peak concentrations from GENEEC and FIRST are in the range of about 46 to 72 µg/L. These are somewhat higher than the central estimate from GLEAMS-Driver (≈16 µg/L) but below the peak estimates from GLEAMS-Driver (≈95 µg/L). The estimates from PRZM/EXAMS are in the range of about 22 to 27 µg/L, only modestly higher than the central estimate from GLEAMS-Driver (≈16 µg/L) and below the peak estimates from GLEAMS-Driver (≈95 µg/L) by a factor of about 4 [≈95 µg/L ÷ 22 to 27 µg/L ≈ 3.52 to 4.32].

The comparisons of the simulations produced by EPA and Gleams-Driver for imidacloprid are similar to many other comparisons noted in other Forest Service risk assessments. Because Gleams-Driver is applied to numerous site/soil combinations and because 100 simulations are conducted for each site/soil combination, the upper bound values from Gleams-Driver often exceed the concentrations obtained from conservative Tier 1 models as well as the more refined Tier 2 models. Because the overall intent of Gleams-Driver is to estimate both central estimates and uncertainty bounds associated with the central estimates, the conservative Tier I and Tier 2 models from EPA typically yield concentrations higher than the central estimate from Gleams-Driver. In any event, the differences between the EPA and GLEAMS-Driver modeling are not substantial; however, the upper bound concentrations from GLEAMS-Driver are consistently greater than the estimates from EPA.

3.2.3.4.5. Monitoring Data

In terms of evaluating the surface water modeling efforts discussed in the previous sections, the most useful monitoring studies are those that associate monitored concentrations of a pesticide in water with defined applications of the pesticide—e.g., applications at a defined application rate to a well characterized field. When available, such studies can provide a strong indication of the plausibility of modeled concentrations of a pesticide in surface water. Only one such study, Daam et al. 2013, was identified in the relevant literature. Since this study involved applications of imidacloprid to a rice paddy, it is not directly useful in assessing the modeling efforts discussed in the two previous sections.

The available monitoring studies on imidacloprid report detected levels of imidacloprid in various geographical locations. Several monitoring studies note that imidacloprid is detected in surface water with a high frequency relative to other pesticides (Ensminger et al. 2013; Hladik and Calhoun 201; Hladik et al. 2014; Sanchez-Bayo and Hyne 2014; Starner and Goh 2012; Wijnja et al. 2014). The reported frequencies range from 15% (samples from Massachusetts reported by Wijnja et al. 2014) to 93% (samples from an agricultural region in Australia reported in Sanchez-Bayo and Hyne 2014). The highest reported frequency of the detection of imidacloprid in surface waters in the United States is 89% (samples from an agricultural region in California reported by Starner and Goh 2012).

Several studies report maximum concentrations of imidacloprid in surface water below 1 µg/L—i.e., 0.67 µg/L in California (Ensminger et al. 2013,Table 1, p. 3705); 0.0353 µg/L in two streams in Georgia (Hladik and Calhoun 2012 Table 4, p. 7); 0.043 µg/L in surface water samples in Iowa (Hladik et al. 2014); and 0.67 µg/L in ground water in New York (U.S. EPA/OPP/EFED 2008a, p. 7). Reports of higher concentrations include, 4.56 µg/L in rivers in an agricultural region of Australia (Sanchez-Bayo and Hyne 2014); 3.34 µg/L in Canadian surface water (Morrissey et al. 2015); 3.29 µg/L in an agricultural region of California (Starner and Goh 2012); 1.462 µg/L in creeks near San Francisco (Weston et al. 2015); and 6.9 µg/L in suburban surface water near Boston (Wijnja et al. 2014). The reported concentration of 6.9 µg/L in surface water a suburb of Boston seems unusual. Wijnja et al. (2014, p. 230) note that the detection of 6.9 µg/L was unusual and that all other detections of imidacloprid were below 1 µg/L. In addition, these investigators note that imidacloprid is used for landscape insect control in the spring and early summers and that the detections of imidacloprid occurred at this time. While the reports by Hladik and Calhoun (2012) and Hladik et al. (2014) are from USGS personnel, imidacloprid is not cited in the reviews of pesticide monitoring data from USGS (2007, 2014). Monitoring data from the Netherlands indicates that surface water concentrations of imidacloprid greater than 1 µg/L occur but are atypical-—i.e, in about the upper 95th percentile (Vijver and Van Den Brink 2014, p. 8, Figure 5).

The relatively high (≈3-7 µg/L) surface water concentrations of imidacloprid are consistent with the modeling data from both GLEAMS-Driver and EPA, as summarized in Table 10. For example, the central estimate of 13.1 µg/L per lb/acre for soil injection would result in a concentration of 5.2 µg/L in pond water at an application rate of 0.4 lb a.i./acre. This is the approximate mid-point of the high concentrations of imidacloprid in surface water noted above [(6.9 µg/L + 4.56 µg/L + 3.29 µg/L) ÷ 3 ≈ 5.13 µg/L]. In addition, as also noted above, these monitored concentrations cannot be associated with a defined application of imidacloprid;

accordingly, the apparent concordance of the monitoring data with the concentrations of imidacloprid in water modeled by GLEAMS-Driver (Section 3.2.3.4.3.2) may be coincidental.

3.2.3.4.6. Concentrations in Water Used for Risk Assessment

The calculations of the concentrations of imidacloprid in surface water used in this risk assessment are based on the GLEAMS-Driver modeling. As discussed in Section 3.2.3.4.4, the modeled WCRs from GLEAMS-Driver are reasonably consistent with the modeling from the U.S. EPA. Specifically, the upper bound estimates from GLEAMS-Driver are above any estimated from EPA but not unreasonably so—i.e., a factor of about 4. Although the available monitoring data cannot be used directly to evaluate the GLEAMS-Driver modeling, the GLEAMS-Driver modeling is consistent and in some ways remarkably concordant with the monitoring data.

As summarized in Table 10, the GLEAMS-Driver modeling for the small pond, relative to the small stream, leads to consistently higher water contaminations rates (WCRs). This result is not unusual, particularly for relatively persistent pesticides such as imidacloprid and its metabolites. The pesticide in the small pond is removed only by degradation or pond overflow. In the small stream, the pesticide in the water is removed by downstream transport, and the only residual contamination from day-to-day is from the concentration of the pesticide in sediment. Consistent with the approach of estimating exposures for the Most Exposed Individual (Section 3.2.3.1.1), the WCR values used in the risk assessment are based consistently on the modelled concentrations in the small pond.

The modeled surface water concentrations of imidacloprid used in the current risk assessment are summarized in Table 11. These values are based on the concentrations from Table 10 for the small pond rounded to two significant places. The concentrations are specified as water WCRs—i.e., 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. The conversion from µg/L (ppb) to mg/L (ppm) is made because mg/L is the unit of measure used in the EXCEL workbooks for contaminated water exposure scenarios in both the human health and ecological risk assessments.

The only unusual aspect of the derivation of the WCRs involves bark applications. As discussed in Section 2.4.3, the current risk assessment adopts the suggestion from Onken (2009) that 10% of the pesticide nominally applied to tree bark will splash onto the ground or vegetation adjacent to the treated tree. This approach is identical to the approach taken in the Forest Service risk assessment for dinotefuran (SERA 2009b). Thus, the WCRs for bark applications given in Table 11 are taken as one-tenth the corresponding value for foliar applications.

As with all Forest Service risk assessments, the ranges between the lower bounds and upper bounds of WCR values are substantial. For example, the lower bound for peak WCR for a small pond associated with soil injection into clay or loam is below the upper bound by a factor of about 140,000 [0.17 ÷ 0.0000012 = 141,666.67]. As detailed in Appendix 8, Table A8-7, this substantial range is largely attributable to the differences in site conditions—i.e., soil, temperature, and rainfall. Thus, in any application of this risk assessment to a specific project, the water contamination rates from the appropriate appendices and/or site specific simulations using GLEAMS-Driver will provide more relevant estimates of the concentrations of

imidacloprid in surface water, compared with the generic rates summarized in Table 11 and used in the WorksheetMaker workbooks that accompany this risk assessment.

It should be noted that the WCRs used in the current risk assessment are substantially higher than those in the previous Forest Service risk assessment (SERA 2005). For example, the WCRs from the previous risk assessment for foliar application were 0.007 (0.005-0.05) for peak exposures and 0.0007 (0.001-0.001) for longer-term exposures (SERA 2005, Table 3-5). As summarized in Table 11 of the current risk assessment, the WCRs for foliar applications are 0.016 (0.0000012 to 0.17) for peak exposures and 0.0084 (0.0000005 to 0.048) for longer-term exposures. The previous Forest Service risk assessment was conducted prior to the development of GLEAMS-Driver and the higher WCRs values in the current risk assessment may be partially attributed to the differences in the models used. Another and much more important difference involves the treatment of the metabolites of imidacloprid. As discussed in Section 3.2.3.4.3.1, the current risk assessment uses inputs from the most recent risk assessment from U.S. EPA/OPP/EFED (2009a, 2014a) which consider all metabolites containing the 6-chloropyridinyl ring as metabolites of concern. This substantially impacts some of the key estimated half-lives for imidacloprid. Specifically, the previous Forest Service risk assessment used half-lives for imidacloprid (parent compound only) of 40 days in soil and 22 days in water (SERA 2005, Table 3-2). To consider the potential risks associated with exposures to imidacloprid metabolites of concern, the current Forest Service risk assessment (Table 9) used half-lives of 359 (188-660) days for soil and 718 (376-1320) for water. As summarized in the footnotes to Table 9, these estimates are based largely on the most recent applications of PRZM/EXAMS by U.S. EPA/OPP/EFED (2007a).

3.2.3.5. Oral Exposure from Contaminated Fish

Many chemicals may be concentrated or partitioned from water into the tissues of aquatic animals or plants. This process is referred to as bioconcentration. Generally, bioconcentration is measured as the ratio of the concentration in the organism to the concentration in the water. For example, if the concentration in the organism is 5 mg/kg and the concentration in the water is 1 mg/L, the bioconcentration factor (BCF) is 5 L/kg [5 mg/kg ÷ 1 mg/L]. As with most absorption processes, bioconcentration depends initially on the duration of exposure but eventually reaches steady state.

Three sets of exposure scenarios are presented: one set for acute exposures following an accidental spill (Worksheets D08a and D08b), one set for acute exposures based on expected peak concentrations of imidacloprid in water (Worksheets D09c and D09d), and another set for chronic exposures based on estimates of longer-term concentrations in water (Worksheets D09a and D09b). The two worksheets for each set of scenarios are included to account for different consumption rates of caught fish among the general population and subsistence populations. Details of these exposure scenarios are provided in Section 3.2.3.5 of SERA (2014a).

The scenarios associated with consumption of contaminated fish are based on the same concentrations of imidacloprid in water used for the accidental spill scenario (Section 3.2.3.4.1.) and the drinking water exposure estimates (Section 3.2.3.4.6).

Experimental bioconcentration factors are generally required by the EPA as part of the registration process. As summarized in Table 1, the EPA waived the requirement for a

bioconcentration study on imidacloprid because imidacloprid is not expected to bioconcentrate in fish. (U.S. EPA/OPP/EFED 2008a, p. 6). This judgment is supported by the open literature study by Ding et al. (2004) which noted little if any bioconcentration of imidacloprid in zebra fish (Ding et al. 2004). Consequently, the bioconcentration factor used in all exposure assessments involving the consumption of contaminated fish is taken as 1 L/kg—i.e., no bioconcentration. Ashauer et al. (2010) report a BCF of about 7 in an aquatic invertebrate (*Gammarus pulex*). This finding is noted for the sake of completeness but does not impact the exposure assessment for 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 include surface water in which members of the general public might swim. The extent to which this might apply to areas treated with imidacloprid is unclear.

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 D10). 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.

As in the corresponding worker exposure scenario, the 1-hour period of exposure is intended as a unit exposure estimate. In other words, both the absorbed dose and consequently the risk will increase linearly with the duration of exposure, as indicated in Worksheet D10. Thus, a 2-hour exposure would lead to an HQ 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 imidacloprid, however, the HQs for this scenario are far below the level of concern, as discussed further in Section 3.4.3.

As with the exposure scenarios for the consumption of contaminated fish, the scenarios for exposures associated with swimming in contaminated water are based on the peak water concentrations of imidacloprid used to estimate acute exposure to drinking water (Section 3.2.3.4.6).

3.2.3.7. Oral Exposure from Contaminated Vegetation

Although none of the Forest Service applications of imidacloprid will involve crop treatment, they may be conducted on some Forest Service lands by individuals or organizations with authorization from the Forest Service to use the lands for crop cultivation. All such agricultural applications are subject to U.S. EPA/OPP regulatory constraints (e.g., tolerance limits), and exposures associated with agricultural applications are not explicitly considered in Forest Service risk assessments.

For pesticides that may be applied to vegetation, Forest Service risk assessments 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, detailed in Worksheets D03a (fruit) and D03b (vegetation) for acute exposure and Worksheets D04a (fruit) and D04b (vegetation) for chronic exposure. The key inputs for these scenarios are the initial residues on the vegetation and the amount of fruit or vegetation consumed for both acute and chronic scenarios. For chronic scenarios, additional key inputs are the half-live of the pesticide on the fruit or vegetation as well as the period used to estimate the average concentration of the pesticide on vegetation.

In most Forest Service risk assessments, the initial concentration of the pesticide on fruit and vegetation is estimated using the empirical relationships between application rate and concentration on different types of vegetation (Fletcher et al. 1994). These residue rates are summarized in Table 12. The rates provided by Fletcher et al. (1994) are based on a reanalysis of data originally compiled by Hoerger and Kenaga (1972) and represent estimates of pesticide concentration in different types of vegetation (mg chemical/kg vegetation) at a normalized application rate of 1 lb a.i./acre. Although the EPA human health risk assessments do not consider exposure scenarios involving direct spray, the residue rates recommended by Fletcher et al. (1994) are used by U.S. EPA/OPP in their most recent ecological risk assessments of imidacloprid (U.S. EPA/OPP/EFED 2007a, p. 26).

Several studies were conducted to measure the initial concentrations of imidacloprid on vegetation after foliar applications. Some of these studies cannot be used to assess the applicability of the standard residues rates from Fletcher et al. (1994) to imidacloprid because they describe concentrations of imidacloprid in solution, which does not allow for estimates of the application rate in units of lb/acre (Chahil et al. 2014; Juraske et al. 2009; Romeh et al. 2009). Such studies are typically focused on the dissipation of imidacloprid from vegetation rather than assessments of potential human exposure. The standard residue rates from Fletcher et al. (1994) and the available studies on imidacloprid that can be used to assess the applicability of the standard rates to imidacloprid are summarized in Table 12. The experimental rates for imidacloprid are reasonably consistent with the residue rates from Fletcher et al. (1994). For example, the experimental rates for turf of 80-90 mg/kg turf per lb/acre (Lin 1992a; Toll 1994) are well within the ranges of residues for short grass from Fletcher et al. (1997)—i.e., 85 (30-240) mg/kg turf per lb/acre. Similarly, the residue rates on grape leaves of about 26 - 27 mg/kg leaves per lb/acre from Arora et al. (2009) are only modestly below the central estimate for broadleaf vegetation from Fletcher et al. (1997)—i.e., 45 (15 - 135) mg/kg turf per lb/acre. The residue rates for fresh tea shoots from Hou et al. (2013) are somewhat more difficult to interpret because the shoots are described only as … *two leaves and a bud* (p. 1762 of paper). The residue rates of about 130 mg/kg shoot per lb/acre derived from Hou et al. (2013) are most similar to the Fletcher et al. (1997) rates for short grass–i.e., 85 (30 - 240) mg/kg grass per lb/acre—but are also in the upper bound of the range for broadleaf vegetation–i.e., 45 (15-135) mg/kg vegetation per lb/acre. One apparent inconsistency in the residue rates for imidacloprid involves potato foliage, which would generally be classified as broadleaf vegetation. The residue rates of 4 - 8 mg/kg foliage from Lin (1992d) are below the estimated lower bound of 15 mg/kg foliage for broadleaf vegetation from Fletcher et al. (1997). With the exception of the data from Lin (1992d), the residue rates on vegetation derived from data on imidacloprid are reasonably consistent with the rates from Fletcher et al. (1997); moreover, none of the data suggests that the rates from Fletcher et al. (1997) will substantially underestimate exposure. The concordance of pesticide-specific residues rates with the rates from Fletcher et al. (1997) is a common pattern

noted in Forest Service risk assessments. This concordance is reasonable because residue rates should largely depend on application rate and leaf area index. It is reasonable to expect that residue rates will not vary substantially for most pesticides, with the possible exception of highly volatile pesticides (which does not include imidacloprid). Consequently, as in most Forest Service risk assessments, the residues rates from Fletcher et al. (1997) summarized in Table 12 are used to estimate the initial residues of imidacloprid on vegetation.

The only exception to the use of rates in Table 12 involves bark application. As discussed in Section 2.4.3, the current risk assessment assumes an application efficiency of 90% in bark applications with 10% of the applied amount splashed onto the ground or vegetation adjacent to the treated tree. Consequently, the residue rates from Table 12 are reduced by a factor of 10 in Worksheet A01 of Attachment 3, the WorksheetMaker workbook for bark applications.

The half-lives on vegetation used in chronic exposure scenarios are based on the same rates used in GLEAMS-Driver modeling (Table 9)—i.e., from 2 to 10 days with a central estimate of 4.5 days, the approximate geometric mean of the range. As summarized in Table 1, this range of half-lives encompasses several registrant-submitted studies as well as studies in the open literature for a variety of vegetation and fruit. Based on these half-times, the longer-term concentrations of the pesticide in various commodities are detailed in Worksheets B05a (fruit), B05b (broadleaf vegetation), B05c (short grass), and B05d (long grass). Only the worksheets for fruit and broadleaf vegetation are used in the human health risk assessment. All four worksheets are used in the ecological risk assessment (Section 4.2). In all cases, a maximum 90-day time-weighted average concentration is calculated for longer-term exposures. In the context of the human health risk assessment, the use of the 90-day rather than a 365-day time-weighted average is intended to reflect the harvesting of a 1-year supply of fruit and/or vegetation during a single season (i.e., about 90 days) under the assumption that degradation will not occur once the commodity is harvested—e.g., the commodities are placed in cold storage, which would slow the degradation of the pesticide.

As in most Forest Service risk assessments, the amount of fruit consumed per day is taken as 0.00168 - 0.01244 kg fruit/kg bw. These values are taken from U.S. EPA/NCEA (1996, Table 9-3, p. 9-11). The value of 0.00168 fruit/kg bw is the 50^{th} percentile value for the consumption of fruit. The lower 5^{th} percentile is given a zero. Thus, the value of 0.00168 fruit/kg bw is used as both the lower bound and central estimate in the worksheets that accompany this risk assessment. For broadleaf vegetation, the consumption value used in the workbooks is 0.0036 (0.00075-0.01) kg vegetation/kg bw. These values are taken from U.S. EPA/NCEA (1996, Table 9-4, p. 9-12) and are the 50^{th} (5^{th} – 95^{th}) percentiles for the consumption of vegetables. These consumption rates are used for both acute and chronic exposures.

It should be noted that the consumption rates for fruit and vegetables represent total consumption of these commodities from all sources. The assumption that an individual would acquire their total stock of fruits and vegetables from foraging in a forest appears unlikely. While this assumption may be viewed as a consideration of the Most Exposed Individual (Section 3.2.3.1.1), it is possible that the use of these consumption rates may grossly overestimate and distort the risk assessment, even for subsistence populations. Estimates of the amount of fruits and vegetables foraged from forests that are consumed by the general public or subsistence

populations were not identified in the relevant literature. U.S. EPA/NCEA (1996) does provide consumption rates for home-grown fruit and vegetables. For homegrown fruit, the consumption rates are 0.00107 (0.000168 - 0.011) kg fruit/kg bw (U.S. EPA/NCEA 1996, Table 12-8, p. 12-11). For homegrown vegetation, the consumption rates are 0.00111 (0.00011 - 0.0075) kg vegetation/kg bw (U.S. EPA/NCEA 1996, Table 12-13, p. 12-15). Note that the central estimate for the consumption of all fruit is higher than the corresponding estimate for homegrown fruit by a factor of about 1.6 [0.00168 ÷ 0.00107 ≈ 1.57]. Similarly, the central estimate for the consumption of all vegetation is higher than the corresponding estimate for homegrown vegetation by a factor of about 3.2 [0.0036 ÷ 0.00111 ≈ 3.243].

It seems reasonable to suppose that the consumption of homegrown fruit or vegetation generally will be greater than the consumption of fruit or vegetation foraged from a forest. If this supposition has merit, the above comparisons suggest that exposure levels given in the WorksheetMaker workbooks for members of the general public may overestimate likely exposures by factors greater than 2 to 3. Again, the relevant literature does not include statistics for the longer-term consumption of foraged fruit or vegetation from forests. In addition, the more recent update of EPA's Exposure Factors Handbook (U.S. EPA/NCEA 2011) does not address the consumption of homegrown vegetation or the consumption of self-harvested fruit and vegetables by subsistence populations.

As noted above, the U.S. EPA/OPP approach to dietary exposure is very different from the approach used in Forest Service risk assessments. In short, the EPA exposure assessments are based on dietary surveys (i.e., the amounts of different commodities consumed by individuals) and tolerance limits on those commodities. In EPA's most recent human health risk assessment (U.S. EPA/OPP/HED 2010a, Table 5.3.1, p. 24), the daily doses of imidacloprid for women of child-bearing age are estimated at about 0.0262 mg/kg bw/day for acute exposures and 0.00466 mg/kg bw/day for longer-term exposures.

As summarized in Worksheet E03 of Attachment 4 (foliar applications), the acute doses for a young woman consuming both contaminated fruit and vegetation are estimated at about 0.0693 (0.0067-0.6146) mg/kg bw/day. The central estimate from Worksheet E03 is higher than the EPA estimate by a factor of about 2.7 [0.0695 ÷ 0.0262 ≈ 2.65]. As also summarized in Worksheet E03 of Attachment 4 (foliar applications), the longer-term doses for a young woman consuming both contaminated fruit and vegetation are estimated at about 0.0111 (0.0011-0.0983) mg/kg bw/day. For these chronic exposures, central estimate from Worksheet E03 is higher than the EPA estimate by a factor of about 2.4 [0.0111 ÷ 0.00466 ≈ 2.39].

The comparison of central estimates from the current risk assessment to the estimates from EPA is somewhat misleading, however, in that the EPA indicates clearly their estimate, at least for acute exposures, is a 95th percentile estimate and not a central estimate. In this respect, a more reasonable comparison may be made based on the upper bound estimates from Worksheet E03 of Attachment 4 (foliar applications). Based on the upper bound comparisons, the estimates used in the current risk assessment are higher than those given by EPA by factors of about 20—specifically about 23.5 for acute exposures [0.6146 ÷ 0.0262 ≈ 23.5] and 21.1 for longer-term exposures [0.0983 ÷ 0.00466 ≈ 21.1]. Given the very different methods used in the EPA risk

assessment (i.e., tolerance based), compared with the current risk assessment (direct deposition based), the higher estimates in the current risk assessment are understandable.

The above discussion is not to suggest that the estimates of dose given in the current risk assessment are in any way validated by the comparison to the EPA estimates. The upper bound estimates used in the current risk assessment are likely to be conservative and consistent with concern for the Most Exposed Individual (Section 3.2.3.1.1). The extent to which the upper bound estimates given in the current risk assessment may substantially overestimate risk, however, cannot be assessed quantitatively.

3.3. DOSE-RESPONSE ASSESSMENT

3.3.1. Overview

The dose-response assessment for potential human health effects is essentially identical to the dose-response assessment in the previous Forest Service risk assessment (SERA 2005). Following standard practices in Forest Service risk assessments, the acute and chronic RfDs are adopted from the values proposed by U.S. EPA, unless there is a compelling reason to do otherwise. The previous Forest Service risk assessment uses an acute RfD of 0.14 mg/kg bw and a chronic RfD of 0.057 mg/kg bw/day adopted from the EPA human health risk assessment (U.S. EPA/OPP 2003). More recent EPA risk assessments (U.S. EPA/OPP/HED 2007a, 2008a, 2010a) confirm the use of the RfDs from U.S. EPA/OPP (2003).

The open literature on imidacloprid includes a considerable amount of information on the toxicity of imidacloprid to humans and experimental mammals, which has been published since the previous Forest Service risk assessment was conducted. Some of the studies conducted outside the United States could raise concerns for both the acute and chronic RfDs. Although these studies appear to be well conducted and include reasonably complete descriptions, they do not specify the source or purity of the active ingredient, imidacloprid. Furthermore, the studies are inconsistent with the well-documented and extensively reviewed studies from EPA and other studies in the open literature. Consequently, there is no compelling reason to propose a dose-response that deviates from EPA.

The data on the toxicity of imidacloprid to both experimental mammals and humans is sufficient to develop dose-severity relationships. Such relationships can be useful in elaborating the risk characterization, if the acute and chronic RfDs are substantially exceeded. As discussed further in Section 3.4, however, acute and chronic RfDs are not exceeded for the application methods that will be used in Forest Service programs, and the dose-severity relationships are discussed for the sake of completeness.

3.3.2. Acute RfD

U.S. EPA/OPP (2003) derives an acute RfD of 0.14 mg/kg on the basis of an acute LOAEL of 42 mg/kg bw for decreased measures of motor and locomotor activity in female rats using an uncertainty factor of 300 (10 for interspecies variability; 10 for intraspecies variability; and 3 for the use of a LOAEL instead of a NOAEL). The LOAEL is derived from an acute oral neurotoxicity study in which male and female Sprague-Dawley rats were given a single gavage dose of 0, 42, 151 or 307 mg/kg body weight technical grade imidacloprid (Sheets 1994a, MRID 43170301, Appendix 1, Table A1-10). A supplemental study was conducted in which rats were given a single gavage dose of technical-grade imidacloprid at 0 (vehicle control) or 20 mg/kg body weight (Sheets 1994b MRID 43285801, Appendix 1, Table A1-10). No mortality, clinical signs of toxicity, neurological effects, or effects on body weight were observed at 20 mg/kg. This acute RfD is maintained in more recent U.S. EPA/OPP human health risk assessments—i.e., U.S. EPA/OPP/HED (2007a, pp. 29-30) and U.S. EPA/OPP/HED (2010a, p. 7).

U.S. EPA chose to derive the acute RfD on the basis of the LOAEL of 42 mg/kg rather than the NOAEL of 20 mg/kg. Dividing the LOAEL of 42 mg/kg by an uncertainty factor of 300 (3 for NOAEL to LOAEL extrapolation; 10 for interspecies variability; 10 for intraspecies variability), yields the acute RfD of 0.14 mg/kg. Using a NOAEL of 20 mg/kg bw (Sheets 1994b) would

typically entail the use of an uncertainty factor of 100 (10 for interspecies variability; 10 for intraspecies variability) resulting in a slightly higher acute RfD of 0.2 mg/kg bw. The difference between the acute RfD based on the LOAEL (0.14 mg/kg bw) and the alternate approach based on the NOAEL (0.2 mg/kg bw) is insubstantial.

As summarized in Appendix 1, Table A1-1, a standard acute toxicity study with technical grade imidacloprid reports a NOAEL in excess of 50 mg/kg bw (Bomann 1989a, MRID 42055331), and no acute toxicity studies contradict the approach taken by U.S. EPA/OPP/HED in that no other acute studies report LOAELs below the LOAEL of 42 mg/kg bw used by EPA. The U.S. EPA/OPP will sometimes derive acute RfDs based on fetal effects in developmental studies. As summarized in Appendix 1, Table A-4, no developmental toxicity studies submitted to the EPA report LOAELs below the 42 mg/kg bw dose used for the acute RfD.

One developmental study from the open literature (Gawade et al. 2013) reports a LOAEL of 30 mg/kg bw/day based on increases in the incidence of malformations and post-implantation losses (i.e., fetal death) in Wistar rats. This study from the Indian literature does not report the source or purity of the imidacloprid used to dose the animals. In addition, the study reports the incidence of malformations in each dose group but does not report the incidence of the number of litters with malformations. Given the reporting deficiencies in this study and the proximity of the 30 mg/kg bw/day LOAEL to the 42 mg/kg LOAEL used by EPA, there is no basis for arguing the derivation of an alternate acute RfD.

Abou-Donia et al. (2008) conducted a developmental neurotoxicity study in which neurological effects were observed in offspring of Sprague-Dawley rats given a single intraperitoneal dose of 337 mg/kg bw/day technical grade imidacloprid (99.5% purity). This study is consistent with registrant studies reviewed by EPA and does not impact the evaluation of the acute RfD.

3.3.3. Chronic RfD

The U.S. EPA/OPP derived a chronic RfD for imidacloprid of 0.057 mg/kg bw/day (U.S. EPA/OPP 2003), which is maintained in the more recent human health risk assessments by EPA—i.e., U.S. EPA/OPP/HED (2007a, p. 40); U.S. EPA/OPP/HED (2008a, p. 18); and U.S. EPA/OPP/HED (2010a, p. 7). This chronic RfD is somewhat below the Acceptable Daily Intake (ADI) of 0.06 mg/kg bw/day recommended by the European Food Safety Authority (EFSA 2013b).

The RfD from EPA is based on the chronic feeding study in rats conducted by Eiben and Kaliner (1991, MRID 42256331). As summarized in Appendix 1, Table A1-3, this 2-year study involved dietary concentrations of 0, 100, 300, or 900 ppm (95.3% technical grade imidacloprid). No effects were observed at 100 ppm; however, thyroid effects were observed at the two higher concentrations. Based on measured food consumption and body weights, the 100 ppm dietary concentration is equivalent to doses of 5.7 mg/kg/day in male rats and 7.6 mg/kg bw/day in female rats. The EPA selected the lower dose of 5.7 mg/kg bw/day and used an uncertainty factor of 100 to account for inter-species extrapolation (a factor of 10) and intra-species variability (a factor of 10).

As detailed in Appendix 1, Table A-1, the chronic NOAEL of 5.7 mg/kg bw/day is supported by several registrant-submitted studies as well as several subchronic studies from the open literature

which report subchronic NOAELs of 10 mg/kg bw/day by gavage in rats (Bhardwaj et al. 2010; Kapoor et al. 2010, 2011).

The only study of concern in the open literature involves the 90-day LOAEL of 0.5 mg/kg bw/day in the study by (Bal et al. 2012a,b) from the Turkish literature. The 90-day LOAEL is based on decreases in body, testes, and epididymal weights of Wistar rats, with the development of abnormal sperm at doses of up to 8 mg/kg bw/day. Note that the two papers by Bal et al. (2012a,b) are similar in design but appear to be two different studies. This presumption is based on the different body weights for the rats reported in Table 1 of the two publications. Other, albeit small, differences in results are apparent in other tables and figures as well. Although these two studies provide detailed descriptions of the experimental procedures and observations, the source and purity of the imidacloprid is not specified; moreover, it is not clear whether the study used technical grade imidacloprid or a formulation of imidacloprid.

The studies by Bal et al. (2012a,b) are not consistent with the standard multi-generation reproduction study in Wistar rats in which no adverse reproductive effects were noted following dietary exposures to imidacloprid (94.4 - 95.4%) at a dose equivalent to 20 mg/kg bw/day (Suter et al. 1990, MRID 42256340). At much higher levels of exposure—i.e., dietary concentrations of technical imidacloprid at 5000 ppm, equivalent to doses of about 50 mg/kg bw—Bloch (1987, MRID 42256330) observed tubular degeneration in the testes of dogs. These animals, however, had severe signs of neurotoxicity accompanied by weight loss and pathology in several other organs including the pituitary.

While the studies by Bal et al. (2012a,b) are a concern, the lack of corroborating studies by a separate group of investigators and the uncertainty concerning the source, purity, and composition of the imidacloprid (i.e., technical versus formulation) preclude a reconsideration of the carefully reviewed and well-documented chronic RfD from the U.S. EPA/OPP.

3.3.4. Surrogate RfD for Occupational Exposures

The U.S. EPA/OPP will sometimes derive separate toxicity values, typically expressed as a NOAEL with a desired Margin of Exposure (MOE), which are applied to worker exposures. These toxicity values typically are between the acute and chronic RfDs, reflecting the fact that workers are repeatedly exposed to the pesticide but that the duration of the exposure is less than lifetime.

As summarized in the EPA's most recent human health risk assessment (U.S. EPA/OPP/HED 2010a, p. 7), the EPA proposes an oral NOAEL of 10 mg/kg bw/day with a MOE of 100 and no additional FQPA safety factor for intermediate short-term exposures to imidacloprid, which is applied to some occupational exposures. This short-term toxicity value is functionally equivalent to a short-term RfD of 0.1 mg/kg bw/day. As discussed in Section 3.3.2, this short-term toxicity value is similar to the acute (single dose) RfD of 0.14 mg/kg bw. Likewise, the same EPA document uses an oral dose of 9.3 mg/kg bw/day (Sheets and Hamilton 1994, MRID 43286401) with a MOE of 100 for intermediate exposures involving oral, dermal, and inhalation exposures (U.S. EPA/OPP/HED 2010a, p. 7). This toxicity value is equivalent to an intermediate RfD of 0.093 mg/kg bw/day. Again, this intermediate toxicity value is close to the acute RfD of 0.14 mg/kg bw/day.

As discussed further in Section 3.4.2 (risk characterization for workers), risks to workers are characterized with both the acute RfD of 0.14 mg/kg bw/day as well as the chronic RfD of 0.057 mg/kg bw/day. Given the minor differences between the acute RfD and the toxicity values for short-term and intermediate exposures, the latter two toxicity values are not used quantitatively in the current risk assessment.

3.3.5. Dose-Severity Relationships

Forest Service risk assessments typically consider dose-severity relationships to elaborate concerns for excursions above the acute or chronic RfD. As discussed further in Section 3.4, considerations of dose-severity relationships are not critical in the current risk assessment because exposures in workers and members of the general public do not exceed the RfDs for the application methods supported for Forest Service programs—i.e., tree injection, soil injection, and bark applications—and the hazard quotients for broadcast applications result in only modest excursions about the RfDs.

Dose-severity relationships can often be crudely characterized in terms of the ratio of the LOAEL to the NOAEL on which the RfD is based. For example, the chronic RfD is based on a NOAEL of 5.7 mg/kg bw/day with a corresponding LOAEL for thyroid damage of 16.9 mg/kg bw/day for male rats in the chronic feeding study by Eiben and Kaliner (1991, MRID 42256331). Based on this relationship, a hazard quotient of about 3 [$16.9 \div 5.7 \approx 2.964$] would be a clear cause for concern.

This approach cannot be taken directly for the acute RfD. As discussed in Section 3.3.2, the acute RfD is based on a LOAEL from a study which did not identify a NOAEL—i.e., a LOAEL of 42 mg/kg bw based on the lowest dose in the study by Sheets (1994a, MRID 43170301). In deriving the acute RfD, however, U.S. EPA/OPP (2003) explicitly uses an uncertainty factor of 3 to approximate a NOAEL from a LOAEL. It should be noted that the factor of 3 in the relationship of a LOAEL to a NOAEL is common and reflects the fact that many toxicology studies are designed so that the doses increase by a factor of about 3. Since NOAELs and LOAELs are simply experimental doses, the factor of 3 for the ratio of the LOAEL to the NOAEL is built into the design of many toxicity studies.

The data on imidacloprid are somewhat unusual because of the considerable number of poisoning reports. As discussed in Section 3.1.4.2, doses of about 75 - 140 mg/kg bw are typically associated with signs of toxicity but not mortality, so long as the individual receives proper supportive medical care. The lower bound is based on the case report of David et al. (2004) in which a dose of 76 mg/kg bw apparently was not associated with severe signs of toxicity or extensive medical care. Estimated doses of about 180 to over 1000 mg/kg bw are typically associated with mortality, despite aggressive supportive medical care.

Taking 14 mg/kg day as the NOAEL approximated in the derivation of the acute RfD—i.e., the LOAEL of 42 mg/kg bw ÷ 3—the minimal toxic dose of 76 mg/kg bw would correspond to an HQ of about 5 [$76 \div 14 \approx 5.429$]. The upper bound of survivable doses —i.e., 140 mg/kg bw – would correspond to an HQ of about 10. Taking 590 mg/kg bw/day as the mid-point of lethal doses, the HQ associated with lethality would be about 42 [$590 \div 14 \approx 42.143$]. These comparisons, however, do not consider the uncertainty factor of 100—i.e., factors of 10 for interspecies and intraspecies variability. Considering this uncertainty factor, the minimally toxic

HQ would be about 500, the HQ associated with serious toxicity would be about 1000, and the HQ associated with likely mortality would be about 4200. These relationships are noted only for the sake of completeness. As discussed further in Section 3.4, none of the HQs for humans approach the HQ of 500 that would be associated with well-documented toxicity (albeit minimal) in humans.

3.4. RISK CHARACTERIZATION

3.4.1. Overview

The risk characterization for the potential human health effects associated with exposure to imidacloprid is similar to the previous Forest Service risk assessment (SERA 2005). This similarity is to be expected, since the dose-response assessment from EPA is essentially unchanged, and, as with the previous Forest Service risk assessment, the EPA's dose-response assessment is adopted without modification.

The exposure assessment for both workers and the general public is considerably more elaborate than the previous risk assessment, based on updated methods for quantifying exposures to both workers and members of the general public (SERA 2014a,b). These elaborations support the previous risk assessment in that no substantial risks to workers or members of the general public are identified for tree injection, soil injection, and bark applications—i.e., the applications that may be used in Forest Service programs and are explicitly supported in the current risk assessment. Even foliar applications, which are not explicitly encompassed by the current risk assessment, do not lead to HQs that are markedly exceed the level of concern (HQ=1).

Notwithstanding the largely benign risk characterization for imidacloprid, absolute safety cannot be guaranteed in any risk assessment. Some accidental exposures, particularly wearing contaminated gloves for a prolonged period of time, are a concern. This concern, however, is common in the use of virtually any pesticide, particularly neurotoxins. So long as proper worker protection is used and accidental exposures to imidacloprid are avoided, there is no basis for asserting that the use of imidacloprid in Forest Service programs will pose substantial risks to workers or members of the general public.

The Forest Service has indicated that imidacloprid may be used in mixtures with dinotefuran. Both of these pesticides are neonicotinoids and appear to act through the same or very similar mechanisms. In programs involving the use of imidacloprid and dinotefuran, it is advisable and would be prudent to consider the potential risks posed by imidacloprid as additive with the risks posed by dinotefuran.

3.4.2. Workers

A summary the HQs for workers is given in Table 13. HQs are provided for each of the accidental exposure scenarios (Section 3.2.2.2) as well as the general exposure scenarios (Section 3.2.2.1). The HQs for the accidental exposure scenarios are based on the acute RfD of 0.14 mg/kg (Section 3.3.2), and HQs for the general exposure scenarios are based on both the acute RfD as well as the chronic RfD of 0.057 mg/kg/day (Section 3.3.3).

None of the HQs for general exposure scenarios involving application methods to be used by the Forest Service—i.e., tree and soil injections and bark application—exceed the level of concern (HQ=1). The exposure assessments for tree injection (Section 3.2.2.1.1) and soil injection (Section 3.2.2.1.2) are deposition-based using the U.S. EPA's Pesticide Handlers Exposure Database (PHED) rather than absorption-based methods used in most Forest Service risk assessments (SERA 2014b). While there are uncertainties in the use of PHED rates for these exposure scenarios, the upper bounds of the chronic HQs are below the level of concern by a factor of 5,000 for tree injection [1÷0.0002] and a factor of 250 [1÷0.004] for soil injection.

Thus, the exposure assessments would need to be grossly in error to alter the risk characterization.

The upper bound of the chronic HQ for bark applications is 0.6, approaching the level of concern. This upper bound HQ, however, is based on the upper 95% prediction interval for a well-designed and well-documented study involving bark applications, as detailed in SERA (2014b). Also, as also detailed in SERA (2014b), the use of upper bound prediction intervals is a conservative approach that is not likely to underestimate worker exposures. While absolute safety can never be guaranteed, the wide margin between the RfDs and the well-documented levels of exposure that are toxic to humans (Section 3.3.5) considerably diminish the concern for the safety of workers involved in bark applications.

While foliar applications are encompassed by the current risk assessment, the upper bound chronic HQ is 1.7, which is only modestly above the level of concern (HQ=1) and below the HQ of 3 for which adverse effects would be a clear concern (Section 3.3.5).

The upper bound HQs for accidental exposure scenarios are also below the level of concern, except for the scenarios in which workers involved in tree injection wear contaminated gloves for 1 hour. As noted in Section 3.2.2.2 and discussed in further detail in Section 3.2.3.4.1, solutions of imidacloprid used for tree injection are much more concentrated than solutions used in other application methods. During tree injection, particular care is warranted to avoid contamination of the skin with concentrated solutions of imidacloprid. While the upper bound HQ of 1.1 is not alarming, the contaminated glove scenario is a unit risk scenario in that the HQ is based on an exposure period of 1 hour (Section 3.2.2.2). Wearing contaminated gloves for prolonged periods leads to exposures that might be hazardous. This caveat is also applicable to soil injection and bark application. The contaminated glove scenarios for both of these application methods approach a level of concern for a 1-hour exposure (HQ=0.9).

3.4.3. General Public

The HQs for members of the general public are summarized in Worksheet E04 of the attachments to this risk assessment. Selected HQs, specifically those that approach or exceed the level of concern (HQ=1) are summarized in Table 14.

No HQs are given in Table 14 for tree injection. As detailed in Worksheet E04 of Attachment 1 (the WorksheetMaker workbook for tree injection), the highest HQ for members of the general public is 0.02, the upper bound HQ for the accidental spill of imidacloprid into a small pond. This HQ is below the level of concern by a factor of 50.

For soil injection, the highest HQ is 1.2, the upper bound of the HQ associated with the accidental spill of imidacloprid into a small pond.

For bark application and foliar application, the highest HQ is 4. For bark applications, this is the upper bound HQ associated with the accidental direct spray of a naked child. For foliar applications, the HQ of 4 is the upper bound of the non-accidental exposure scenarios associated with the consumption of contaminated vegetation.

The upper bound HQ of 4 for the consumption of contaminated vegetation following foliar spray would be a concern. As discussed in Section 3.3.5 (Dose-Severity Relationships), the HQ of 4 is modestly about the HQ of 3 which would raise concern for potential adverse effects. This HQ does not have a practical impact on the current risk assessment because the Forest Service will not use imidacloprid in foliar applications.

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 imidacloprid.

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 imidacloprid used in Forest Service programs.

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

As discussed in detail in Sections 3.1.14 (Inerts and Adjuvants) and 3.1.15 (Impurities and Metabolites), imidacloprid formulations contain inert components, and the metabolism of imidacloprid may involve the formation of a 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. As noted specifically in several sections of the hazard identification (Section 3.1), the recent literature from outside of the United States suggests that some imidacloprid formulations may be more toxic than technical grade imidacloprid. The extent to which this information is relevant to U.S. formulations cannot be assessed with confidence.

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. Notwithstanding this limitation and as discussed in Section 3.1.16, some pesticide adjuvants with inhibit cytochrome P450 isozymes (e.g., piperonyl butoxide) would likely enhance the toxicity of imidacloprid. While the interaction with piperonyl butoxide has not been demonstrated in mammals, this interaction has been documented in insects (Puinean et al. 2010), as discussed further in Section 4.1.2.4.1. Antioxidants are not generally used as adjuvants; nonetheless, it is worth noting that antioxidants may reduce the toxicity of imidacloprid.

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 imidacloprid. 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. The most recent human health risk assessment on imidacloprid states:

> *Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to imidacloprid and any other substances and imidacloprid 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 imidacloprid has a common mechanism of toxicity with other substances.*
>
> U.S. EPA/OPP/HED 2010a, p. 40

This language is essentially standard in many pesticide risk assessments from the U.S. EPA.

This language does not seem justified for imidacloprid. Imidacloprid is a neonicotinoid, and it seems reasonable to suggest that the mechanism of action of imidacloprid, at least with respect to neurotoxicity, is likely to be similar to that of other neonicotinoids (Section 3.1.2).

This observation may be particularly important with respect to dinotefuran (SERA 2009a). As noted in Section 2.3.3, the Forest Service (e.g., McCullough et al. 2013) indicated that mixtures of imidacloprid and dinotefuran may be applied to hemlock for the control of the hemlock wooly adelgid (HWA). In any program in which imidacloprid and dinotefuran are applied as a mixture or applications of imidacloprid and dinotefuran are made over a short period of time, it would be advisable for the Forest Service to employ a utility in WorksheetMaker (SERA 2011a, Section 3.4.3) that allows for combining HQs for different pesticides. In the case of imidacloprid and dinotefuran (or any other neonicotinoid), the assumption of dose-addition would be appropriate.

3.4.7. Note on Treatment of Maple Trees

Some species of maple may be treated with imidacloprid for the control of the Asian longhorned beetle, *Anoplophora glabripennis* (Kreutzweiser et al. 2008a; Ugine et al. 2011, 2012, 2013). Sugar maple trees are commonly tapped as a source of maple syrup. As discussed further in Section 4.2.3.3.3.1 and summarized in Table 30, concentrations of imidacloprid in maple foliage are much higher than the concentrations of imidacloprid in the foliage of ash or hemlock. It is only modestly speculative to suggest that the injection of sugar maple would lead to contamination of the maple sap with imidacloprid. It seems reasonable to suggest concern for the consumption of maple syrup derived from maple trees treated with imidacloprid. The product labels for IMA-jet specifically notes that imidacloprid should not be used to treat … *syrup-producing sugar maples where sap is harvested*. This cautionary language is appropriate.

4. ECOLOGICAL RISK ASSESSMENT

4.1. HAZARD IDENTIFICATION

4.1.1. Overview

Imidacloprid is an effective insecticide that is selective to insects and other invertebrates. In general, imidacloprid has a relatively low toxicity to vertebrates. For example, acute LD_{50} values in mice are on the order of 130 - 150 mg/kg bw, while the average oral LD_{50} value in the honeybee is about 0.2 mg/kg bw—i.e., bees are more sensitive than mice in terms of acute oral toxicity by factors of about 650 - 750. For aquatic organisms, differences in the toxicity of imidacloprid to vertebrates and invertebrates are more substantial. The lowest acute LC_{50} value in fish is 163 mg/L, while the average EC_{50} value in the most sensitive species of aquatic invertebrates is about 0.0013 mg/L—i.e., the difference in toxicity is a factor of over 125,000 [163 mg/L ÷ 0.0013 mg/L ≈ 125,385]. As discussed in Section 3.1.2, the differential toxicity of imidacloprid in vertebrates and invertebrates appears to reflect differences in the affinity of imidacloprid to the nAChR receptors in these animals. In addition, differences in the binding of imidacloprid to the nAChR receptor appear to account for some of the variability in the toxicity of imidacloprid to different populations of terrestrial invertebrates of the same species. Reflecting the low toxicity of imidacloprid to vertebrates, the EPA classifies imidacloprid as moderately toxic in mammals, moderately toxic to practically nontoxic in birds, and practically nontoxic in fish. Similarly, the EPA classifies imidacloprid as "*very highly toxic*" to bees and aquatic invertebrates (U.S. EPA/OPP/EFED 2008a, p. 10). These classifications are clearly justified.

For terrestrial invertebrates, the most active area of research is focused on the potential effects of imidacloprid on the honeybee and specifically the relationship of imidacloprid exposure to colony collapse disorder. While it is beyond the scope of the current risk assessment to assess the multiple stressors that may be associated with colony collapse disorder, standard laboratory toxicity studies as well as mesocosm and field studies on imidacloprid clearly indicate that extremely low levels of exposure can be lethal to bees. As noted in a general review of the many factors that might be associated with colony collapse disorder, neonicotinoid pesticides may be a contributing factor but are not likely to be a sole factor in colony collapse disorder (Staveley et al. 2014). With respect to imidacloprid, three studies conducted at the level of the bee hive demonstrate that long-term (≈91 day) exposures to concentrations as low as 20 ppb of imidacloprid in sucrose can lead to hive death during overwintering (Lu et al. 2012, 2014). In an independent study, colony death was not observed at concentrations of 0.5 and 5 ppb following somewhat shorter-term exposures of about 32 days (Faucon et al. 2005). In addition, the more recent study by Dively et al. (2015) confirms the observations of both the 5 ppb no-effect level noted by Faucon et al. (2005) and the 20 ppb effects level noted by Lu et al. (2012). All three of these studies were conducted independently by different groups of investigators, and the confirming study by Dively et al. (2015) was funded by the USDA Agricultural Research Service.

Although the effect of imidacloprid on bees has received substantial attention, the literature regarding the effect of imidacloprid on aquatic invertebrates is equally substantial and more detailed, at least in terms of the number of species on which data are available. While imidacloprid is generally more toxic to aquatic invertebrates than to fish, there are considerable

variations in sensitivity among different groups of aquatic invertebrates, spanning a factor of over 250,000. The Ephemeroptera, Ostracoda, Diptera, and Hemiptera are among the more sensitive groups of aquatic invertebrates. Bivalves, most species of Cladocera and *Artemia* are among the least sensitive groups of aquatic invertebrates.

Despite the extensive data on imidacloprid, toxicity data for some groups of organisms are quite limited. Specifically, there is little information regarding the toxicity of imidacloprid to reptiles and terrestrial-phase amphibians.

4.1.2. Terrestrial Organisms

4.1.2.1. Mammals

The toxicity studies used to assess the potential hazards of imidacloprid to humans (Section 3.1 and Appendix 1) are applicable to the risk assessment for mammalian wildlife. As summarized in Section 3.1, the mechanism of action of imidacloprid as a nicotinic acetylcholinesterase agonist has been well studied. Neurotoxic effects are characteristic of acute, high-dose exposures. The most sensitive adverse effects (i.e., effects occurring at the lowest doses) involve decreases in body weight and effects on the thyroid. The available literature on imidacloprid does not include field studies to investigate its impact on mammalian wildlife.

While human health risk assessments typically focus on the most sensitive species, the ecological risk assessment is concerned with systematic differences in toxicity among different groups of mammals. The available acute toxicity data on imidacloprid are not sufficient to quantify differences in species sensitivity; however, they suggest that smaller mammals may be somewhat more sensitive than larger mammals. This supposition is based on the acute LD_{50} values for technical grade imidacloprid in mice, which range from about 130 to 150 mg/kg bw (Bomann 1989b; El-Gendy et al. 2010), and the modestly higher LD_{50} values for rats, which range from 424 to 475 mg/kg bw (Bomann 1989a). The supposition that larger animals are less sensitive than smaller mammals in acute exposures to imidacloprid is supported, albeit modestly, by the estimates of nonlethal doses of imidacloprid in humans, which can range up to 1000 mg/kg bw. The data on humans, however, are only weakly supportive of the supposition because they are based on poisoning cases in which aggressive supportive care was given following poisoning (Section 3.1.4.2). No acute toxicity data are available on canids. The chronic toxicity data on imidacloprid do not suggest that smaller mammals are more sensitive than larger mammals to imidacloprid. LOAELs are similar in mice (about 66 mg/kg bw/day based on reduced body weight, Watta-Gebert 1991a), rats (about 50-70 mg/kg bw/day based on body weight, Eiben and Kaliner 1991), and dogs (about 40-70 mg/kg bw/day based on liver toxicity, Allen et al. 1989).

In the absence of clear, well-documented, and consistent differences in toxicity among different groups of mammals, separate dose-response assessments for different groups of mammals are not warranted, as discussed further in Section 4.3.2.1.

4.1.2.2. Birds

Avian studies on the effects of imidacloprid are summarized in Appendix 2. These studies included acute gavage (Table A2-1), acute dietary (Table A2-2), reproduction (Table A2-2), and subchronic toxicity (Table A-4) exposures. In addition, there are several studies focusing on feeding aversion (Table A2-5) and two field studies (Table A2-6).

4.1.2.2.1. Acute Exposure

Based on acute gavage studies, birds appear to be somewhat more sensitive than mammals. As discussed in Section 4.1.2.1, acute LD_{50} values for technical grade imidacloprid in mice and rats are in the range of about 130 - 425 mg/kg bw. As summarized in Appendix 2, Table A-2, acute LD_{50} values for technical grade imidacloprid in birds range from about 25 to 152 mg/kg bw. All of these LD_{50} values are from registrant-submitted studies, except for the LD_{50} of 50 mg/kg bw for chickens reported in Balani et al. (2011), a study from the Indian literature.

Most LD_{50} values for birds are in the range of 25 - 50 mg a.i./kg bw. The only exception is the reported LD_{50} of 152 (103 - 227) mg/kg bw for bobwhite quail from the study by Toll (1990a, MRID 42055308). Based on the reported confidence intervals, bobwhite quail are significantly less sensitive than Japanese quail—i.e., the LD_{50} of 31 (22-50) mg/kg bw from Grau 1988b, MRID 43310401). Because these studies were not matched—i.e., conducted at the same time under comparable conditions—the assessment of the significance of the differences using confidence intervals may be specious. U.S. EPA/OPP/EFED (2008a, p. 10) characterizes imidacloprid as "Moderately Toxic" to birds, based on the LD_{50} of 152 mg a.i./kg bw from Toll (1990a, MRID 42055308).

Balani et al. (2011) cite 50 mg/kg bw as the "*apparent LD_{50}*" but do not describe any details of an acute LD_{50} study. As discussed below, the Balani et al. (2011) study focuses on sublethal effects, so perhaps the "*apparent LD_{50}*" was adopted from the literature on imidacloprid simply as a rationale for the sublethal doses used in this study. Like many of the studies conducted outside of the United States, Balani et al. (2011) do not report the source and purity of imidacloprid or whether the test material was technical grade imidacloprid or an imidacloprid formulation.

Only one toxicity study clearly involving a formulation has been identified—i.e., the acute gavage study by Stafford (1991, MRID 42055309) involving a 2.5% granular formulation. As discussed in Section 3.1.4.1, imidacloprid formulations appear to be less toxic than technical grade imidacloprid, when doses are expressed as mg a.i./kg bw. Nonetheless, in the study by Stafford (1991, MRID 42055309), the reported oral LD_{50} of 41 mg a.i./kg bw is within the range of LD_{50} values for technical grade imidacloprid.

As summarized in Appendix 2, Table A2-2, acute dietary studies were conducted in bobwhite quail (Toll 1990b, MRID 42055310), Japanese quail (Grau 1994a, MRID 43310402), and mallard ducks (Toll 1991a, MRID 42055311). Consistent with the acute gavage studies noted above, Japanese quail (100% mortality at 625 ppm) appear to be more sensitive than bobwhite quail (LC_{50} of 1536 ppm). Based on the dietary LC_{50} of 1536 ppm in bobwhite quail (Toll 1990b, MRID 42055310), U.S. EPA/OPP/EFED (2008a, p. 10) characterizes imidacloprid as "*…practically non-toxic to birds on a subacute level*".

Mallards appear to be less sensitive than quail (LC_{50} >4,797 ppm). Food consumption and body weight data are not available for these studies. As indicated in a previous Forest Service risk assessment for which both body weights and food consumption rates in acute dietary studies were available for quail and mallards (SERA 2007), approximate food consumption rates in acute dietary studies are about 0.4 kg food/kg bw for mallards and 0.3 kg food/kg bw for quail. These food consumption rates are from standard studies using very young birds. Using the

consumption value of 0.3 kg food/kg bw for quail, the LC_{50} of 1536 ppm from Toll (1990b) (MRID 42055310) corresponds to an LC_{50} dose of about 426 mg a.i./kg bw. This toxicity value is somewhat lower than the gavage LD_{50} of 152 mg/kg bw for bobwhite quail reported by Toll (1990a, MRID 42055308). This pattern is common in toxicity studies in both birds and mammals. Acute gavage studies generally lead to higher peak body burdens than acute dietary studies. An issue with this comparison, however, is the lack of data on food consumption from the dietary study. As discussed below (Section 4.1.2.2.4), feeding aversion studies indicate that birds may avoid feeding on materials contaminated with imidacloprid.

4.1.2.2.2. Standard Reproduction Studies

The U.S. EPA/OPP typically requires reproduction studies in both ducks and quail. These studies must provide all raw data to the EPA and follow GLP (Good Laboratory Practices) standards. As summarized in Appendix 2, Table A2-3, one reproduction study is available in bobwhite quail (Toll 1991b, MRID 42055312) and three studies are available in mallard ducks (Toll 1991c, MRID 42055313; Hancock 1994b, MRID 43466501; Stafford 1992, MRID 42480502).

Based on NOAECs, imidacloprid is somewhat more toxic to quail (NOAEC=36 ppm from Toll 1991b) than to mallards (NOAEC = 125 ppm from Toll 1991c).

The NOAEC of 36 ppm in quail is associated with a decrease in egg shell thickness at 61 ppm. Although mortality was observed in some parents at 61 ppm, it was not attributed to treatment and was not observed in adults at higher concentrations (up to 243 ppm). The only other adverse effect observed in adult quail was a significant reduction in body weight in the absence of decreased food consumption, which occurred at 243 ppm. Thus, the effect on egg shell thickness at 61 ppm occurred in the absence of compound-related toxicity in adults. In quail offspring, the only other adverse effect observed at 61 ppm was a decrease in hatchling body weight.

Hancock (1994b) reports no effects in mallards at dietary concentrations of up to 47 ppm. Toll (1991c, MRID 42055313) also reports no effects at dietary concentrations of 64 and 125 ppm; however, at 234 ppm, the highest concentration tested, the adverse effects include a decrease in egg production, a decrease in the percentage of normal hatchlings, and a decrease in hatchling survival. The study by Stafford (1992, MRID 42480502) in mallards appears to be a follow-on study to Toll (1991c, MRID 42055313) in that the study was conducted at the same facility. Unlike the earlier study by Toll (1991c), Stafford (1992) reports a decrease in egg shell thickness and a statistically significant increase in the number of cracked eggs at 128 ppm. U.S. EPA/OPP/EFED appears to have reevaluated the Stafford (1992) study and classifies 61 ppm as a LOAEC for egg shell thinning with a NOAEC of 47 ppm (U.S. EPA/OPP/EFED 2007a, p. 39).

4.1.2.2.3. Other Repeated Dose Studies

As summarized in Appendix 2, Table A2-4, subchronic toxicity studies were conducted in white leghorn chickens (Balani et al. 2011) and Red-legged partridges (Lopez-Antia et al. 2013, 2015). The gavage study by Balani et al. (2011) was conducted in India and does not specify the source of the imidacloprid or whether the test material was technical grade imidacloprid or an imidacloprid formulation. The dietary studies by Lopez-Antia et al. (2013, 2015) were conducted in Spain and used Escocet, a 35% a.i. w/v from Bayer CropScience. Escocet is a

liquid formulation of imidacloprid available in Spain but not in the United States (http://www.bayercropscience.es/BCSWeb/www/BCS_ES_Internet.nsf/id/ES_Escocet?open&ccm=200010) .

The studies by Lopez-Antia et al. (2013, 2015) were both conducted at relatively high doses over short periods of time. In Lopez-Antia et al. (2013), the partridges (breeding pairs) were dosed at 31.9 and 53.4 mg a.i./kg bw (based on measured body weights and food consumption) for a period of 10 days. At the higher dose, more than half of the birds died. Although there are no reported acute LD_{50} values for partridge, the higher dose is similar to acute LD_{50} values for several species of birds (Section 4.1.2.2.1). At the lower dose, signs of toxicity included changes in blood chemistry, a decrease in egg shell thickness, and an impaired cellular immune response (characterized as a decrease response in the phytohemagglutinin skin test—i.e., measuring swelling in response to an injection of phytohemagglutinin). The phytohemagglutinin skin test is a common assay for cellular immune response in birds and is also used with amphibians (Brown et al. 2011). The decrease in egg shell thickness was noted only at the lower dose. Lopez-Antia et al. (2013) do not discuss the failure to observe a dose-response relationship for egg shell thickness. The high dose group involved only two surviving breeding pairs (Table 3, p. 133 of Lopez-Antia et al. 2013). Possibly, the failure to observe a decrease in egg shell thickness at the higher dose was due to the relative insensitivity of the surviving birds to imidacloprid. Among several measures of clinical chemistry, no effects were noted on blood glucose.

The Lopez-Antia et al. (2015) study also involves relatively high doses, 8.8 and 44 mg/kg bw (based on measured body weights and food consumption). The study was designed to dose the partridges initially in November for 25 days with a second dosing in the following March for 10 days. All birds in the high dose group died during the initial dosing period with a mean survival time of 12.7 days for males and 6.7 days for females. Again, this mortality in the high dose group is consistent with the acute oral toxicity studies in birds (Section 4.1.2.2.1). Adverse effects in partridges in the low dose groups included a significant decrease in body weight, a significant reduction in clutch size, and a significant increase in time to first egg laying. As with the earlier study, an impaired cellular immune response was indicated by increased swelling in the phytohemagglutinin skin test.

Unlike the studies by Lopez-Antia et al. (2013, 2015), the study by Balani et al. (2011) used low doses of 1.25, 1.67, or 2.5 mg a.i./kg bw/day by gavage for 28 days, and observed no overt signs of toxicity. In the high dose-group only, Balani et al. (2011) observed a significant decrease in blood glucose. As discussed in Section 3.1, a decrease in blood glucose in rats was noted by Eiben (1988a, 42256334), but this is not an effect commonly observed in mammals. Although Balani et al. (2011) discuss the effect of imidacloprid on the thyroid, and thyroid disorders can impact blood glucose, there is no discussion of thyroid effects in the chickens used in the bioassays. As noted above, no effect on blood glucose was noted in partridges dosed at higher levels (31.9 and 53.4 mg/kg bw/day) in the study by Lopez-Antia et al. (2013). Consistent with mammalian studies, Balani et al. (2011) report biochemical changes consistent with liver toxicity.

The supposition by Balani et al. (2011) that the decrease in blood glucose may have been associated with a potential effect on the thyroid is supported by the more recent study by Pandey and Mohanty (2015) who noted pathological changes in the thyroid and changes in thyroid

hormones at a dose of about 0.15 mg a.i./kg bw for 30 day (see Appendix 2, Table A2-4 for details). As discussed in Section 3.1.8, imidacloprid is clearly toxic to the thyroid of mammals. Based on the study by study by Pandey and Mohanty (2015), this also appears to be case in birds.

4.1.2.2.4. Feeding Aversion

As summarized in Appendix 2, Table A2-6, several registrant-submitted studies suggest that birds avoid feeding on grains contaminated with imidacloprid, so long as there is access to an uncontaminated food source, as demonstrated in blackbirds (Avery et al. 1993a,b MRID 42856201), doves (Hancock 1994a, MRID 43197501), and sparrows (Hancock 1994a, MRID 43197501). In the open literature, feeding aversion was demonstrated in studies with partridges (Lopez-Antia et al. 2014).

Food aversion studies are designed to give birds or other animals a choice of foods to assess the possible avoidance of contaminated foods (Mineau and Palmer 2013). In the case of broadcast applications, such studies may not be good predictors of the potential for birds to consume contaminated foods (see discussion by Mineau and Palmer 2013, p. 34-35). As discussed in Section 2, Forest Service programs will not involve broadcast applications; thus, the concerns raised by Mineau and Palmer (2013) may not have a substantial impact on the assessment of Forest Service programs.

A somewhat greater concern with the available food aversion studies involves the concentrations tested. As summarized in Appendix 2, Table A2-6, the concentrations used in food aversion studies range from about 225 to 5000 mg a.i./kg food. As summarized in Worksheets B05a-B05d of Attachment 4 (broadcast applications), the upper bounds of expected peak concentrations of imidacloprid on commodities range from about 6 mg a.i./kg food (fruit in Worksheet B05a) to 240 mg a.i./kg food (short grass in Worksheet B05c). In the anticipated use of imidacloprid by the Forest Service in bark applications, the concentrations are lower by a factor of 10 (Section 3.2.3.7 and Section 4.2.2.3).

The available studies on food avoidance do not address the low concentrations of imidacloprid anticipated after bark applications. This data gap is a concern, because the study by Avery et al. (1993a,b, MRID 42856201) clearly demonstrates that food avoidance is concentration dependent—i.e., no avoidance at 278 mg a.i./kg food with avoidance at 833 and 2500 mg a.i./kg food. For the purpose of the hazard identification, the available information on food avoidance in birds does not diminish concern for imidacloprid exposures likely to be associated with bark applications in Forest Service programs.

4.1.2.2.5. Field Studies

As summarized in Appendix 2, Table A2-6, only two studies which might be classified as field studies are available on imidacloprid—i.e., Toll and Fischer (1993, MRID 42737101) and Hallman et al. (2014).

The registrant-submitted study by Toll and Fischer (1993, MRID 42737101) is a relatively small-scale, but well-controlled, study in which populations of wild birds were monitored at golf courses treated with imidacloprid at a rate of 0.5 lb a.i./acre as well as at golf courses not treated with imidacloprid. The duration of the study was only 5 - 7 days. While no overt effects on

birds were noted, the design of this study does not seem particularly sensitive or powerful because only survival was assayed and for only a brief period of time.

The study by Hallman et al. (2014) is analogous to an epidemiology study in that the paper involves a survey of bird populations over a prolonged period (1994 - 2010) and attempts to demonstrate that the use of imidacloprid in a large study area (i.e., the Netherlands) is associated with a decline in bird populations. The paper is detailed, well-reported, and uses appropriate statistical methods to account for multiple comparisons. The authors assert a high degree of confidence in concluding that imidacloprid had an adverse impact on insectivorous bird populations in The Netherlands: *At imidacloprid concentrations of more than 20 nanograms per litre, bird populations tended to decline by 3.5 per cent on average annually.* The authors go on to note that the decreases in the populations of insectivorous birds are secondary to impacts on invertebrate populations, rather than a primary effect from the toxicity of imidacloprid to birds. In some respects, this conclusion is a tautology: If applications of imidacloprid are sufficient to reduce the populations of insects, a secondary effect on populations of birds that eat insects seems reasonable, if not inevitable.

As with many epidemiology studies on human populations, the ability of a study such as that of Hallman et al. (2014) to demonstrate causality is limited. As noted in the discussion by Hallman et al. (2014) bird populations have been declining in Europe for several decades—i.e., prior to the introduction and widespread use of imidacloprid. Hallman et al. (2014) demonstrate associations between imidacloprid exposures and declines in bird populations; however this single study does not offer a compelling basis for reasoning that imidacloprid is the primary or even significant cause of the decline in bird populations. This assertion is not intended to be dismissive of the concerns raised by Hallman et al. (2014). As detailed at some length by Mineau and coworkers (Mineau and Whiteside 2013; Mineau and Palmer 2013), there is an emerging body of literature and data indicating that increasing levels of pesticides over time may be associated with adverse effects on bird populations. The specific roles of pesticides, relative to or combined with other factors in the environment (e.g., habitat loss and alterations in climate), raise concerns substantially beyond the scope of this risk assessment.

Caution in the interpretation of broad-scale studies on the assessment of imidacloprid risks to birds, particularly in the focused applications proposed by the Forest Service, seems further justified by the scarcity of incident reports on adverse effects associated with applications of imidacloprid. In a report from France, Berny et al. (1999) provide monitoring data on partridges (n=12) and pigeons (n=6) which were collected dead in the field and found to contain detectable levels of imidacloprid. Particularly after applications of granular formulations or treated seeds (which is the case in the report by Berny), incidental poisonings of birds with imidacloprid may occur. In the United States, such incidental poisonings are tracked by the EPA. As noted in U.S. EPA/OPP/EFED (2008a, p. 11), an individual reported that birds died after consuming grubs from a lawn treated with imidacloprid for grub control. Further details of the potential exposures of the birds to imidacloprid are not provided. In any event, the Forest Service will not be involved in broadcast applications of granular formulations.

4.1.2.3. Reptiles and Amphibians (Terrestrial-Phase)

In the absence of toxicity data on terrestrial-phase amphibians, the U.S. EPA typically uses birds as a surrogate for terrestrial-phase amphibians, and this approach is cited in the recent EPA

ecological risk assessments (U.S. EPA/OPP/EFED 2007a, 2008a). Neither the EPA risk assessments nor the compendia of amphibian studies by Pauli et al. (2000) contain information on the toxicity of imidacloprid to terrestrial-phase amphibians.

A concern with the use of birds as a surrogate for amphibians involves the permeability of amphibian skin to pesticides and other chemicals. Quaranta et al. (2009) have noted that the skin of the frog *Rana esculenta* is much more permeable to several pesticides than pig skin and that these differences in permeability are consistent with differences in the structure and function of amphibian skin relative to mammalian skin. The only information on dermal exposures of amphibians to imidacloprid is the study by Van Meter et al. (2014) who monitored the uptake of technical grade imidacloprid from soil following treatment at a rate of about 0.5 lb a.i./acre (specified as 5µg/cm^2 in the publication). Soil concentration factors in five species of frogs ranged from 0.065 to 0.17 after an 8-hour exposure to imidacloprid soil concentrations of about 2 mg/kg soil. In other words, the amphibians absorbed but did not concentrate imidacloprid from the soil. Van Meter et al. (2014) do not describe the type of soil used in this study. As summarized in Table 1, the soil-water partition coefficients of imidacloprid range from about 0.5 to about 17. Given the short period of exposure and the possibility of significant binding of the imidacloprid to soil, the lower concentrations of imidacloprid in the amphibians, relative to the concentrations in soil, are not striking.

Little additional information is available on the potential effects of imidacloprid on terrestrial-phase amphibians. Mehlhorn et al. (2005) conducted an efficacy study on a veterinary preparation of 10% w/v imidacloprid and 2.5% w/v moxidectin for the control of parasites in terrestrial-phase reptiles. This is a study from the German literature using a formulation from Bayer AG, Leverkusen, Germany. Moxidectin is a medication for treating parasitic worms (e.g., http://www.animalhealth.bayer.com/4895.0.html).

The study by Mehlhorn et al. (2005) involved dermal doses of 32, 64, or 160mg a.i./kg bw imidacloprid alone with 4-fold lower doses of moxidectin. While this study is not focused on toxicity, Mehlhorn et al. (2005) note mortality in one species of snake (*Thamnophis sauritus*, a ribbon snake) and one species of lizard (*Takydromus sexlineatus*, a grass lizard). The number of animals responding is not presented clearly:

> *Among the latter* (referring to the animals that died), *which were probably injured during their importation to Germany, one in four animals died 3 days after treatment, while the rest were free of any symptoms. Thus for all reptiles for which the sensitivity to a product is unknown, the treatment should be started at low dosages to avoid side effects.*
>
> Mehlhorn et al. (2005, p. S100)

The statement concerning low dosages suggests that the dead reptiles had been given the highest or at least the mid-dose. In any event, mortality in reptiles at doses in the range of 64 to 160 mg a.i./kg bw is consistent with the oral toxicity data on birds.

Cordone (2015) conducted oral bioassays in sexually mature male lizards – i.e., *Podarcis sicula* also known as the Italian wall lizard – using a Confidor 200 SL formulation. The acute oral

LD_{50} was estimated at 503.76 mg/kg bw with a confidence interval of 379.01 to 628.51 mg/kg bw and a NOAEC for gross signs of neurotoxicity of 21.5 mg/kg bw. As discussed further in Section 4.3.2.2, this estimated NOAEC is substantially higher than the NOAEC of about 3 mg/kg bw in birds. Cordone (2015) also conducted a subchronic study in *Podarcis sicula* involving doses of 10, 50, and 100 mg/kg bw every other day for two weeks with sacrifice at day 16 following the first dose. The lowest dose was associated with significant (p<0.01) decreases in spermatogonia (≈87% of controls) and secondary spermatocytes (88% of controls) accompanied by a dose-related decrease in plasma testosterone and 17β-estradiol. Lastly, Cordone (2015 subjected lizards to a 30-day mixed exposure mesocosm study involving both contaminated soil and contaminated water (0.75 mg a.i./L). The concentration of imidacloprid in the soil, however, is not specified. At the end of the 30-day exposure period, decreases were noted in both plasma testosterone and 17β-estradiol (Figure 6 in Cordone 2015).

4.1.2.4. Terrestrial Invertebrates

4.1.2.4.1. General Considerations

As discussed in Section 1 (Introduction), the number of studies on terrestrial invertebrates has increased substantially since the previous Forest Service risk assessment on imidacloprid (SERA 2005), and this increase represents a highly diverse set of studies assessing different types of exposures and looking at many different endpoints. The following discussion is focused on the studies that are most useful to the current risk assessment in terms of identifying the spectrum of sensitivity within and among different groups of terrestrial invertebrates.

Information on the acute toxicity of imidacloprid to terrestrial invertebrates is summarized in several tables of Appendix 4:

- Table A4-1: Honeybee
- Table A4-2: Bumblebees (*Bombus* sp.)
- Table A4-3: Bees, Other Species
- Table A4-4: Hymenoptera, Other
- Table A4-5: Hemiptera
- Table A4-6: Coleoptera
- Table A4-7: Other Insects
- Table A4-8: Mites and Spiders
- Table A4-9: Other Arthropods
- Table A4-10: Earthworms
- Table A4-11: Other Invertebrates
- Table A4-12: Multispecies Field Studies

Most of the tables in Appendix 4 are organized in a similar manner starting with acute lethality studies, longer-term toxicity studies, studies focused on sublethal effects, and mesocosm/field studies. The acute lethality studies are subdivided into studies on technical grade imidacloprid versus formulations of imidacloprid, and each of these subgroupings is organized by route of exposure (i.e., oral and topical), as warranted by the data. In tables covering more than one species, the subsections are organized by species. The last table in Appendix 4 (i.e., field studies involving observations on multiple species), is organized alphabetically by citation.

As discussed in SERA (2014a), a focus of the hazard identification for terrestrial invertebrates is the identification of sensitive and tolerant groups of organisms. While numerous studies are available on imidacloprid, the diversity in the design of these studies limits the ability to compare results among species. For example, many studies are available on the oral toxicity of imidacloprid to insects. These studies, however, involve several different methods of administration. Many of the toxicity studies in bees involve oral exposure to imidacloprid dissolved in sucrose solutions. Studies in other groups of insects, however, involve leaf uptake (e.g., Prabhaker et al. 2011), twig uptake (Eisenback et al. 2010), treated sugar cubes (e.g., Kavi et al. 2014), cotton wicks soaked in a sugar solution (Gerry and Zhang 2009), leaf dip (e.g., Karunker et al. 2008), the consumption of contaminated vegetation following tree injection (Mota-Sanchez et al. 2009) or spray (James 1997), and various types of artificial diets (e.g., Arain et al. 2014; Kunkel et al. 2001). Even within nominally similar studies, such as leaf uptake, the results of different studies are not directly comparable because of differences in how the leaves were treated.

Another issue with attempts to identify patterns in sensitivity among different groups of terrestrial invertebrates involves differences in sensitivity among different populations of the same species. As with mammals (Section 3.1.3.1), imidacloprid is metabolized by many terrestrial invertebrates via the cytochrome P450 enzyme system. The enhanced metabolism of imidacloprid by cytochrome P450 enzymes is an important component in the development of resistance to imidacloprid (e.g., Bass et al. 2011; Ding et al. 2013, 2014; Johnson et al. 2012; Karunker et al. 2008, 2009; Puinean et al. 2010; Thany 2010).

The metabolism of imidacloprid is generally regarded as a detoxification mechanism. This assessment is based on comparative toxicity studies of imidacloprid with imidacloprid metabolites in the honeybee (Decourtye et al. 2003; Nauen et al 2001; Suchail et al. 2001) and whitefly (Nauen et al. 1999). As summarized in Table 15, the olefin metabolite of imidacloprid is modestly more toxic than imidacloprid in honeybees (i.e., a factor of about 2) and substantially more toxic than imidacloprid in whitefly (i.e., a factor of about 10). In addition, the study in whitefly indicates that the 4-hydroxy metabolite is modestly more toxic (i.e., a factor of about 1.6) than imidacloprid. All four studies on the comparative toxicity of imidacloprid metabolites assayed the 5-hydroxy metabolite and found that this metabolite is less toxic than imidacloprid by factors of about 5 - 10. While data on the toxicity of the other metabolites of imidacloprid are included in only one or two of the comparative studies in Table 15, these data indicate that the dihydroxy, urea, and 6-chloronicotinic acid metabolites of imidacloprid are essentially nontoxic. This assessment is consistent with the studies cited above which note that the induction of cytochrome P450 enzymes is associated with resistance in insect populations.

Resistance is typically quantified as the ratio of a dose associated with a defined response (e.g., LC_{50}) in resistant populations to the dose associated with the same response in a sensitive population. Resistance factors of about 5 - 10 are commonly reported in the literature on imidaclorprid (e.g., Alyokhin et al. 2007; Basit et al. 2013; Castle et al. 2014; Gerry and Zhang 2009; Ovcarenko et al. 2014; Riaz et al. 2013; Rust et al. 2014; Unruh and Willett 2008). In some instances, resistance factors can exceed 100 (e.g., Ding et al. 2014; Karunker et al. 2008; Srigiriraju et al. 2010). The highest documented resistance factor of imidacloprid is 2300, which

is the resistance factor in female houseflies reported by Kavi et al. (2014). As discussed by Kavi et al. (2014), resistance to imidacloprid may not be based solely on the enhanced ability to metabolize imidacloprid but may also be due to differences in the target site (i.e., nAChR) among different populations. Resistance associated with changes in nAChR is also noted by Tan et al. (2008), Liu et al. (2005), and Zhang et al. (2008). Resistance is often a factor that impacts efficacy. Efficacy, however, is not a focus of the current risk assessment. Nonetheless, the potential for resistance in different populations of the same species complicates the current risk assessment in that resistance (or more generally variability in sensitivity among different populations) complicates the assessment of systematic differences in sensitivity among different groups of terrestrial invertebrates.

4.1.2.4.2. Arthropods (other than soil-dwelling organisms)

As discussed in SERA (2014a, Section 4.1.2.4), assays for toxicity to the honeybee are standard EPA requirements for pesticide registration, and acute toxicity data on the honeybee involving oral and contact assays are commonly used as a surrogate for other terrestrial invertebrates. Relative to other Forest Service risk assessments, however, the data available on the toxicity of imidacloprid to the honeybee as well as other terrestrial invertebrates are extraordinarily detailed and complex. As discussed in Section 1 (Introduction), much of the recent literature on imidacloprid is focused on the concern with its toxicity to bees and the potential association of its use with colony collapse disorder (e.g., Belien et al. 2009; Chauzat et al. 2009, 2011; Dively et al. 2015; Gill et al. 2012; Lu et al. 2012, 2014; Whitehorn et al. 2012).

4.1.2.4.2.1. Variations in Sensitivity

A fundamental concern in ecological risk assessment is the variation in sensitivity among groups of organisms. In terms of comparative toxicity among different groups of terrestrial invertebrates, the most extensive data set involves topical applications. These studies involve placing a known amount of a solution of the test substance onto the surface of the organism. Topical applications are common to standardized studies in bees and other invertebrates. The results of the bioassays are typically expressed in the literature as LD_{50} values in units of mass per organism (e.g., ng/bee). While the Forest Service prefers to use no effect levels rather than lethal doses for the dose-response assessment (Section 4.3.2.4), LD_{50} values are preferable for comparisons of relative potency among species. Another reasonably comparable set of acute toxicity studies in several groups of organisms involve direct spray or immersion. While not as standardized or controlled as topical applications, direct spray or immersion studies are conducted on several groups of organisms and can be used to elaborate the assessment of sensitivities among different groups of terrestrial invertebrates.

4.1.2.4.2.1.1. Topical Application

An overview of the acute topical LD_{50} values for terrestrial invertebrates is provided in Table 16 and illustrated in Figure 4. As summarized in Table 16, direct comparisons among the different species and studies are compromised by the use of different durations of exposure (i.e., 24 - 144 hours) as well as the use of formulations versus technical grade imidacloprid. In addition, the source of the imidacloprid is not identified in some of the studies, and, again, it is not clear if these studies used technical grade imidacloprid or a formulation of imidacloprid. Another issue complicating the comparison involves differences in the body weights of the organisms. With the exception of the study by Kaakeh et al. (1996), the studies summarized in Table 16 give LD_{50} values in units of mg/organism rather than mg/kg bw. For comparing toxicity studies among

organisms that differ substantially in body weight, doses expressed in units of mg/kg bw are preferable. Three of the studies summarized in Table 16 specify the body weights of the organisms used (i.e., Eisenback et al. 2010; Radwan and Mohamed 2013; Valdovinos-Nunez et al. 2009). For the other organisms included in Table 16, representative body weights are taken from the sources specified in Footnote 2 of Table 16. Data on two additional topical LD_{50} values for hemipterans, *Apolygus lucorum* (Tan et al. 2012) and *Triatoma infestans* (Carvajal et al. 2014), are not considered in Table 16 because well-documented estimates of body weights for these species could not be identified. In addition, no body weight data were identified for *Ctenocephalides felis* (the cat flea), and for this species, the average body weight for six other species of fleas from Khokhlova et al. (2002) was used as a surrogate. Similarly, adult body weights for *Osmia cornifrons*, a Japanese orchard bee, could not be identified, and body weights for *Osmia cornuta* were used as a surrogate.

In addition to uncertainties associated with dosing, the identification of sensitive and tolerant groups of invertebrates is limited by the numbers of species on which data are available—i.e., four species of bees [Hymenoptera from the families Apidae and Megachilidae], three species of Coleoptera, two species of Diptera, and one species each of Hemiptera (*Myzus persicae*, the green peach aphid) and Blattodea (*Blattella germanica*, the German cockroach). These limitations in the data are emphasized because this data set on topical applications to arthropods is the most robust data set on relative toxicity for imidacloprid, which is an extremely well-studied pesticide in terrestrial invertebrates. As discussed above, however, the variability in the studies on imidacloprid limits generalizations involving relative sensitivities among the different groups of invertebrates.

Within the above and admittedly substantial limitations, the available data suggest that honeybees are among the most sensitive terrestrial invertebrates. The reported LD_{50} values for imidacloprid in the honeybee span a factor of about 13 [242.6 ng/bee ÷ 17.8 ng/bee ≈ 13.553]. This variability is influenced substantially by two LD_{50} values for formulations—i.e., 200 ng/bee for a Provado formulation and 242.6 ng/bee for a soluble concentrate formulation. Limiting the comparison to LD_{50} values for technical grade imidacloprid, the range of LD_{50} values varies by a factor of about 4 [78 ng/bee ÷ 17.9 ng/bee ≈ 4.3576]. As discussed in Section 4.1.2.4.1, this factor is well within the range of toxicity values for different populations of various species of terrestrial invertebrates. While surveys of intra-laboratory variability were not identified for honeybee assays, intra-laboratory variability of up to a factor of about 10 is noted in acute toxicity studies of aquatic invertebrates (e.g., Parkhurst et al. 1992). Thus, the variability in the reported topical LD_{50} values for the honeybee does not appear to be remarkable.

Nannotrigona perilampoides, a species of stingless bee of the Megachilidae rather than Apidae family, would appear to be more sensitive than the honeybee, based on the LD_{50} value of 1.1 ng/bee reported by Valdovinos-Nunez et al. (2009), which is lower than the reported honeybee LD_{50} values of 17.9 - 62.4 mg/bee for technical grade imidacloprid. This greater sensitivity, however, appears to be an artifact of differences in body weights. Valdovinos-Nunez et al. (2009) note that the *N. perilampoides* used in their study weighed only an average of 8.2 mg. Adjusting the LD_{50} to units of mg/kg bw, the LD_{50} for *N. perilampoides* is about 0.135 mg/kg bw which is virtually identical to the LD_{50} of 0.133 mg/kg bw for *Bombus impatiens* from the study by Marletto et al. (2003) and close to the µg/g LD_{50} values from several bioassays on *Apis*

mellifera. Adjusting the LD_{50} values for body weights in the assays with technical grade imidacloprid, the geometric mean of LD_{50} values in the honey bee with 95% confidence intervals is 0.32 (0.10 - 1.0) mg/kg bw. The LD_{50} values for *Bombus impatiens* (0.133 mg/kg bw) and *N. perilampoides* (0.135) are at the lower bound of the 95% confidence interval for the LD_{50} values for honeybees, suggesting no substantial or statistically significant differences in sensitivity among honeybees, bumble bees, and the stingless bee (*Nannotrigona perilampoides*).

Osmia cornifrons, another species of the Megachilidae family, appears to be substantially less sensitive than the honeybee to imidacloprid. This comparison is based on the study by Biddinger et al. (2013) who assayed both *Apis mellifera* and *Osmia cornifrons* with a Provado formulation. Based on the LD_{50} value in terms of ng/bee, *Osmia cornifrons* is more tolerant than *Apis mellifera* by a factor of 19 [3800 ng/bee ÷ 200 ng/bee]. Based on estimates of the LD_{50} values in terms of µg/g bw, the difference is somewhat less—i.e., about a factor of 14 [23.75 ÷ 1.724 ≈ 13.776]. Thus, while the available data suggest that the sensitivities of Apidae to imidacloprid may be similar, generalizations concerning the relative sensitivities of Megachilidae are not justified.

The available data on three species of Coleoptera suggest that this group of insects may be somewhat more tolerant than bees. In this respect, it is noteworthy that the two higher LD_{50} values for the Coleoptera are from the study by Eisenback et al. (2010) which involved a 10-day observation period. If the observations were made at 48-hours, similar to most of the other LD_{50} values summarized in Table 16, the LD_{50} values would be at least as high as those summarized in Table 16. In other words, while the study by Eisenback et al. (2010) involved a longer period of observation than the other studies in Table 16, this factor does not impact the assessment that the coleopteran species assayed by Eisenback et al. (2010)—i.e., *Laricobius nigrinus* and *Sasajiscymnus tsugae*—appear to be at least somewhat more tolerant to imidacloprid than hymenopterans and dipterans.

The other orders of insects in Table 16 and Figure 4 are each represented by a single species: the German cockroach (*Blattella germanica*, Blattodea), the green peach aphid (*Myzus persicae* Hemiptera), the yellow fever mosquito (*Aedes aegypti*, Diptera), and the cats flea (*Ctenocephalides felis*, Siphonaptera). Rust et al. (2014) notes substantial variability in the sensitivities of nine populations of cat flea, suggesting that differences in the sensitivities of different populations may obscure any differences in the underlying sensitivities among orders.

4.1.2.4.2.1.2. Spray or Immersion Assays

Clearly, toxicity studies involving the direct spray of a pesticide are relevant to environmental exposures associated with broadcast applications. Although the Forest Service does not plan to use broadcast applications of imidacloprid in its programs, this method of treatment is fundamental to the use of imidacloprid in agriculture. Toxicity studies involving direct spray typically express the exposure either in units of mass per surface area (e.g., g/ha) or in units of concentration. For imidacloprid, relatively few direct spray toxicity studies report exposures in units of mass per surface area (e.g., Gradish et al. 2010; Elzen 2001). There are several acute toxicity studies that report LC_{50} values in units of mg/L. In bioassays that involve dipping extremely small insects in various solutions of the test compound, LC_{50} values are also expressed in units of mg/L. Immersion assays are considered along with direct spray toxicity studies for

the assessment, albeit crude, of differences in sensitivity among and within groups of terrestrial invertebrates.

The LC_{50} values involving direct spray or immersion are summarized in Table 17 and illustrated in Figure 5. Data are available on four species of bees from the studies by Bailey et al. (2005) and Scott-Dupree et al. (2009). While not apparent from the citations, both studies were conducted at the same facility (University of Guelph, Guelph, Ontario) under the supervision of Scott-Dupree. Though not conducted concurrently, these studies appear to use identical protocols and may be viewed essentially as matched bioassays. Consistent with the studies involving topical application (Section 4.1.2.4.2.1.1), these direct spray bioassays indicate that the honeybee and bumblebee are about equally sensitive to imidacloprid. Two other species of bee—i.e., the alfalfa leafcutting bee (*Megachile rotundata*) and an orchard bee (*Osmia lignaria*)—appear to be more sensitive than the honeybee by factors of about 13 [22 mg/L ÷ 1.7 mg/L ≈ 12.94] to 31 [22 mg/L ÷ 0.7 mg/L ≈ 31.43]. Both of these species of apparently sensitive bees are from the family Megachilidae rather than Apidae. While the differences in toxicity between the Apidae and Megachilidae are within the range of variability associated with resistance in different populations of the same species, the bees used in the studies by Bailey et al. (2005) and Scott-Dupree et al. (2009) were purchased commercially, and there is no indication of substantial pesticide exposure to the populations used in these bioassays. Nonetheless, at least some species of bees, particularly those from the Megachilidae family, may be more sensitive than honeybees, bumblebees, and other Apidae.

Unlike the case with the topical studies (Section 4.1.2.4.2.1.1), direct spray studies are available on species of Hymenoptera other than bees, specifically two species of wasps (*Diadegma insulare* and *Trichogramma cacoeciae*). While the studies on the species of wasps are from different groups of investigators (as specified in Table 17), the reported LC_{50} values in the narrow range of 1.25 to 2.3 mg/L, are strikingly similar. These LC_{50} values are also strikingly similar to the LC_{50} for the Megachilidae bees discussed above—i.e., 0.7 and 1.7 mg/L. Taken together, these data on four species of Hymenoptera, other than those from the family Apidae, suggest that at least some Hymenoptera other than Apidae are as sensitive as sensitive species of Apidae bees to imidacloprid. A reservation with the comparisons involving predatory or parasitic wasps, however, is that a likely route of exposure for these wasps involves feeding on host species. These types of exposures are not encompassed by the comparisons based on spray or immersion assays.

In addition to the toxicity studies on the Hymenoptera, bioassays are available on five species of Hemiptera. The LC_{50} values are highly variable ranging from 0.38 mg/L in *Aphis pomi* (Lowery et al. 2005) to 138.21 mg/L in *Agonoscena pistaciae* (Amirzade et al. 2014). These LC_{50} values span a factor of about 350 [138.21 mg/L ÷ 0.38 mg/L ≈ 347.92]. While this variability is within the range of variations seen within different populations of the same species (i.e., factors of up to 2300, as discussed in Section 4.1.2.4.1), it does not seem reasonable to suggest that the variability in the Hemiptera is random or associated with differences in resistance in the different populations assayed. As indicated in Table 17, three of the studies on the Hemiptera used different formulations—i.e., Confidor and Admire formulations. Four of the bioassays from the study by Lowery et al. (2005) used an Admire formulation, and the variability is relatively modest—i.e., a factor of about 20 [6.9 mg/L ÷ 0.38 mg/L ≈ 18.16]. This variability appears to be

associated with differences in sensitivity between *Aphis pomi* and *Aphis spiraecola* as well as differences in the levels of resistance in the populations of *Aphis pomi* and *Aphis spiraecola* assayed by Lowery et al. (2005). The much higher LC_{50} of 138.21 mg/L for *Agonoscena pistaciae* reported by Amirzade et al. (2014) could be due to true species-specific differences, resistance in the population of *Agonoscena pistaciae*, the use of a less toxic formulation (in this case a Confidor formulation), or other unidentified factors. In the absence of additional information, generalizations concerning the sensitivities of Hemiptera relative to Hymenoptera would be largely speculative.

One dip bioassay is available in a spider—i.e., the LC_{50} of 40.44 mg/L in a wolf spider (*Pardosa pseudoannulata*) from the study by Chen et al. (2012). Unlike the dip assays in Hemiptera, the study by Chen et al. (2012) involves dipping the spiders for 20 seconds rather than 2 seconds. Although a lower LC_{50} might be anticipated, given the prolonged exposure, LC_{50} of about 40 mg/L is similar to the LC_{50} values in Apidae (22 and 32.2 mg/L) as well as a hemipteran (i.e., the LC_{50} of 40 mg/L in *Nilaparvata lugens* from the study by Bullangpoti et al. 2007).

4.1.2.4.2.1.3. Other Data on Relative Sensitivity

Other data that can be used to assess patterns in sensitivity among species include oral toxicity studies in bees as well as a matched set of leaf uptake bioassays in hymenopterans and hemipterans by Prabhaker et al. (2011).

Oral toxicity studies in bees are relatively standard and common bioassays in which bees, typically fasted prior to treatment, are exposed to a sucrose solution containing the test compound. The amount of the test compound consumed by the bees over the period of several hours is measured, and the average dose per bee is calculated. The bees are typically observed for 48 - 96 hours (e.g., OECD 1998). Acute oral toxicity studies with imidacloprid and imidacloprid formulations are summarized in Table 18. Five assays with technical grade imidacloprid are available in *Apis mellifera* and one of these bioassays involves Africanized bees. The mean LD_{50} (with 95% confidence intervals) for the four bioassays with non-Africanized honeybees is 0.20 (0.027 - 1.4) mg/kg bw. This LD_{50} for oral exposure is similar to the LD_{50} for topical application—i.e., 0.32 (0.10 - 1.0) mg/kg bw, as discussed in Section 4.1.2.4.2.1.1. The oral LD_{50} for Africanized honeybees is 0.70 µg/g bw. While this LD_{50} for Africanized honeybees is higher than the mean LD_{50} for non-Africanized honeybees by a factor of 3.5, the difference is not statistically significant. Given the variability in LD_{50} and other similar toxicity values, there is no basis for asserting that Africanized honeybees are likely to be less sensitive than non-Africanized honeybees to imidacloprid. As with the topical and spray bioassays, the oral LD_{50} for bumblebee—i.e., 0.13 µg/g bw from the study by Marletto et al. (2003)—suggests that bumblebees and honeybees have similar sensitivities to imidacloprid. Tom et al. (2015) report an acute oral LD_{50} of 23.54 ng/bee for *Melipona quadrifasciata,* a species of stingless bee native to Brazil. While Tom et al. (2015) do not report the body weights of the bees used in this assay, Contrera et al. (2006) reports a body weight for this species of about 8 mg/bee. Thus, the dose of 23.54 ng/bee would correspond to an estimated LD_{50} of about 2.9 µg/g bw [23.54 ng/bee ÷ 8 mg = 2.9425 ng/mg or µg/g]. Based on this estimated LD_{50}, *Melipona quadrifasciata* may be somewhat more tolerant to imidacloprid than the honey bee or bumblebee.

The leaf uptake bioassays by Prabhaker et al. (2011) are noteworthy because matched bioassays were conducted on four species of Hymenoptera and two species of Hemiptera. As summarized in Table 19, the LC_{50} values for the Hymenoptera ranged from about 0.25 to 2.6 g a.i./L and were lower than the comparable LC_{50} values for Hemiptera—i.e., 2.78 and 5.18 g a.i./L. The units for the LC_{50} values refer to the concentrations of imidacloprid in the solutions used to treat the leaves prior to exposure of the insects. As discussed in Section 4.1.2.4.1, many leaf uptake bioassays are available on imidacloprid; however, comparisons among these studies are precluded by differences in how the leafs were treated, differences in the species of leaves that were treated, and the exposure conditions (e.g., duration) for the insects. Comparisons within the study by Prabhaker et al. (2011) are useful because these factors were identical for the six species assayed in the study. As summarized in Table 19, the confidence limits for most of the LC_{50} values overlap. Nonetheless, this study supports the observation from contact bioassays (Section 4.1.2.4.2.1.1) that Hymenoptera appear to be somewhat more sensitive than Hemiptera to imidacloprid.

4.1.2.4.2.2. Sublethal Effects

Information on the sublethal effects of imidacloprid in terrestrial invertebrates is dominated by studies in bees. As with acute toxicity studies, sublethal toxicity studies are highly diverse, making comparisons difficult. These studies differ in both the nature of the exposures (i.e., route, vehicle, and duration) and the endpoints assayed.

The most coherent and comparable group of studies involves exposures of bees to food (typically sucrose solutions) contaminated with imidacloprid. In many of these studies, summarized in Table 20, exposures are characterized as concentrations of imidacloprid in sucrose. In a few of the studies (i.e., Dively et al. 2015; Laycock et al. 2012; Lu et al. 2014; Schneider et al. 2012; Schmuck et al. 2001), the concentrations of imidacloprid in solution along with estimates of sucrose consumption and the number of bees exposed are used to estimate doses in units of ng/bee. These studies, along with additional bee studies in which doses are expressed in units of ng/bee, are summarized in Table 21. Table 21 also includes a study by Tan et al. (2014) on a mirid—i.e., *Apolygus lucorum* (Hemiptera: Miridae)—which assayed reproductive effects following a topical application of imidacloprid. Both Tables 20 and 21 specify the species assayed, the endpoints and duration of exposure, the NOAEL/NOAEC and LOAEL/LOAEC (when both are available), and the citation. Both tables are sorted by increasing LOAEL/LOAEC.

Several of the studies expressing exposures as concentrations are field or mesocosm studies focused on assessing the impact of imidacloprid exposures on colony or hive health. These studies are reasonably consistent indicating short-term NOAECs in the range of 10 ppb (Scholer and Krischik 2014) to 20 ppb (Schmuck et al. 2001) and adverse effects on colony health in the range of 20 ppb (Scholer and Krischik 2014). The study by Pareja et al. (2011) is somewhat atypical in that it assayed honeycombs in abandoned hives in Uruguay in an attempt to examine the association of depopulated beehives with pesticide exposure. This study is similar to a retrospective epidemiology study. Pareja et al. (2011) found imidacloprid at a mean concentration of 377 µg/kg (ppb) in the honeycombs of abandoned hives. While this type of study cannot prove causality, the concentrations of imidacloprid in the honeycombs are higher

than concentrations of imidacloprid in sucrose solutions that are clearly associated with adverse effects on colony health.

As summarized in Table 20, several additional studies report decreases in foraging activity at concentrations ranging from 3.7 to 100 ppb. The greenhouse study on *Bombus impatiens* by Scholer and Krischik (2014) involved treating mesocosms of one queen and 30 - 50 workers (eight colonies per treatment level) with imidacloprid in sucrose at a concentration of 0, 10, 20, 50, or 100 ppb for 11 weeks. Queen mortality increased in a dose-relate manner and colony weights decreased in a dose-related manner over the 11-week treatment period (see Appendix 3, Table A3-2 for details). The decreases in colony health appear to be associated with decreased foraging activity by workers. The NOAEC for adverse effects was 10 ppb. Although colony deaths are not noted by Scholer and Krischik (2014), this study did not involve observations beyond the 11-week exposure period. Similarly, the study by Schmuck et al. (2001) noted no adverse effect on colony health at a concentration of 20 ppb over a 39-day (≈5.5 week) exposure period, however, as with the study by Scholer and Krischik (2014), no observations of colony health were made beyond the 39-day exposure period.

Longer-term studies with bee colonies involving exposure periods of 2 or more months with observations extending to the overwintering period were conducted by Dively et al. (2015), Faucon et al. (2005), and Lu et al. (2012, 2014). The studies by Dively et al. (2015) and Faucon et al. (2005) note no significant adverse effects on colony health at a dietary concentration of 5 ppb. At concentrations of 20 ppb and higher, no substantial adverse effects were noted during summer exposure period; yet, colony deaths were noted during overwintering (Dively et al. 2015; Lu et al. 2012, 2014).

As detailed in Appendix 3 (Table A3-1), the study by Lu et al. (2012) noted marked mortality during overwintering. Specifically, imidacloprid exposure was initiated in July and terminated in September. Initially, low concentrations were used —i.e., 0.1 to 10 µg/kg sucrose—for 4 weeks followed by 9 weeks of exposure to imidacloprid concentrations of 20, 40, 200, or 400 µg/kg sucrose (ppb). At 12 weeks post-exposure (December), no hive mortality was noted. After this time, however, mortality in the treated hives increased substantially. By week 23 (the end of the study), mortality was noted in 1 of 4 control hives. Mortality in the treated hives was 4/4 at 20 ppb, 3/4 at 40 ppb, 4/4 at 200 ppb, and 4/4 at 400 ppb. In discussing these results, Lu et al. (2012, p. 6, column 1) express reservations with the small number of hives used in the study. The authors, however, do not specifically address the statistical significance of the hive mortality. Taking the experimental unit as the hive, the mortality of 1/4 in the control hives versus 4/4 (seen in 3 of the 4 treatment groups) has a p-value of (p=0.071429) using the Fisher Exact Test. In the absence of a clear dose-response relationship for hive death at end of the study, the four dose-groups can be pooled to give a combined response rate for hive death in treated hives of 15/16. Compared with the control response (1/4), the pooled response rate is statistically significant with a p-value of 0.012416 using the Fisher Exact Test. The more recent study by Lu et al. (2014) used only a single and relatively high concentration of 135 ppb but noted the same general pattern of response—i.e., no substantial adverse effects until overwintering of the hives. The studies by Lu et al. (2012, 2014) have been criticized by Entine (2014a,b); however, the critiques focus more on the interpretation of the studies with respect to colony collapse disorder rather than on the substance or details of the studies.

Faucon et al. (2005) noted no adverse effects at the colony level during overwintering following exposure to concentrations of 0.5 or 5 ppb of imidacloprid in sucrose for about 30 days. As discussed above, the adverse effects noted by Lu et al. (2012) occurred following somewhat longer-term exposures (about 63 days) to concentrations of 20 - 400 ppb of imidacloprid in sucrose. Thus, the studies by Lu et al. (2012) and Faucon et al. (2005) suggest that colony death associated with overwintering may occur following exposures to concentrations equal to or higher than 20 ppb imidacloprid and that the apparent threshold for this effect is a concentration of 5 ppb.

More recently, Dively et al. (2015) conducted longer-term feeding experiments similar to those of Lu et al. (2012) and Faucon et al. (2005) using doses of 0, 5, 20, or 100 µg a.i./kg diet (honey mixed with a high protein pollen supplement). As detailed in Appendix 3, Table A3-1, Dively et al. (2015) conducted two sets of independent experiments, one in 2009 and the other in 2010. The experiment in 2010 appears to have been subject to cross-contamination …*apparently due to drifting and possibly some robbing because hives were placed close to each other in apiaries* (Dively et al. 2015, p. 16). In addition, the 2010 experiment noted higher mortality in both control and treated groups due to … *abnormally higher temperatures during the winter which resulted in over-consumption of the stored food* (Dively et al. 2015, p. 19). These issues did not occur in the 2009 experiment. In the 2009 experiment, a significant dose-response relationship was observed in colony mortality during overwintering—i.e., 1/10 in controls, 2/10 in the 5 ppb group, 3/10 in the 20 ppb group, and 6/10 in the 100 ppb group.

As summarized in Table 20, several of the bee studies indicate that imidacloprid adversely affects foraging activity. These and other bee studies note an inhibition of the proboscis extension response (Decourtye et al. 2003; Guez et al. 2001; Lambin et al. 2001; Eiri and Nieh 2012; Williamson and Wright 2013)—i.e., an indication of altered feeding behavior—as well as feeding inhibition (Cresswell et al. 2014; Laycock et al. 2012; Tan et al. 2014). Feeding inhibition associated with exposures to imidacloprid were observed also in Hemiptera (Cameron et al. 2013; He et al. 2011, 2013), Coleoptera (He et al. 2012), and Isopoda (Drobne et al. 2008). Feeding inhibition is a common observation in toxicity studies. As discussed in other sections of this risk assessment, feeding suppression was noted also in mammals (Section 3.1.6 and Section 3.1.9.2) as well as birds (Section 4.1.2.2.4).

Because imidacloprid can cause feeding inhibition, studies reporting only concentrations add uncertainty in estimating the dose to the organism. Uncertainties with food consumption are not a limitation in studies that report doses in units of ng/organism, and these studies are summarized in Table 21. As noted above, a few studies report exposures as concentrations but provide estimates of doses (ng/insect) or information sufficient to calculate doses. These studies (i.e., Dively et al. 2015; Laycock et al. 2012; Lu et al. 2014; Schneider et al. 2012; Schmuck et al. 2001) are summarized in both Table 20 and Table 21.

Adverse effects on colony health during overwintering appear to be the most sensitive endpoint. As detailed in Appendix 4, Table A4-1, Dively et al. (2015) provide data on the cumulative dose for each exposure group (i.e., concentration) and the number of bees in each group. The colony sizes reported by Dively et al. (2015)—i.e., about to 18,000 bees per colony—are in the normal

range for feral colonies—i.e., 12,000 (for the initiation of queen rearing) to 20,000 (for swarming) (Winston 1987, p. 192). Taking the dosing and measured colony populations reported by Dively et al. (2015) as well as the exposure period of 12 weeks (84 days), the doses per bee per day are about 0.011 ng/bee/day in the 5 ppb group, 0.043 ng/bee/day in the 20 ppb group, and 0.203 ng/bee/day in the 100 ppb group. As noted in Appendix 3, Table A3-1, the publication by Dively et al. (2015) indicates that cumulative doses in the colonies were 16.6, 63.7 and 322.6 mg for the 5, 20, and 100 ppb exposure groups. A preliminary assessment of these reported cumulative doses led to dose estimates that would be lethal to bees in a short period of time. Dr. Dively was queried on these doses in the preparation of the current risk assessment. Dr. Dively (2015) responded to this query indicating that the unit designation of milligrams (mg) reported in the publication is a typographical error and that the correct units are micrograms (µg).

The study by Lu et al. (2014, p. 125) states that the average dose associated with a concentration of imidacloprid in sucrose of 135 ppb was 0.74 ng/bee/day. In discussing this estimate, Lu et al. (2014) indicate that a total of 258 µg a.i. per week was administered over a period of 13 weeks (91 days) and state that the number of bees is assumed to be 50,000. Although the basis for this assumption is not specified, the number of worker bees in commercial bee colonies can reach 50,000 to 60,000 in mid-summer (Sagili and Burgett 2011). Based on these estimates, the dose would be about 0.737143 ng/bee/day [258,000 ng/week x 13 weeks ÷ (50,000 bees x 91 days) ≈ 0.737143 ng/bee/day] or 0.74 ng/bee/day when rounded to 2 significant places. The study by Lu et al. (2012, Table 1) provides information on the doses per hive; however, estimates of doses per bee cannot be determined because the number of bees is not specified.

4.1.2.4.3. Soil Invertebrates

Because imidacloprid may be applied directly to soil, the potential for adverse effects on soil invertebrates is an obvious concern. Most of the studies on soil invertebrates involve earthworms, and these studies are summarized in Appendix 3, Table A3-10. Some studies on earthworms involve direct exposure to liquid solutions of imidacloprid or contact with filter paper treated with solutions of imidacloprid (e.g., Luo et al 1999; Zhang et al. 2000). While these studies are included in Appendix 3 for the sake of completeness, the majority and the most relevant studies involve earthworms exposed directly to soil contaminated with different concentrations of imidacloprid.

Acute toxicity studies in earthworms are typically conducted for a period of 14 days. The 14-day acute LC_{50} values with technical grade imidacloprid range from 1.99 mg a.i./kg soil (Chen et al. 2014b) to 2.82 mg a.i./kg soil (Wang et al. 2012). The 14-day LC_{50} values for formulations of imidacloprid range from 2.8 mg a.i./kg soil (Capowiez et al. 2005) to about 25.5 mg a.i./kg soil (Alves et al. 2013). Kreutzweiser et al. (2008b) conducted somewhat longer-term 35-day soil mesocosm studies with two species of earthworms using a Merit formulation of imidacloprid. In this study, *Dendrobaena octaedra* (LC_{50} = 5.7mg a.i./kg soil) was more sensitive than *Eisenia fetida* (LC_{50} = 25 mg a.i./kg soil) by a factor of about 4.

As also summarized in Appendix 3, Table A3-10, numerous studies were conducted on the sublethal effects of imidacloprid in earthworms. Several studies note effects on burrowing behavior or signs of oxidative stress at imidacloprid soil concentrations of 0.2 to about 0.7 mg/kg soil (Capowiez et al. 2003, 2006; Dittbrenner et al. 2010, 2011; Zhang et al. 2014). In a study

assaying the impact of imidacloprid on sperm deforming in *Eisenia foetida*, Luo et al (1999) note a NOAEC of 0.1 mg a.i./kg soil. This study, however, did not assay for burrowing behavior.

In an avoidance study, Alves et al. (2013) noted that *Eisenia andrei* avoids imidacloprid at a concentration of 0.13 mg a.i./kg soil. Alves et al. (2013) also conducted a 56-day chronic reproduction study in earthworms and noted an EC_{50} of about 4 mg a.i./kg soil with a corresponding LOAEL of 0.75 mg a.i./kg soil for decreased reproduction. A NOAEL for reproductive effects was not determined. Adverse effects on reproduction were also noted in the mesocosm study by Fernandez-Gomez et al. (2011) at a concentration of 2 mg a.i./kg soil. A transient effect of earthworm abundance is reported in the field study by Kunkel et al. (1999). The effect was noted after two Merit formulations were applied at rates in the range of 0.3 to 0.4 lb a.i./acre.

In addition to reproductive effects in earthworms, reductions in egg production were observed in the Japanese beetle at soil concentrations of 0.1 - 0.2 mg a.i./kg soil (George et al. 2007), and decreases in the number of springtail [Collembola] juveniles were observed at a soil concentration of 0.06 mg a.i./kg soil (Alves et al. 2014).

4.1.2.5. Terrestrial Plants (Macrophytes)

As with most insecticides, the U.S. EPA has not required assays on the toxicity of imidacloprid to terrestrial plants (U.S. EPA/OPP/EFED 2007a, p. 43). In the problem formulation for the registration review of imidacloprid, U.S. EPA/OPP/EFED (2008a, p. 12) notes two complaints from individuals who applied imidacloprid formulations to turf and noted subsequent browning of the lawn. The EPA does not comment specifically on the association of the imidacloprid applications to the lawns with subsequent lawn damage. As discussed in the Forest Service risk assessment on dinotefuran (SERA 2009a), another neonicotinoid insecticide, the EPA received Tier 1 phytotoxicity studies—i.e., studies using single doses at the highest labelled application rate—and no signs of phytotoxicity were noted.

As discussed in Section 4.1.2.4, imidacloprid is used extensively on crops, trees, and other plants for the prevention of damage due to insects. If imidacloprid were highly toxic to plants, it seems likely that phytotoxicity would be well documented in the literature, which is not the case. In the study by Weichel and Nauen (2004) involving foliar applications of imidacloprid, damage to hops was observed when imidacloprid was applied with an adjuvant but not when imidacloprid was applied without the adjuvant. Ford et al. (2011) also noted foliar damage to soybean seedlings hydroponically grown in a solution containing 100 mg a.i./L imidacloprid. The foliar damage was attributed to oxidative stress. No damage was observed in other plants assayed, including, spinach, cotton, corn, and grape seedlings. In an earlier study involving soil applications of imidacloprid to thale cress (*Arabidopsis thaliana*, a small dicot), Ford et al. (2010) noted that imidacloprid reduced the impact of powdery mildew (*Golovinomyces orontii*) by inducing salicylic acid production in the plants.

Several studies using a U.S. formulation of imidacloprid labeled for insect control in cotton (i.e., Trimax from Bayer CropSciences), report that imidacloprid appears to enhance the tolerance of cotton to heat stress (Gonias et al. 2003, 2004, 2008). These effects were observed in the absence of insect pests. In addition, an increase in cotton yield was observed in a field study, again, in the absence of insect infestations (Gonias et al. 2006).

4.1.2.6. Terrestrial Microorganisms

The U.S. EPA/OPP does not require bioassays for microbial toxicity. The EPA does have a protocol for a 12-week soil-core microcosm assay; however, this test is focused on functional changes to soil, based on observations of plant growth. Assays for effects on microorganisms are optional (U.S. EPA/OCSPP 2012a). This assay does not appear to have been conducted with imidacloprid.

In the open literature, the effects of imidacloprid on soil microorganisms were examined in both soil exposures (Cycon and Piotrowska-Seget 2015; Cycon et al. 2013; Deborah et al. 2013; Kreutzweiser et al. 2008b; Singh and Singh 2005a; Tu 1995; Wang et al. 2014) and bacterial cultures (Ahemad and Khan 2011a,b,c; Ingram et al. 2005). Three of the soil studies involve periods of exposure comparable to those in the U.S. EPA/OCSPP (2012) assay—i.e., 56 days in the studies by Cycon and Piotrowska-Seget (2015) and Cycon et al. (2013) and 150 days in the study by Singh and Singh (2005a). These longer-term studies note decreases in some groups of soil microorganisms. In the studies by Cycon and Piotrowska-Seget (2015) and Cycon et al. (2013), conducted with 99.8% pure technical grade imidacloprid, the effects were transient at concentrations of 1 mg a.i./kg soil but evident over the 56-day observation period at 10 mg a.i./kg soil. The study by Singh and Singh (2005a) involves seed treatments at a concentration of 10 g/kg seed. Decreases were observed in some groups of soil microorganisms; however, recovery and rebound were observed in all groups by day 120 of the study. The shorter-term studies (2 - 14 days) to higher concentrations (10 mg a.i./kg soil) also note decreases in some groups of soil microorganisms (Tu 1995); Wang et al. 2014). Based on 2-day exposures to imidacloprid in soil at concentrations of 10, 20, 40, or 80 mg a.i./kg soil, Wang et al. (2014) estimated an IC_{50} (i.e., a 50% reduction in the growth rate for soil microorganisms) of 95.7 mg a.i./kg soil. At discussed further in Section 4.2.3.3, the IC_{50} is higher than anticipated concentrations of imidacloprid in soil by a factor of over 100. In a 35-day study at imidacloprid concentrations of up to 1400 mg/kg soil, Kreutzweiser et al. (2008b) observed no adverse effects on the ability of soil microorganisms to degrade leaf litter.

Deborah et al. (2013) report transient but concentration-related decreases in soil invertase activity (i.e., an enzyme involved in the hydrolysis of sucrose to fructose) at 24 hours following exposures to imidacloprid at 0.2, 0.5, or 0.7 mg a.i./kg soil (Figure 4 in paper). By 48 hours, the inhibition was significant at 0.2 and 0.7 mg a.i./kg soil but not at 0.5 mg a.i./kg soil (Figure 5 of study). The study by Deborah et al. (2013) was conducted in India, and the source and purity of the test material is unclear as is the nature of the test material (i.e., technical grade or formulation).

The cell culture studies by Ahemad and Khan (2011a,b,c) assayed effects in nitrogen-fixing bacteria following 48-hour exposures to imidacloprid at culture concentrations of 100, 200, or 300 µg/L. The imidacloprid is specified as "*Technical 100% EC*". The term *EC* typically refers to an emulsifiable concentrate formulation; however, the nature and source of the formulation or technical grade material is not otherwise specified. In all cases, the exposures were associated with a significant decrease in salicylic acid, dihydroxy benzoic acid, indole acetic acid, as well as other endogenous compounds which are generally regarded as beneficial to plants. As discussed in the publications, these effects might be associated with adverse effects on plants; however, such effects have not been demonstrated in the field. As noted above, the U.S. EPA/OCSPP

(2012) assay for effects on soil microflora is focused on plant effects because this is the endpoint of clear relevance in terms of impacts on the ecosystem.

The study by Ingram et al. (2005) assayed imidacloprid as the Merit 75 WP formulation in both cell cultures and soil slurries at concentrations of 70, 350, or 700 mg a.i./L. Imidacloprid had no adverse effect on *Proteus vulgaris* (i.e., a bacterium which produces urease) or soil urease activity.

4.1.3. Aquatic Organisms

4.1.3.1. Fish

Information on the toxicity of imidacloprid to fish is summarized in Appendix 4. This information includes several acute toxicity studies in fish (Table A4-1), one standard early-life stage study in trout (Table A6-2), and a mesocosm study in medaka (Table A4-3).

With the exception of open literature studies on zebra fish by Scheil and Kohler (2009b) and Tisler et al. (2009), all of the acute studies were submitted to the EPA in support of the registration of imidacloprid. Based on the indefinite LC_{50} of >83 mg a.i./L in rainbow trout (Bowman and Bucksath 1990b, MRID 42055315) and the LC_{50} of 163 mg a.i./L in sheepshead minnow (Ward 1990a, MRID 42055318), the EPA classifies imidacloprid as practically nontoxic to fish on an acute basis (U.S. EPA/OPP/EFED 2008a, p. 10). U.S. EPA/OPP/EFED (2008a) cites but does not discuss an LC_{50} of 211 mg a.i./L in rainbow trout (Grau 1988a, MRID 42055316). Nonetheless, this LC_{50} is consistent with the indefinite LC_{50} in trout as well as the LC_{50} in sheepshead minnow. All of the registrant-submitted studies involved fry (i.e., young post-embryonic fish), as required by EPA.

The open literature study by Scheil and Kohler (2009b) involves zebra fish eggs, in which no effects were noted at concentrations of up to 50 mg/L. This NOAEC is similar to the NOAECs from the fry studies—i.e., 25 - 50 mg a.i./L. The study by Tisler et al. (2009) in zebra fish embryos yields LC_{50} values for both technical grade imidacloprid (LC_{50} = 241 mg a.i./L) and a Confidor formulation (LC_{50} = 214 mg a.i./L) which are comparable to the LC_{50} of 211 mg a.i./L in trout (Grau 1988a, MRID 42055316).

The early-life stage study in trout involves 98-day flow-through exposures of fertilized eggs with development through the fry stage. While the initial analysis of the study indicated a NOAEC of 9.8 mg a.i./L with an LOAEC of 19 mg a.i./L based on reduced body weight and length on Day 90 (Cohle and Bucksath 1991, MRID 42055320), a later reevaluation of the data for Day 36, identified a NOAEC of 1.2 mg a.i./L with an LOAEC of 2.3 mg a.i./L based on fry growth (Gagliano 1992, MRID 42466501). In other words, the impact of imidacloprid on fry growth appears to have been transient, with an effect on Day 36 at relatively lower concentrations which was not apparent by the end of the study. As discussed further in Section 4.3.3.1, the EPA risk assessments, U.S. EPA/OPP/EFED (2008a, p. 17) and U.S. EPA/OPP/EFED (2007a, p. 41) use the lower Day 36 NOAEC, which is clearly appropriate.

As detailed in Appendix 4, Table A4-3, the study by Sanchez-Bayo and Goka (2005) involves outdoor exposures of Japanese medaka to a 1% a.i. formulation of imidacloprid applied to a rice paddy mesocosm. The concentrations of imidacloprid were initially about 0.24 mg/L but

dropped rapidly to as low as 0.001 mg/L over the 118-day duration of the study. Most of the decrease was apparently attributable to heavy rainfall from typhoons. A mortality of 5% was noted in the first 2 days, which the study authors attributed to imidacloprid. As noted in Appendix 4, Table A4-3, however, the mortality rate is not statistically significant using the Fisher Exact test. The only statistically significant adverse effect was an increase in the incidence of a microbial ciliate parasite in the imidacloprid exposed fish. The authors suggest that this effect could be due to immune suppression. While the supposition of immune suppression may be reasonable, assays of immune function were not conducted. The applicability of this study to the current Forest Service risk assessment is limited primarily by the use of the imidacloprid formulation specified in the paper as *Admire GR* containing 1% imidacloprid. While the term *Admire*™ is used by Bayer CropScience for imidacloprid formulations, a product label could not be identified for a 1% granular formulation. Presumably, the Admire™ formulation used by Sanchez-Bayo and Goka (2005), a study conducted in Japan, involved a formulation marketed in Japan, not in the United States.

4.1.3.2. Amphibians (Aquatic-Phase)

The EPA ecological risk assessments, U.S. EPA/OPP/EFED (2007a, 2008a), do not provide information on the toxicity of imidacloprid to aquatic-phase amphibians. As is the general practice, U.S. EPA/OPP uses fish as surrogates for aquatic-phase amphibians, in the absence of toxicity data, and the EPA adopted this approach for imidacloprid (e.g., U.S. EPA/OPP/EFED (2008a, p. 11).

While the use of fish as a surrogate for aquatic-phase amphibians is a standard approach, a mechanistic study by Seifert and Stollberg (2005) suggests that imidacloprid may act atypically in at least one amphibian. Using 99% pure imidacloprid to treat *Xenopus laevis* embryonic frog muscle cell cultures, these investigators noted that imidacloprid appears to act as a nAChR antagonist rather than agonist in this test system. The inhibition of acetylcholine ($5x10^{-7}$M) and nicotine ($5x10^{-6}$ M) was noted at concentrations of imidacloprid as low as $3.3x10^{-6}$ M (≈8.4 µg/L). As discussed in Section 3.1.2, imidacloprid acts as a nAChR agonist in mammals as well as insects, albeit with a much greater affinity for nAChR in insects, relative to mammals. Comparable studies on the mechanism of action of imidacloprid in fish are not available. If the mechanism of imidacloprid in amphibians is substantially different from the mechanism of action in fish, the use of fish as a surrogate for aquatic-phase amphibians may be questionable.

Notwithstanding this concern, LC_{50} values in aquatic-phase amphibians for technical grade imidacloprid are in the range of 165 - 219 mg a.i./L. Details of these studies are discussed below. As noted in Section 4.1.3.1, comparable LC_{50} values in fish for technical grade imidacloprid are in the range of 25 - 50 mg a.i./L. Based on this comparison, the use of fish as a surrogate for aquatic-phase amphibians appears reasonable and may be somewhat conservative—i.e., may overestimate risks to amphibians.

The above comparison is based only on acute toxicity studies in amphibians, details of which are given in Appendix 5, Table A5-1. No information on the longer-term toxicity of imidacloprid to aquatic-phase amphibians, field studies in involving effects on aquatic-phase amphibians, or incident reports concerning the effects of imidacloprid on aquatic-phase amphibians were identified in the available literature.

The citation of Julian and Howard (1999, MRID 44875001) in Appendix 7 was identified from EPA files in the previous Forest Service risk assessment (SERA 2005). Typically, only registrant-submitted studies are assigned an MRID number. The Julian and Howard (1999) study, however, appears to have originated as a Master's Thesis by Julian (2000) which was subsequently published with other information by Howard et al. (2003). For brevity, these three citations are simply referenced as Howard et al. (2003) in the discussion below. This study is from the U.S. literature and used a Merit 75% a.i. "*powder*" formulation. While not specifically identified as such in the papers, the description of the formulation is consistent with Merit 75 WP. As indicated in Table 2, Merit 75 WP is one of the formulations explicitly considered in the current risk assessment.

All of other studies summarized in Appendix 7 were conducted outside United States. The published acute toxicity studies were conducted in China (Feng et al. 2004), South Africa (Channing 1998), and Argentina (Perez-Iglesias et al. 2014). Feng et al. (2004) used technical grade imidacloprid (>95% purity), and Perez-Iglesias et al. (2014) used a 35% a.i. formulation not marketed in the United States (Glacoxan Imida, 35% a.i., from Punch Química S.A., Argentina). The South African study by Channing (1998) does not specify the source or nature of the imidacloprid used (i.e., formulation vs a.i.).

Including formulations, the reported 96-hour LC_{50} values for imidacloprid in amphibians range from 17.4 mg a.i./L (an unspecified formulation, Channing 1998) to 468 mg a.i./L (a Merit formulation, Howard et al. 2003). As noted above, Channing (1998) does not specify the source or nature of the material assayed; accordingly, the relevance of the reported LC_{50} to the current risk assessment is not clear. As discussed above, the 48-hour LC_{50} values of 184.5 - 468 mg a.i./L are from Howard et al. (2003). These LC_{50} values are similar to the 48-hour LC_{50} values for technical grade imidacloprid from Feng et al. (2004)—i.e., 165 - 219 mg a.i./L, which suggests that the inerts used in the Merit 75% a.i. formulation do not contribute substantially to the toxicity of the formulation to amphibians.

Perez-Iglesias et al. (2014) report a 48-hour LC_{50} of 58.2 mg a.i./L for Glacoxan Imida, 35% a.i, an Argentinian formulation of imidacloprid,. While the study by Perez-Iglesias et al. (2014) is well reported, the LC_{50} of 58.2 is below LC_{50} values for technical grade imidacloprid and the Merit formulation by factors of about 3 to 8 [$165 \text{ to } 468 \div 58.2 \approx 2.8 \text{ to } 8.04$].
As also summarized in Appendix 7, Perez-Iglesias et al. (2014) conducted a series of DNA assays which indicate that exposure to the Glacoxan Imida formulation increased the incidence of genetic damage—i.e., damage based on micronuclei and the Comet assay, two standard assays for DNA damage.

Given the greater acute toxicity of Glacoxan Imida, relative to technical grade imidacloprid and the Merit formulation, the results from Perez-Iglesias et al. (2014) concerning DNA damage may seem only marginally relevant to the current risk assessment. Nonetheless, qualitatively similar results—i.e., positive responses in micronucleus and Comet assays—are reported by Feng et al. (2004). As discussed above, the study by Feng et al. (2004) was conducted in China but used technical grade imidacloprid (>95% purity). It is worth noting, however, that the micronucleus assay involves *in vivo* exposures, and signs of DNA damage (small nuclei) were only at relatively high concentrations (i.e., 8 and 32 mg a.i./L). Feng et al. (2004) reports a LOAEL of

0.05 mg a.i./L for the Comet assay. While this result is supported by the data (Table 4 in the publication by Feng et al. 2004), the Comet assays involved *in vitro* exposure of erythrocytes for a 1-hour period. Thus, the LOAEL of 0.05 mg a.i./L is not directly applicable to the dose-response assessment (Section 4.3.3.2).

4.1.3.3. Aquatic Invertebrates

Unlike the case with fish (Section 4.1.3.1) and amphibians (Section 4.1.3.2), the literature concerning the effects of imidacloprid on aquatic invertebrates is rich and diverse, with most of the studies coming from the open literature rather than registrants. As with the literature on terrestrial invertebrates (Section 4.1.2.4), the design and focus of open literature studies are highly diverse reflecting differences in the intent and interest of the investigators. This diversity complicates comparisons among studies because of difference in the species tested, endpoints assayed and the nature of the exposures. The following discussion focuses on the endpoints and patterns in the available data that are most relevant to the current risk assessment.

4.1.3.3.1. Acute Toxicity

Information on the acute toxicity of imidacloprid to aquatic invertebrates is summarized in several tables of Appendix 6:

- Table A6-1: *Daphnia magna* and other Cladocera
- Table A6-2: Amphipods
- Table A6-3: Midges (Diptera, *Chironomus* sp.)
- Table A6-4: Other Diptera
- Table A6-5: Ostracods
- Table A6-6: Other Freshwater Invertebrates
- Table A6-7: Other Saltwater Invertebrate

Table 22, which provides an overview of the information in Appendix 6, is organized by invertebrate group. For the most part, these groups designate different orders or classes of crustaceans [i.e., Amphipoda (scuds), Anostraca (fairy shrimp), Cladocera (daphnids), Decapoda (10-legged invertebrates), Isopoda (sowbug), Mysida (opossum shrimps) and Ostracoda (seed shrimp)] and insects (i.e., Diptera, Ephemeroptera, Hemiptera, Megaloptera, and Trichoptera). Several bioassays are available for some of these orders (e.g., Cladocera and Amphipoda). Other orders are represented by only a single study of a single species (i.e., the Anostraca, Decapoda, and Megaloptera). In addition, bioassays of single species are available for the Annelida phyla and two classes from the Mollusca phyla (i.e., Gastropoda and Bivalvia). While the diversity of the organisms is greater than that for most pesticides, the number of species on which toxicity data are available is still small, relative to the number of species that may be exposed to imidacloprid. The most thoroughly covered group is the Cladocera with a total of 17 acute bioassays. Even for this group, however, only six species are represented, and three of these species are represented with only single bioassays.

While the following discussion focuses on patterns of sensitivity among groups and species, the generalizations are not intended to be overly general and definitive, particularly for groups represented by only one or a few bioassays or species. For example, the phylum Annelida is represented by only a single species, *Lumbriculus variegatus*, from the study by Alexander et al. (2007). The organisms used in the study by Alexander et al. (2007) were only about 2.5 cm long

and weighted an average of 1.17 mg. *Lumbriculus variegatus*, however, can range in size to up to 10 cm (Wards Scientific 2008). In the addition, the annelids also include flatworms (Turbellaria) which weigh up to about 20 mg (Whitney 1944) and leaches (Hirudinea) which can vary greatly in size (e.g., Pennak 1953). As with many chemicals, some data are available on imidacloprid indicating that body size can impact sensitivity to imidacloprid (Bottger et al. 2012). While the differences in sensitivity noted by Bottger et al. (2012) are not remarkable, the diversity of aquatic invertebrates and the well documented differences in sensitivity within relatively narrow groups of organisms suggest the need for caution in attempting to characterize differences in sensitivity among groups of organisms that are not well studied.

In terms of the endpoints examined, only LC_{50} and EC_{50} values are given in Table 22. As discussed in Section 4.3 (dose-response assessment) and discussed further in SERA (2014a), the Forest Service prefers to base dose-response assessments on NOAECs or similar toxicity values rather LC_{50} or EC_{50} values. For the purpose of identifying differences in sensitivity among groups or species, LC_{50} and EC_{50} values are used because they have better statistical properties than NOAECs in that estimates of LC_{50} and EC_{50} values incorporate all the available data on the dose-response curve and are often accompanied by confidence intervals.

The difference between LC_{50} and EC_{50} values is more important for some groups of organisms than others. For very small invertebrates, such as daphnids and other Cladocera, EC_{50} values are generally defined as the estimate of the concentration associated with immobility in 50% of the organisms. This approach is taken both because it is difficult to assess whether a very small organism is dead as opposed to immobile and because immobility is essentially a fatal condition in the environment. Thus, virtually all studies in daphnids and other Cladocera report EC_{50} values for immobility rather than LC_{50} values. As summarized on Table 22, the only study reporting a true LC_{50} value in Cladocera is the study by Chen et al. (2010) which reports an LC_{50} of 0.00207 mg a.i./L for *Ceriodaphnia dubia*. In this study, the heartbeats of the organisms were assayed under a microscope, and death was defined as a lack of heartbeat. The other bioassay on *Ceriodaphnia dubia* reports a more standard EC_{50} of 0.57162 mg a.i./L (Hayasaka et al. 2012b) which is higher than the LC_{50} reported by Chen et al. (2010) by a factor of over 275 [$0.57162 \div 0.00207 \approx 276.145$].

For larger invertebrates, it is easier to determine both the LC_{50} and EC_{50}. As would be expected in such cases where both values are reported, EC_{50} values are lower than LC_{50} values. In some instances, the difference between the LC_{50} and EC_{50} values are small, and in other cases the differences can be quite large even within the same group of organisms. For example, as summarized on Table 22, Roessink et al. (2013) report LC_{50} values for Hemipterans that are higher than simultaneously determined EC_{50} values by factors ranging from only about 1.04 [$0.0375 \div 0.0359 \approx 1.0446$ for *Plea minutissima*] to greater than about 450 [$>10.0 \div 0.0182 \approx 549.45$]. Similar substantial differences are noted in other publications (e.g., Ashauer et al. 2011; Bayo and Goka 2006a). In the following discussion of differences among species as well as in the dose-response assessment, the more sensitive EC_{50} values are typically used if available. The only exception involves the Diptera (other than midges). As summarized on Table 22, five LC_{50} values from five different studies in five different species are available on dipterans (other than midges), as opposed to only one EC_{50} value for this group. With the exception of the paired LC_{50} and EC_{50} values from Roessink et al. (2013) on *Chaoborus obscuripes*, the LC_{50} values for the

other species of dipterans are lower than the EC_{50} from Roessink et al. (2013). Thus, for this group of organisms, the LC_{50} values represent a more conservative (i.e., lower numbers) and better grounded (more species) assessment.

Another variable to consider in the assessing the acute toxicity data on imidacloprid is the distinction between bioassays using technical grade imidacloprid, designated as *TGAI* in Table 22, and bioassays using formulations, designated in Table 22 as *Form*. In general, there is little difference between the toxicity of imidacloprid and imidacloprid formulations. The best represented species is *Daphnia magna* for which the EC_{50} values for imidacloprid (n=4) range from 10.44 to 97 mg a.i./L, and the corresponding values for the formulations (n=7) range from 30 to 96.5 mg a.i./L. Other comparisons are based only on single studies. For example, in the study by Stoughton et al. (2008) with *Chironomus tentans*, the EC_{50} for imidacloprid (0.00575 mg a.i./L) is virtually identical to the EC_{50} for an Admire 240F formulation (0.0054 mg a.i./L). Based on data in two different species of Ephemeroptera (Table 22), the reported LC_{50} value for imidacloprid is in the mid-range of LC_{50} values for formulations. As discussed further in Section 4.1.3.3.2, no substantial or systematic differences between the toxicity of imidacloprid and formulations of imidacloprid are apparent in chronic studies of aquatic invertebrates. Thus, data on both imidacloprid and imidacloprid formulations are combined in the discussion of apparent differences in sensitivity among groups or species of aquatic invertebrates.

Based on the above discussion, a summary of the apparent differences in sensitivity among various groups of aquatic invertebrates is provided in Table 23 and illustrated in Figure 6. The last column of Table 23 and the y-axis of Figure 6 are the cumulative frequencies of the toxicity data for the various groups of aquatic invertebrates, based on ordered sensitivity to imidacloprid. The individual values for the cumulative frequency are based on the following equation:

Equation 1

$$Freq_i = \frac{i - 0.5}{N}$$

where $Freq_i$ is the cumulative frequency for the i^{th} value and N is the number of values in the data set. For example, the data on imidacloprid consists of 20 EC_{50} or LC_{50} values. The lowest value is an EC_{50} of 0.0013 mg a.i./L. Thus, the frequency for the first point (i=1) is calculated as (1-0.5) ÷ 20 or 0.025. Similarly, the second lowest EC_{50} value (i=2) is 0.0052 mg a.i./L, which is assigned a frequency of (2-0.5) ÷ 20 or 0.075.

The x-axis in Figure 6 represents the EC_{50} and LC_{50} values, which are given on a logarithmic scale, under the standard assumption that LC_{50} and EC_{50} values for different chemicals or different groups of organisms have a lognormal distribution. Each of the LC_{50} and EC_{50} values, in turn, is based on the geometric mean of the corresponding values from Table 22. With the exception of Diptera (as discussed above), EC_{50} values are generally used rather than LC_{50} values, because EC_{50} values are generally more sensitive (i.e., lower) than LC_{50} values.

The cumulative frequency distributions of toxicity values are related to figures often referred to as *species sensitivity distributions* (e.g., Awkerman et al. 2008; Posthuma et al. 2002). As discussed by Posthuma et al. (2002), species sensitivity distributions can be used quantitatively

as tools in probabilistic risk assessment. Probabilistic methods are not routinely used in Forest Service risk assessments. Nonetheless, cumulative distribution plots, like those in Figure 6, are useful for illustrating differences in and among different groups of organisms.

The cumulative frequency distributions used in this risk assessment, however, differ from species sensitivity distributions, in that species sensitivity distributions typically provide only one data point for each species. As discussed above, the data from Table 22 are generally grouped at the level of the order or genus, depending on the available data. Because the Cladocera are so well represented and because the toxicity values are so variable within this order of Branchiopods, the Cladocera are separated by genus and/or species—i.e., *Daphnia* sp., *Ceriodaphnia dubia*, *Ceriodaphnia reticulata*, *Chydorus sphaericus* (a marine cladoceran), and *Moina macrocopa*. Similarly, midges (*Chironomus* sp.) are separated from other Diptera because midges are a standard genus of benthic organisms used in bioassays required by EPA. In addition, as discussed below, midges appear to be somewhat more sensitive than other dipterans to imidacloprid.

The range of toxicity values among the different groups of organisms is substantial. Based on the mean values in Table 23, the range spans a factor of over a quarter-million (268,842) with Ephemeroptera being the most sensitive (mean EC_{50} of 0.0013 mg a.i./L) and brine shrimp (*Artemia* sp.) being the least sensitive (a single LC_{50} of 361.23 mg a.i./L from Song et al. 1997). There is no reason to regard the upper bound LC_{50} of 361.23 mg a.i./L from Song et al. (1997) as a possible outlier. The study by Song et al. (1997) is well documented and includes three other species—i.e., *Daphnia magna* and two dipterans (Aedes aegypti and *Aedes taeniorhynchus*. As summarized in Table 22, the LC_{50} for *Daphnia magna* of 10.44 mg a.i./L reported by Song et al. (1997) is only modestly below the mean value of about 47 mg a.i./L and is quite similar to EC_{50} value for *Daphnia magna* reported by Sanchez-Bayo and Goka (2006a, EC_{50} = 11.822 mg a.i./L). The mean EC_{50} of 0.0013 mg a.i./L for Ephemeroptera presented in Table 23 is based on two species from the study by Roessink et al. (2013). The two reported EC_{50} values are virtually identical—i.e., 0.00177 mg a.i./L for *Cloeon dipterum* and 0.00102 mg a.i./L for *Caenis horaria*. As summarized in Table 22, the study by Roessink et al. (2013) involves LC_{50} and/or EC_{50} determinations in several species. The most robust comparisons of the LC_{50} values from Roessink et al. (2013) with other studies involve LC_{50} determinations in Amphipoda. The LC_{50} of 0.316 mg a.i./L for *Gammarus pulex* reported by Roessink et al. (2013) is virtually identical to the LC_{50} of 0.27 mg a.i./L for *Gammarus pulex* reported by Beketov and Liess (2008) and is only modestly below LC_{50} values of 0.526 mg a.i./L for *Hyalella azteca* (England and Bucksath 1991) and 0.8 mg a.i./L for *Gammarus fossarum* (Lukancic et al. 2010a,b). Although the range of reported toxicity values for aquatic invertebrates is substantial, the extremes of this range should not be perceived as outliers or regarded as otherwise questionable.

As illustrated in Figure 6, the pattern of LC_{50} and EC_{50} values is clearly biphasic. There is a relatively steep slope for the more sensitive invertebrates covering the Ephemeroptera to the Megaloptera. This group includes all the orders of aquatic insects for which data are available (i.e., Diptera, Ephemeroptera, Hemiptera, Megaloptera, and Trichoptera). As reviewed by Morrissey et al. (2015), Ephemeroptera is the most sensitive order of aquatic insects to other neonicotinoids. Given the mode of action and role/design of imidacloprid as an insecticide, the sensitivity of aquatic insects to imidacloprid is to be expected. In addition, more sensitive

invertebrates include several but not all groups of aquatic Crustacea (i.e., Class Malacostraca/Orders Amphipoda and Mysida, Ostracoda, and one species, *Ceriodaphnia dubia*, of Class Branchiopoda/Order Cladocera). The sensitive aquatic invertebrates also include one species of aquatic worm, *Lumbriculus variegatus*. The bioassay of *Lumbriculus variegatus* conducted by Alexander et al. (2007) reports an EC_{50} of 0.0062 mg a.i./L based on immobility. As discussed above, Annelida is a highly diverse phylum. The *Lumbriculus variegatus* were near the lower bound of size for this species. Accordingly, it conceivable that other populations of this species as well as other classes within Annelida vary appreciably in their sensitivity to imidacloprid and other pesticides. Thus, classifying Annelida generally sensitive to imidacloprid does not seem justified.

As also illustrated in Figure 6, the slope segment for less sensitive aquatic invertebrates (i.e., the points on the right side of the figure) is shallower than the slope segment for the more sensitive aquatic invertebrates, indicating a greater variability within the less sensitive group of organisms. In a more formal probabilistic analysis, it seems likely that these two groups could be segregated statistically and would be analyzed separately. The less sensitive organisms range from the Decapoda and Isopoda (about equally sensitive to imidacloprid and both members of the Malacostraca class) to several members of the class Branchiopoda (i.e., *Daphnia* and *Moina*, both genera of cladocerans, and a species of *Artemia*). Other members of this less sensitive group of aquatic invertebrates include mollusks (both Bivalvia and Gastropoda) as well as other species of Cladocera.

As noted at the start of this discussion, caution is warranted in interpreting the strength of the above generalizations. Many of the classes and orders are represented by very few or a single species. The need for caution is also illustrated by the Cladocera, the best represented order of aquatic invertebrates with 17 bioassays covering six species. While most these Cladocera are clearly less sensitive than other crustacean and insects of which data are available, the studies on *Ceriodaphnia dubia* by Chen et al. (2010, LC_{50}≈0.00207 mg a.i./L) and Hayasaka et al. (2012b, EC_{50}≈0.57 mg a.i./L) suggest that this species of Cladocera may be more sensitive, and perhaps substantially more sensitive, than other Cladocera. As indicated in Table 23, the LC_{50} from Chen et al. (2010) and the EC_{50} from Hayasaka et al. (2012b) are combined to estimate the geometric mean toxicity value used in Figure 6. The difference between these two toxicity values for *Ceriodaphnia dubia* is substantial [0.57 ÷ 0.00207 ≈ 275.36]. As discussed above, the study by Chen et al. (2010) is somewhat unusual in that death was determined by microscopic examination for heartbeat. The nature of the examination is described in the paper only as follows: …*were considered dead when there was no movement of the external and thoracic appendages or the heart following gentle prodding with a glass pipette following observation under microscopic magnification* (Chen et al. 2010, p. 133, column 2). If the LC_{50} from Chen et al. (2010) were censored, the EC_{50} of 0.57 mg a.i./L would place *Ceriodaphnia dubia* in the less sensitive group with the EC_{50} somewhat higher than that for Decapoda (0.3008 mg a.i./L) and Isopoda (0.3085 mg a.i./L). Nonetheless, even if the toxicity value from Chen et al. (2010) were censored, the range of toxicity values for all Cladocera would span a factor of about 170 [97.0 ÷ 0.57162≈169.693]. Given this variability in a well-represented order of Crustacea, it seems reasonable to suggest that the true sensitivity and variability in sensitivities in poorly represented phyla, classes, or orders (e.g., Megaloptera, Annelida, Gastropoda, Anostraca, Decapoda, and

Bivalvia) are characterized only marginally. This concern is addressed further in the dose-response assessment (Section 4.3.3.3).

4.1.3.3.2. Chronic Toxicity

Information on the chronic toxicity of imidacloprid to aquatic invertebrates is summarized in several tables of Appendix 6, Table A6-9. An overview of the available studies is given in Table 24. Even for a well-studied pesticide, the data on the chronic toxicity of imidacloprid to aquatic invertebrates is unusually rich and diverse. Of the 14 available studies, only three studies are submitted by registrants, including the standard chronic reproduction study in *Daphnia magna* (Young and Blake 1990), the chronic toxicity study in *Chironomus tentans* (the standard species used by EPA for benthic invertebrates), and the reproduction study in *Mysidopsis bahia* (a standard species used by EPA for saltwater and brackish water invertebrates). All of the other studies are from the open literature.

The chronic toxicity values for different groups of aquatic invertebrates are summarized in Table 25 and illustrated in Figure 7. The approach used to develop Table 25 is similar to that used to develop the corresponding table on acute toxicity. The specific considerations in assessing the chronic studies are discussed below. Table 24 and Table 25 also summarize EC_{10} values from the mesocosm study by Kreutzweiser et al. (2008c) for stonefly (*Pteronarcys dorsata*) and crane fly (*Tipula* sp.). These two studies are also illustrated in Figure 7. Mesocosm studies are discussed below in Section 4.1.3.3.3.

As with the acute toxicity studies, the best represented group of aquatic invertebrates is the Cladocera, with five studies on technical grade imidacloprid and three studies on formulations of imidacloprid. Also as with the acute studies, no substantial or systematic differences are apparent in the chronic toxicity of imidacloprid and imidacloprid formulations to Cladocera. Comparisons among other groups of organisms are limited to Amphipoda with only one study on technical grade imidacloprid and five studies on imidacloprid formulations. The study by Nyman et al. (2013) on technical grade imidacloprid uses an atypical endpoint (inhibition of feeding); thus, compromising any comparisons with the formulation studies.

Most of the open literature studies are comparable to standard EPA studies in terms of duration, typically covering exposure periods of 21 - 28 days. The study by Stoughton et al. (2008) gives both 10 day and 28 day observation periods. While these data are included for the sake of completeness in Table 24, the responses over the two observation periods are not remarkably different, and only the 28-day observations are discussed in the following analysis. The 8-day reproduction study in *Ceriodaphnia dubia* by Chen et al. (2010) does not identify a NOAEL or EC_{10}. As discussed below, NOAEL and EC_{10} values are used in the comparative analysis of species, which precludes an explicit consideration of Chen et al. (2010). Nonetheless, it is important to note that the LOAEL of 8.093 mg a.i./L reported by Chen et al. (2010) is comparable to the LOAELs in *Daphnia magna* (i.e., 2.5 - 12 mg a.i./L). As discussed in the previous section, *Ceriodaphnia dubia* appears to be much more sensitive than *Daphnia magna* in acute toxicity studies. Based on the available chronic toxicity studies, *Ceriodaphnia dubia* and *Daphnia magna* appear to have similar sensitivities to imidacloprid.

While the open literature studies are generally similar in duration to EPA studies, they differ in the variety of endpoints reported (i.e., feeding inhibition, immobilization, survival, and

reproduction), the nature of responses reported (NOAELs/LOAELs versus EC_{10} and EC_{50} values), and the use of both constant and pulse exposures.

Only two studies involve feeding inhibition—i.e., Agatz and Brown (2013b) and Nyman et al. (2013). Agatz and Brown (2013b) is a relatively short-term study (7 days) in *Daphnia magna*. In some respects, this study may not contribute substantially to the comparison of species sensitivities because of the substantial spacing in concentrations between the NOAEL (0.15 mg a.i./L) and the LOAEL (12 mg a.i./L). In other words, the low NOAEL for feeding does not contradict the other higher NOAELs in *Daphnia magna* (i.e., 1.25 - 2.5 mg a.i./L), all of which are below the LOAEL reported by Agatz and Brown (2013b). The study by Nyman et al. (2013) reports an NOAEC for feeding inhibition of 0.09 mg a.i./L in *Gammarus pulex*. This study is not used in the analysis below because this endpoint is remarkably less sensitive than the EC_{10} for immobility of 0.00295 mg a.i./L reported by Roessink et al. (2013) in the same species.

Studies involving exposures to both pulses and the more standard constant (or nearly so) concentrations used in standard EPA studies are available for *Hyalella azteca* (Amphipoda) and *Chironomus tentans* (Diptera) from the study by Stoughton et al. (2008). In the case of *Chironomus tentans*, the NOAECs for pulse exposures (about 0.00347 mg a.i./L) are higher than the NOAECs for constant exposures (about 0.0011 mg a.i./L), and in the case of *Hyalella azteca* the 28-day NOAECs are about the same (i.e., 0.00344 - 0.00353 mg a.i./L). In either case, the differences are not substantial, and the data on constant and pulsed exposures are pooled in the species comparisons below.

The distinction of NOAECs and LOAECs from EC_{10} and EC_{50} values appears to reflect the preferences of the individual investigators. While these two sets of values are not equivalent, the EPA's benchmark dose approach (U.S. EPA 2012) essentially recommends the EC_{10} as a surrogate for an NOAEC. Based on the available data on imidacloprid, comparisons of NOAEC and EC_{10} values for the same species are limited to the data on *Gammarus pulex*. As discussed above, the two studies on this species use different endpoint, which compromises any comparison of the NOAEC to the EC_{10} value.

As illustrated in Figure 7, the general pattern in the sensitivity of different groups of organisms based on a consideration of chronic NOAEC and EC_{10} values is similar to the patterns for acute toxicity. The most sensitive group of organisms is Ephemeroptera. Other relatively sensitive organisms include the insects (Megaloptera and Hemiptera) as well as aquatic Crustacea (i.e., Class Malacostraca/Orders Amphipoda and Mysida). The plot of the chronic data in Figure 7 looks different from the plot of acute data in Figure 6 because the only representative of the more tolerant organisms is *Daphnia magna*. Nonetheless, the relative acute and chronic sensitivities of Ephemeroptera and *Daphnia magna* are strikingly similar—i.e., a factor of 35,328 based on acute toxicity (Table 23) and a factor of 40,213 based on chronic toxicity (Table 25). The only remarkable difference, as discussed above, is that the limited available data on the chronic toxicity of *Ceriodaphnia dubia* suggests that this species is not remarkably more sensitive than *Daphnia magna* in longer-term exposures to imidacloprid.

4.1.3.3.3. Mesocosm Studies

Mesocosm studies on imidacloprid are summarized in Appendix 6, Table A6-10. An overview of these studies is given in Table 26. These studies range from relatively simple indoor systems

involving one or two organisms (i.e., Beketov and Liess 2008; Kreutzweiser et al. 2007, 2008c), which might be better characterized as microcosm studies, to larger and more complex outdoor systems (e.g., Colombo et al. 2013; Hayasaka et al. 2012a,c). Mesocosm studies are intended to be more realistic than laboratory bioassays and may provide a more sensitive measure of toxicity (i.e., effects at lower concentrations), compared with laboratory bioassays.

At least for imidacloprid, the mesocosm studies do not suggest effects at concentrations lower than those seen in standard bioassays. This pattern is best illustrated quantitatively in the study by Kreutzweiser et al. (2008c). While most of the mesocosm studies summarize effects in terms of NOAELs and LOAELs for changes in abundance, Kreutzweiser et al. (2008c) provide estimates of EC_{10} and EC_{50} values for mortality, which are directly comparable to similar values reported in acute and chronic bioassays. Kreutzweiser et al. (2008c) used aquaria mesocosms with stream water and sediment as well as two species of stream insects (stonefly [*Pteronarcys dorsata*] and crane fly [*Tipula* sp.]) to assess the impact of water concentrations of 12, 24, 48 or 96 µg/L imidacloprid on the degradation and shredding of sugar maple leaves over a 14-day period. As summarized in Table 24, Kreutzweiser et al. (2008c) report LC_{10} values of 20.8 µg/L for stonefly and 16.2 µg/L for crane fly. In addition, as detailed in Appendix 6, Table A6-10, Kreutzweiser et al. (2008c) also report LC_{50} values of 0.071 µg/L for stonefly and 0.139 µg/L for crane fly. As illustrated in Figure 7, the EC_{10} values are substantially left-shifted from the chronic bioassays in other aquatic invertebrates. In other words, the mesocosm toxicity values are higher than the comparable values from chronic bioassays. This comparison, however, may be of limited significance, because the 14-day exposure period is less than the more typical 21- to 28-day exposure periods used in the chronic bioassays. In addition, the EC_{10} values are based on lethality; whereas, most of the reported NOAELs and LOAELs for other mesocosm studies are based on changes in populations (Table 26). Nonetheless, the EC_{10} and EC_{50} values are also associated with a sublethal effect, an inhibition of leaf shredding. Another issue with comparing the results from Kreutzweiser et al. (2008c) with the results from other acute and chronic bioassays is that none of the acute or chronic toxicity studies (Section 4.1.3.3.1 and Section 4.1.3.3.2) involves bioassays on species of *Pteronarcys* or *Tipula*. *Pteronarcys* is a member of the Plecoptera order, and no other Plecoptera assays involving imidacloprid were identified in relevant literature. Crane fly (genus *Tipula*) is a species of Diptera. As summarized in Table 23, the geometric mean of the acute LC_{50} values for Diptera is 0.0281 mg/L, which is a factor of about 5 below the LC_{50} of 0.139 mg/L reported by Kreutzweiser et al. (2008c) [$0.139 \div 0.0281 \approx 4.964$]. Based on this comparison, the 14-day toxicity values from Kreutzweiser et al. (2008c) for a dipteran are higher than the comparable 96-hour values from acute toxicity studies of other dipterans.

Similar patterns are apparent in the comparison of other NOAECs from mesocosm studies (Table 26) to NOAECs from chronic toxicity studies (Table 25). The reported NOAEC values from chronic bioassays for sensitive species (i.e., all except Daphnia magna in Table 25) are in the range of 0.0000281 mg/L (Ephemeroptera) to 0.00348 mg/L (*Hyalella azteca*, Amphipoda). Apart from the NOAELs for mortality from Kreutzweiser et al. (2007, 2008c), the reported NOAECs from the mesocosm studies are in the range of 0.0004 mg/L (the TWA for Ephemeroptera) to 0.012 mg/L (the NOAEL for Amphipoda from Mohr et al. 2012). For the Ephemeroptera, the mesocosm NOAEL is higher than the bioassay NOAEL by a factor of about

14 [0.0004 ÷ 0.0000281 ≈ 14.235]. For Amphipoda, the mesocosm NOAEL is higher than the bioassay NOAEL by a factor of about 3 [0.012 ÷ 0.00348 ≈ 3.448].

The above comparison does not consider the artificial stream mesocosm study by Beketov and Liess (2008). This study reports only LOAELs for drift in a species of Ephemeroptera (0.00097 mg/L) and Amphipoda (0.030 mg/L). The LOAEL for Amphipods is substantially above the LOAEL of 0.002 mg/L for population abundance in Amphipoda from the mesocosm study by Moring et al. (1992). In addition, the LOAEC for drift is essentially identical to the geometric mean of the acute EC_{50} (immobility) for Amphipoda (i.e., 0.0256 mg/L from Table 23). Thus, the LOAEC for drift from Beketov and Liess (2008) would not be viewed as a particularly sensitive endpoint. The corresponding LOAEL of 0.00097 mg/L for Ephemeroptera from Beketov and Liess (2008) is only modestly less than the geometric mean acute EC_{50} of 0.0013 mg/L for Ephemeroptera (Table 23) [0.0013 ÷ 0.00097 ≈ 1.34]. Overall, the observations from Beketov and Liess (2008) are consistent with the acute toxicity of imidacloprid from laboratory bioassays.

In addition to the mesocosm studies discussed above, Appendix 6, Table A6-10, summarizes two relevant mesocosm studies that address the potential effects of leaf litter contaminated with imidacloprid on aquatic invertebrates (Kreutzweiser et al. 2007, 2008). Kreutzweiser et al. (2007) focus on leaves from ash trees treated at field rates and excess rates of imidacloprid (i.e., mimicking exposures that could be associated with Forest Service treatments for the control of the emerald ash borer). Similarly, Kreutzweiser et al. (2008a) focus on leaves from maple trees treated at field rates and excess rates of imidacloprid (i.e., mimicking exposures that could be associated with Forest Service treatments for the control of the Asian long horned beetle). In both studies, no adverse effects were noted in treatments at recommended field rates; however, adverse effects were noted in treatments at rates far in excess of field treatment rates. In terms of a qualitative hazard identification, these studies clearly indicate that imidacloprid could leach from contaminated leaves into water and reach concentrations harmful to aquatic invertebrates. The design of the studies, however, is not directly related to a field application. In other words, the studies involve putting an essentially arbitrary number of leaves into an arbitrary volume of water. For example, the study by Kreutzweiser et al. (2007) involves placing 12 ash leaves into a system containing 6 liters of stream water and 300 mL of stream detritus. Adverse effects were noted in species of *Pteronarcys* or *Tipula* exposed to leaves from trees treated at excessive rates, while no effects were noted the same species exposed to leaves from trees treated at normal field rates. If, however, more leaves were used or if the volume of water were less, adverse effects might have been observed at field rates. Similarly, if fewer leaves and/or a greater volume of water were used, no effects might have been observed even from leaves of trees treated at excessive field rates. As discussed further in Section 4.2.5, the potential for adverse effects in aquatic invertebrates from contaminated leaves seems clear. Whether or not adverse effects might occur, would depend on several site-specific factors that cannot be objectively or generically estimated.

4.1.3.3.4. Population Survey

No true field-scale studies—i.e., studies that look at populations of aquatic invertebrates following relatively defined applications of typical uses of imidacloprid in a large area—were identified in the relevant literature. One large scale assessment of monitoring data, however, is considered prior to the discussion of mesocosm studies. Van Dijk et al. (2013) published an

analysis of aquatic invertebrate population surveys in the Netherlands along with large scale monitoring data. This is a slightly unusual analysis is somewhat analogous to a retrospective epidemiology study. Van Dijk et al. (2013) attempt to correlate water concentrations of imidacloprid with changes in the abundance of different groups of aquatic invertebrates. Based on their analysis, Van Dijk et al. (2013) suggest imidacloprid causes decreases in invertebrate abundance at surface water concentrations of 13 - 67 ng/L (i.e., 0.000013 - 0.000067 mg/L). The statistical significance underlying this assertion relates to significant *p*-values in the F-test for the regression. Put simply, this test determines if the slope of the regression line is significantly different from zero. While the analysis by Van Dijk et al. (2013) appears to be carefully conducted and is well reported, there are issues with the F-test for large samples. Specifically, large numbers of data points can lead to statistically significant differences in the F-test (i.e., the slope is not equal to zero) while the correlation may not account for a substantial amount of the variability in the data. This appears to be the case with the analysis by Van Dijk et al. (2013). As detailed in Table 1 of this publication, highly significant *p*-values (well below <0.01) for the F-test are associated with squared correlation coefficients in the range of about 0.006 - 0.19. In other words, the concentration of imidacloprid in water (the explanatory variable) accounts for only about 0.6% - 19% of the variability in the data. The analysis by Van Dijk et al. (2013) was reviewed by Vijver and Van Den Brink (2014) who note the difficulty in associating the trends observed by Van Dijk et al. (2013) with a single pesticide (i.e., imidacloprid) under conditions where exposures to multiple pesticides clearly occurred. Notwithstanding concerns with the Van Dijk et al. (2013) analysis, this study in conjunction with the data on sensitive species of Ephemeroptera, is considered further in the dose-response assessment for aquatic invertebrates (Section 4.3.3.3).

4.1.3.3.5. Metabolites

Information on the toxicity of imidacloprid metabolites to aquatic invertebrates is summarized in Appendix 6, Table A6-11. All of the available studies were submitted to the EPA in support of the registration of imidacloprid, and no new studies were identified in the open literature. All of the registrant-submitted studies are covered in the previous Forest Service risk assessment on imidacloprid (SERA 2005); accordingly and the discussion of these studies is little changed from the earlier risk assessment.

None of the imidacloprid metabolites tested (urea metabolite NTN 33519; 6-chloronicotinic acid and NTN 33823) were as acutely toxic as technical grade imidacloprid in tests with the midge (*Chironomus tentans*) or amphipod (*Hyalella azteca*) (Bowers1996a; Bowers and Lam 1988; Rooney and Bowers 1996; Dobbs and Frank 1996b). The lowest definitive LC_{50} for any imidacloprid metabolite is 51.8 mg a.i/L—i.e., the 96-hour LC_{50} for the hydroxyl metabolite of imidacloprid in *Hyalella azteca* (Rooney and Bowers 1996, MRID 43946601). As summarized in Table 22, the LC_{50} of this species is 0.526 mg a.i./L, below the toxicity of the hydroxyl metabolite by a factor of about 100 [$51.8 \div 0.526 \approx 98.47$]. Based on the available information, there is no basis for identifying the metabolites of imidacloprid as potentially hazardous to aquatic invertebrates, relative to the hazards posed by imidacloprid itself.

4.1.3.4. Aquatic Plants

4.1.3.4.1. Algae

Information on the toxicity of imidacloprid to algae is summarized on Appendix 7, Table A7-1. This information is essentially identical to the studies summarized in previous Forest Service risk assessment on imidacloprid (SERA 2005). Only two new studies from the open literature have been identified—i.e., Kungolos et al. (2009) and Tisler et al. (2009).

The study by Kungolos et al. (2009) uses an unspecified Confidor formulation from Greece, and it is not clear if the reported indefinite IC_{50} of >1000 mg/L is in units of formulation or a.i. Given that the reported concentration of 1000 mg/L is higher than the water solubility of technical grade imidacloprid (≈600 mg a.i./L as summarized in Table 1), it is likely that the 1000 mg/L concentration is in units of formulation. Kungolos et al. (2009) do not, however, specify the proportion of a.i. in the formulation.

The study by Tisler et al. (2009) uses a Confidor 200 SL formulation as well as technical grade imidacloprid. The 72-hour EC_{10} of 106 mg a.i./L reported by Tisler et al. (2009) for technical grade imidacloprid in a species of green alga (*Desmodesmus subspicatus*) is consistent with the 5-day (120 hour) NOAEC of >119 mg/L reported by Gagliano and Bowers (1991, MRID 42256374) for another species of green alga (*Selenastrum capricornutum*). Based on EC_{10} values, Tisler et al. (2009) note that the Confidor formulation is more toxic than technical grade imidacloprid by a factor of about 20, when concentrations are compared on an a.i. basis[106 mg a.i./L ÷ 5.6 mg a.i./L ≈ 18.9]. This study, however, is not directly applicable to the current risk assessment because Confidor formulations are not specifically designated for use in Forest Service programs (Table 2). Nonetheless, as discussed below, these results are consistent with data on Merit 2F, which appears to be more toxic than technical grade imidacloprid.

Two other toxicity studies on algae were submitted to the EPA by the registrants and involve the use of either technical grade imidacloprid or the Merit 2F (21.6% a.i.) formulation. The free standing NOAECs for technical grade imidacloprid range from 10 mg a.i./L in *Scenedesmus subspicatus* (Heimbach 1989, MRID 42256374) to 119 mg a.i./L in *Pseudokirchneriella subcapita* (Gagliano and Bowers 1991, MRID 42256374). For risk characterization, U.S. EPA/OPP/EFED (2007a, 2008a) uses the lower NOAEC of 10 mg a.i./L. The toxicity data on Merit 2F (21.6% a.i.) indicate a NOAEC of 6.69 mg a.i./L in *Navicula pelliculosa*. That this NOAEC is somewhat lower than the NOAEC used in the EPA risk assessments is of no consequence to the risk characterization (Section 4.4.3.4.1).

As summarized in Appendix 7, Table A7-2, the mesocosm study by Moring et al. (1992, MRID 42256306) notes transient decreases in mixed algal populations at a concentration far below the 10 mg a.i./L NOAEC used by EPA. As discussed in Section 4.1.3.3, this study focuses on the impact of imidacloprid on aquatic invertebrates, and the transient changes in algal populations reported by Moring et al. (1992) may be incidental. Although this study was submitted to U.S. EPA, it is not cited in the most recent EPA ecological risk assessments on imidacloprid (U.S. EPA/OPP/EFED 2007a, 2008a). The study is, however, cited in the Canadian Water Quality Guidelines for imidacloprid, and the effects on phytoplankton at 0.02 mg a.i./L with a NOAEC of 0.006 mg a.i./L are documented (CCME 2007). The observations by Moring et al. (1992)

cannot be dismissed; however, the significance of the transient effect on algae is marginal relative, to the much better documented effects on aquatic invertebrates (Section 4.1.3.3).

4.1.3.4.2. Aquatic Macrophytes

Aquatic macrophytes are not addressed in the toxicity data on imidacloprid. The EPA problem formulation for the registration review of imidacloprid (U.S. EPA/OPP/EFED 2008a, p. 11) indicates that duckweed (*Lemna gibba*) will be used in the ecological risk assessment on imidacloprid. No reference to a completed study in duckweed was identified.

As summarized in Appendix 7, Table A7-3, Daam et al. (2013) report a 7-days EC_{50} of 740 mg a.i./L using a Confidor 200 SL formulation and *Lemna minor*, another species of duckweed,. No further details of the response (e.g., NOAEC or slope) are given in the publication. This EC_{50} in duckweed is higher than the EC_{50} of 116 mg a.i./L for Confidor 200 SL in *Desmodesmus subspicatus*, a green alga (Tisler et al. 2009) by a factor of about 6 [$740 \div 116 \approx 6.38$]. As summarized in Appendix 7, Table A7-1, Daam et al. (2013) report an indefinite EC_{50} of >600 mg a.i./L in another species of green alga, *Selenastrum capricornutum*. Based on this admittedly limited comparison, *Lemna* do not appear to be more sensitive to imidacloprid than algae.

4.1.3.5. Aquatic Microorganisms

Aquatic microorganisms are not addressed in the toxicity data on imidacloprid. As discussed in Section 4.1.3.3.4 (aquatic invertebrate mesocosm studies), water concentrations of imidacloprid that caused adverse effects in two species of aquatic invertebrates did not adversely affect microbial respiration or decomposition rates (Kreutzweiser et al. 2007, 2008c).

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 1: Tree injection
- Attachment 2: Soil injection
- Attachment 3: Bark Applications
- Attachment 4: Foliar Broadcast applications

Athough the Forest Service does not intend to use foliar applications of imidacloprid, this application method is explicitly considered in the current risk assessment as a contrast to the more focused application methods that the Forest Service will use—i.e., tree and soil injection as well as bark application.

In the ecological risk assessment, a major uncertainty in exposure scenarios for terrestrial animals involves the proportion of an animal's diet that might be contaminated with imidacloprid. As with all Forest Service risk assessments (SERA 2014a), the exposure assessments considered this section assume that 100% of the diet is contaminated because objective methods are not available to support an alternative approach. Deviations from the assumption of 100% contamination are discussed in the risk characterization (Section 4.4) as necessary.

The exposure scenarios that are more or less standard in Forest Service risk assessments are not all relevant to the specific application methods considered in the current risk assessment of imidacloprid (Section 3.2). Hence, the exposure scenarios used in the Forest Service risk assessments on dinotefuran (SERA 2009a), another neonicotinoid, and emamectin benzoate (SERA 2010b), another pesticide applied by tree injection are adapted to the current risk assessment.

Table 27 summarizes the exposure assessments for mammals and birds. All of the standard exposure scenarios are relevant for assessing the effects of broadcast foliar applications with respect to birds and mammals. As in the human health risk assessment, bark applications are treated similarly to foliar applications, except that the nontarget losses (i.e., the pesticide not remaining on the tree bark) are taken as 10% of the nominal application rate. For tree and soil injection, non-accidental exposure assessments omit scenarios for the consumption of contaminated vegetation by mammals and birds. The exposure scenarios for imidacloprid contaminated vegetation are not considered quantitatively for tree and soil injection. Exposure scenarios for imidacloprid involving contaminated vegetation are not considered quantitatively for tree and soil injection. While exposures to contaminated vegetation through a variety of scenarios cannot be ruled out for soil and tree injection, the only exposure scenarios that can be reasonable quantified involve contaminated surface water.

Exposure scenarios for honeybees and phytophagous insects are also considered for all application methods. Forest Service risk assessments of insecticides typically assess risks to honeybees based on a direct spray scenario. Pathways for direct spray and spray drift are considered for foliar and bark applications of imidacloprid. For phytophagous insects and foraging honeybees, exposures are estimated for all application methods, although the information used to estimate exposures is based on different data sets for the different application methods.

Exposures for aquatic organisms are based on the same estimates used in the risk assessment for human health effects (Section 3.2.3.4).

4.2.2. Mammals and Birds

All of the exposure scenarios that are more or less standard in Forest Service risk assessments for broadcast applications are not relevant to all of the specific application methods considered in the current risk assessment of imidacloprid. Summaries of the specific exposure scenarios considered for each of the application methods covered in the current risk assessment are provided in Table 27. These tables are structurally similarly to Table 6, which summarizes the exposure scenarios considered in the human health risk assessment.

Table 28 provides an overview of the mammalian and avian receptors considered in the current risk assessment. These data are discussed in the following subsections. Because of the relationship of body weight to surface area as well as to the consumption of food and water, for any type of exposure, the dose for small animals is generally higher, in terms of mg/kg body weight, than the dose for large animals. The exposure assessment for mammals considers five nontarget mammals of varying sizes: small (20 g) and medium (400 g) sized omnivores, a 5 kg canid, a 70 kg herbivore, and a 70 kg carnivore. Four standard avian receptors are considered: a 10 g passerine, a 640 g predatory bird, a 2.4 kg piscivorous bird, and a 4 kg herbivorous bird. Because of presumed differences in diet, (i.e., the consumption of food items), all of the mammalian and avian receptors are not considered in all of the exposure scenarios (e.g., the 640 g predatory bird is not used in the exposure assessments for contaminated vegetation).

4.2.2.1. Direct Spray

Direct spray scenarios are relevant to the broadcast application of virtually any pesticide. For imidacloprid, however, the Forest Service will not use broadcast applications. In addition, incidental direct spray could occur in bark applications. For tree injection and soil injection, a direct spray of a mammal or bird is not a reasonable exposure scenario. Consequently, direct spray scenarios for imidacloprid are included only in Attachment 3 (bark application) and Attachment 4 (foliar application). As discussed in Section 2.1, the Forest Service does not anticipate using foliar applications of imidacloprid.

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. The first spray scenario (Worksheet F01a) concerns the direct spray of half of the body surface of a 20 g mammal during a pesticide application. This exposure assessment assumes first-order dermal absorption using the first-order dermal absorption rate coefficient (k_a) discussed in Section 3.1.3.2.2. The second exposure assessment (Worksheet F01b) assumes complete

absorption over Day 1 of exposure. This assessment is included in an effort to encompass increased exposures due to grooming.

Exposure assessments for the direct spray of a large mammal are not developed. As discussed further in Section 4.4.2.1, the direct spray scenarios lead to HQs far below the level of concern, and an elaboration for body size would have no impact on the risk assessment.

4.2.2.2. Dermal Contact with Contaminated Vegetation

As discussed in the human health risk assessment (Section 3.2.3.3), the 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 as well as a transfer rate from the contaminated vegetation to the skin. Unlike the human health risk assessment for which estimates of transfer rates 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. The lack of data regarding the kinetics of this process precludes a quantitative assessment for this exposure scenario.

For imidacloprid, the failure to quantify exposures associated with dermal contact adds relatively little uncertainty to the risk assessment, since the consumption of contaminated vegetation is dominant route of exposure, as discussed below.

4.2.2.3. Ingestion of Contaminated Vegetation or Prey

The exposure scenarios for the consumption of contaminated vegetation are similar to the exposure scenarios considered in the human health risk assessment (Section 3.2.3.7), except that the ecological risk assessment considers a wider variety of vegetation—i.e., long and short grass, in addition to fruit and broadleaf vegetation, which are considered in the human health risk assessment. As with the human health risk assessment, residues on vegetation following bark application are assumed to be one-tenth of the residues following broadcast application. Also as in the human health risk assessment and consistent with past Forest Service risk assessments, quantitative exposure scenarios are not developed for the consumption of contaminated vegetation or prey following soil injection and tree injection.

The acute and chronic exposure scenarios are based on the assumption that 100% of the diet is contaminated, which may not be realistic for some acute exposures and seems an unlikely event in chronic exposures—i.e., animals may move in and out of the treated areas over a prolonged period of time. While estimates of the proportion of the diet contaminated could be incorporated into the exposure assessment, the estimates would be an essentially arbitrary set of adjustments. The proportion of the contaminated diet is linearly related to the resulting HQs, and its impact is discussed further in the risk characterization (Section 4.4.2.1).

The estimated food consumption rates by various species of mammals and birds are based on field metabolic rates (kcal/day), which, in turn, are based on the adaptation of estimates from Nagy (1987) by the U.S. EPA/ORD (1993). These allometric relationships account for much of the variability in food consumption among mammals and birds. There is, however, residual variability, which is remarkably constant among different groups of organisms (Table 3 in Nagy

1987). As discussed by Nagy (2005), the estimates from the allometric relationships may differ from actual field metabolic rates by about ±70%. Consequently, in all worksheets involving the use of the allometric equations for field metabolic rates, the lower bound is taken as 30% of the estimate and the upper bound is taken as 170% of the estimate.

The estimates of field metabolic rates are used to calculate food consumption based on the caloric value (kcal/day dry weight) of the food items considered in this risk assessment and estimates of the water content of the various foods. Estimates of caloric content are summarized in Table 29. Most of the specific values in Table 29 are taken from Nagy (1987) and U.S. EPA/ORD (1993).

Along with the exposure scenarios for the consumption of contaminated vegetation, similar sets of exposure scenarios are provided for the consumption of small mammals by either a predatory mammal (Worksheet F10a) or a predatory bird (Worksheet F10b) and the consumption of contaminated insects by a small mammal, a larger (400 g) mammal, and a small bird (Worksheets F09a-c).

4.2.2.4. Ingestion of Contaminated Water

The methods for estimating imidacloprid concentrations in water are identical to those used in the human health risk assessment (Section 3.2.3.4.6.1). As with the human health risk assessment and the previous Forest Service risk assessments covering tree injection, imidacloprid concentrations in surface water are estimated quantitatively only for the accidental spill scenario for tree injection.

Body weight and water consumption are the major differences in the exposure estimates for birds and mammals, relative to humans. Like food consumption rates, water consumption rates, which are well characterized in terrestrial vertebrates, are based on allometric relationships in mammals and birds, as summarized in Table 28.

Like food consumption, water consumption in birds and mammals varies substantially with diet, season, and many other factors. Quantitative estimates regarding the variability of water consumption by birds and mammals are not well documented in the available literature and are not considered in the exposure assessments. Nevertheless, as summarized in Table 11, the upper and lower bound estimates of imidacloprid concentrations in surface water vary substantially (e.g., by a factor of 47,500 for acute exposures and a factor of over 500,000 for chronic exposures following bark applications). Given this degree of variability in the estimated concentrations of imidacloprid in surface water, it is unlikely that a quantitative consideration of the variability in water consumption rates of birds and mammals would have a substantial impact on the risk characterization. In addition and as discussed further in Section 4.4.2.1 (risk characterization for mammals) and Section 4.4.2.2 (risk characterization for birds), exposures associated with the consumption of contaminated surface water are far below the level of concern (HQ=1) even for broadcast applications. Consequently, extreme variations in the estimated consumption of contaminated water by mammals and birds would have no impact on the risk characterization for mammals and birds.

4.2.2.5. Consumption of Contaminated Fish

In addition to the consumption of contaminated vegetation, insects, and other terrestrial prey (Section 4.2.2.3), the consumption of contaminated fish by piscivorous species is a potentially significant route of exposure to imidacloprid. Exposure scenarios are developed for the consumption of contaminated fish after an accidental spill (Worksheets F03a-c), expected peak exposures (Worksheets F011a-c), and estimated longer-term concentrations (Worksheets F17a-c). These exposure scenarios are applied to 5 and 70 kg carnivorous mammals as well as a 2.4 kg piscivorous bird. The 70 kg carnivorous mammal is representative of a small or immature brown bear (*Ursus arctos*), which is an endangered species that actively feeds on fish (Reid 2006). As summarized in Table 22, the 5 kg mammal is representative of a fox, and the 2.4 kg bird is representative of a heron.

Imidacloprid exposure levels associated with the consumption of contaminated fish depend on the imidacloprid concentration in water and the bioconcentration factor for imidacloprid in fish. The concentrations of imidacloprid in water are identical to those discussed in Section 4.2.2.4. As discussed in Section 3.2.3.5, imidacloprid does not bioconcentrate substantially in fish; accordingly, the bioconcentration for imidacloprid is taken as 1 L/kg—i.e., no bioconcentration of imidacloprid in fish is assumed. This approach is consistent with the assessment provided in U.S. EPA/OPP/EFED (2008a, p. 6).

4.2.3. Terrestrial Invertebrates

4.2.3.1. Direct Spray and Drift

Direct spray and spray drift exposure scenarios are typically used only in foliar broadcast applications. As discussed in Section 2, the current risk assessment does not support broadcast applications of imidacloprid; nonetheless, a workbook for broadcast applications is included as Attachment 4 to the current risk assessment. As discussed in Section 2, bark applications are assumed to be 90% efficient in terms of the amount of pesticide applied to the bark, and 10% of the applied pesticide is lost to the area surrounding the tree due to splashing and drift. Thus, Attachment 3 for bark applications also includes the scenarios for direct spray, drift, and contaminated vegetation but these scenarios are based on an application of one-tenth of the nominal application rate. These direct spray scenarios for a terrestrial invertebrate are included as Worksheet G09 of the workbooks for bark applications (Attachment 3) and foliar broadcast applications (Attachment 4). Since this exposure scenario is not relevant to tree injection (Attachment 1) or soil injection (Attachment 2), Worksheet G09 is not included in the attachments for these application methods.

The honeybee is used as a surrogate for other terrestrial invertebrates in most Forest Service risk assessments (SERA 2014a) as well as most EPA risk assessments (e.g., U.S. EPA/OPP/EFED 2008a, p. 10). This approach is fairly standard, because acute toxicity studies in the honeybee are required for the registration of pesticides that may be applied by broadcast applications (U.S. EPA/OCSPP 2012b) and honeybee toxicity studies are often the only data available on the toxicity of many pesticides to terrestrial invertebrates. As discussed in Section 4.1.2.4, this is not the case with imidacloprid, and toxicity data are available on a wide variety of terrestrial invertebrates. Nonetheless, as discussed in Section 4.1.2.4.2.1.1 and illustrated in Figure 4, honeybees are among the terrestrial invertebrates most sensitive to imidacloprid. Consequently,

the direct spray and spray drift scenarios are applied to the honeybee in the current risk assessment.

Direct spray exposure scenarios for terrestrial invertebrates are modelled as a simple physical process based on the application rate and surface area of the organism (SERA 2014a). 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 amount of a pesticide 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. The estimated proportions of the nominal application rate at various distances downwind given in Worksheet G09 are based on Tier 1 estimates from AgDRIFT (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 a pesticide may occur. The impact of foliar interception varies according to 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. (1993) report 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 G09, foliar interception rates of 0% (no interception), 50%, and 90% are used.

During applications of imidacloprid or any other pesticides, it is likely that terrestrial invertebrates other than bees will be subject to direct spray or spray drift. As noted above, toxicity data are available on numerous terrestrial invertebrates. Potential risks to other invertebrates are discussed in the risk characterization (Section 4.4.2.4).

4.2.3.2. Ingestion of Contaminated Vegetation or Prey

Two exposure scenarios are considered for the consumption of contaminated vegetation or prey. The first involves the consumption of contaminated vegetation from a treated tree and the second involves the consumption of other vegetation incidentally contaminated with imidacloprid. All of these exposure scenarios address the four types of vegetation detailed in Table 12, which are in turn adopted from the approach used in U.S. EPA/OPP/EFED (2001, p. 44). As summarized in Table 12, residue rates for small insects are approximated using the residue rates for broadleaf vegetation and the residue rates for large insects are approximated using residue rates for fruits, pods, and seeds. Thus, while the discussion of these exposure scenarios focuses on phytophagous insects, the scenarios for broadleaf vegetation and fruits encompass potential exposures to insectivorous insects.

4.2.3.2.1. Foliage from Nontarget Vegetation

All Forest Service risk assessments for broadcast or directed foliar applications include exposure assessments for the consumption of contaminated vegetation by herbivorous insects, provided that toxicity data are available on or can be approximated for herbivorous insects (SERA 2014a, Section 4.2.3.2). As summarized in Section 4.1.2.4.2, the available data on the toxicity of imidacloprid to insects support this exposure scenario.

As discussed in Section 2, the Forest Service will not use foliar applications of imidacloprid, which are discussed in the current risk assessment only to elaborate, by contrast, the risk

characterization for the primary application methods to be used by the Forest Service—i.e., tree and soil injections. In addition, as discussed in Section 2.4.3, bark applications are explicitly covered in the current risk assessment to support FIFRA 2(ee) bark applications of imidacloprid. As detailed in Section 3.2.3.7, estimates of loss from a bark application to the surrounding area range from 5% (Cowles 2009) to 10% (Onken 2009). As with the Forest Service risk assessment on dinotefuran (SERA 2009a), the current risk assessment on imidacloprid uses the 10% estimate for unintended loss in bark applications. Thus, the application efficiency to the bark is assumed to be 90% and the offsite loss to nontarget vegetation is assumed to be 10% of the nominal application rate.

Based on the above considerations, the consumption of nontarget vegetation incidentally contaminated with imidacloprid is considered in the EXCEL workbooks for bark applications (Attachment 3) and foliar applications (Attachment 4). As discussed in Section 3.2.3.7, the difference between these two workbooks for this exposure scenario is that the standard residue rates for vegetation are used for foliar applications but are reduced by a factor of 10 (i.e., 10% incidental loss to nontarget vegetation) for bark applications.

Estimates of the amount of vegetation that herbivorous insects might consume are identical to the exposure scenarios for the consumption of contaminated vegetation from treated trees (Section 4.2.3.2.1). These exposure scenarios are detailed in Worksheets G07a-d of Attachment 3 (bark applications) and Attachment 4 (directed foliar applications).

4.2.3.2.2. Foliage from Treated Trees

Because imidacloprid is used to treat trees, the consumption of contaminated vegetation (i.e., leaves or needles) from treated trees is an obvious exposure pathway for herbivorous insects. Unlike the case with bark application, which may involve the contamination of nontarget vegetation, there is no basis for asserting that tree injection is likely to cause significant contamination to nontarget vegetation. Soil injection may be associated with the eventual contamination of some nontarget vegetation near the treated tree; however, a greater source of contamination for herbivorous insects would involve the consumption of vegetation from the target tree. Consequently, exposure assessments in the workbooks for tree injection (Attachment 1) and soil injection (Attachment 2) focus on the consumption by herbivorous insects of vegetation from the treated trees.

The exposure scenarios for the consumption of vegetation from treated trees are given in Worksheet G07a (maple), Worksheet G07b (ash), and Worksheet G07c (hemlock). Additional information on residues of imidacloprid in tree leaves or needles is likely to result from further research on the use of imidacloprid for tree treatments. In any specific Forest Service program, particularly for trees other than maple, ash, and hemlock, other estimates of pesticide residues in vegetation may be available. As a convenience for other users of these worksheets, Worksheet G07d is provided as a placeholder for data on other species that may become available. Concentrations of imidacloprid for other tree species may be filled in in Worksheet G07d. All of these worksheets are linked to the exposure summary (Worksheet G08a) and the summary of hazard quotients (Worksheet G08b). These worksheets are included in the EXCEL workbooks for tree injection (Attachment 1) and soil injection (Attachment 2).

The estimated concentrations of imidacloprid in leaf tissues are discussed in Section 4.2.3.2.2.1 and the estimates of the amount of material consumed by an insect are given in Section 4.2.3.2.2.2.

4.2.3.2.2.1. Concentrations in Foliage

A key input parameter for developing this exposure scenario involves the concentration of imidacloprid in the leaves or needles from the treated tree. As discussed in Section 2, imidacloprid may be used in Forest Service programs to treat several different kinds of trees, including ash (for the control of the emerald ash borer), eastern hemlock (for the control of the hemlock woolly adelgid), and maple (for the control of the Asian longhorned beetle). As summarized in Table 30, data are available on the concentrations of imidacloprid in ash, hemlock, and maple following applications of imidacloprid by tree injection, soil injection, and soil drench.

The first column in Table 30 summarizes the type of treatment and application rate in terms of g a.i./inch tree diameter at breast height (DBH). The second column of Table 30 gives monitored residues in leaves or needles in units of µg/g, and the third column gives the residue rates in units of µg/g leaves per g/inch DBH. As detailed in the methods document for the preparation of Forest Service risk assessments (SERA 2014a, Section 3.2.3.7) and discussed in the previous section (Section 4.2.3.2.1), residue rates in units of mg/kg vegetation per lb a.i./acre applied are typically used in exposure assessments for broadcast applications, based on estimates from Fletcher et al. (1994). For applications to trees, this approach does not appear to be appropriate. As discussed in Section 2, application rates for imidacloprid to trees will depend on the application method and the size of the tree. The reason for this variability is that the intent of the treatment is to ensure that an effective amount of pesticide is absorbed by or injected into the tissue of the tree. For example, as summarized in Table 30, the study by Dilling et al. (2010) illustrates that a relatively low dose by tree injection (i.e., 0.056 g a.i./inch DBH) and a much higher dose by soil injection (i.e., 1 g a.i./inch) result in comparable levels of imidacloprid in the needles of hemlock (i.e., about 0.19 µg a.i./g needle for tree injection versus about 0.18 µg a.i./g needle for soil injection). As another example, Ugine et al. (2013) note no significant difference in the residues in smaller maple (<61 cm DBH) injected at a rate of 0.22 g a.i./inch DBH and larger maple (≥ cm DBH) injected at a rate of 0.44 g a.i./inch DBH.

The most striking pattern in Table 30 is difference between residues in leaves or needles among the different species of trees. With the exception of the intentional over-dose of an ash tree in the study by Kreutzweiser et al. (2007)—i.e., about 14 g/inch DBH—all of the treatments summarized in Table 30 involved labelled application rates designed to yield an effective concentration of imidacloprid in the tree tissue. The concentrations in the leaf tissue for the different tree species are strikingly different. The highest concentrations are found in maple (about 6 - 50 µg a.i./g leaf) followed by ash (about 0.1 - 1.3 µg a.i./g leaf) and then hemlock (about 0.04 - 0.22 µg a.i./g leaf). These striking differences clearly indicate that the movement and distribution of imidacloprid within trees is highly dependent on the tree species. In other words, the pharmacokinetics of imidacloprid in trees appears to be highly species-specific.

This variability is addressed in the current risk assessment by providing different exposure scenarios for ash, hemlock, and maple trees. For the treatment of maple, the estimated residues in trees are taken as 14 (6.2 - 49) µg a.i./g leaf from the study by Ugine et al. (2013) rounding the

concentrations to two significant figures. For ash, the estimated residues are taken as 0.85 (0.1 - 1.28) µg a.i./g leaf based on a composite of the data from Kreutzweiser et al. (2007) and Mota-Sanchez et al. (2009). As discussed above, the residue of 81.3 µg a.i./g leaf in ash from the study by Kreutzweiser et al. (2007) is not used because this residue is associated with an experimental application that is a factor of 10 above the highest labeled application rate for imidacloprid. For hemlock, the estimated residue is taken as 0.1 (0.03 - 0.2) µg a.i./g needle as a composite of the data from Cowles et al. (2006) and Dilling et al. (2010).

As also summarized in Table 30, Acimovic et al. (2014) report residues of 0.5 to 2.2 mg/kg leaf tissue in mature apple trees following tree injections of 1 g a.i./tree. Acimovic et al. (2014), however, do not report the size of the trees and thus residue rates cannot be derived. In addition, the residues were measured at 14 to 42 days after treatment and may not reflect maximum residues in leaves. In an earlier study, USDA/AHPIS (2003) reports leaf residues about 7.6 (3.3 to 54) µg a.i./g leaf tissue for a variety of tree species following tree injection of imidacloprid at a rate of about 0.22 g a.i./inch DBH. These concentrations are in the range of concentrations reported by Ugine et al. (2013) in maple.

4.2.3.2.2.2. Foliage Consumption by Insects

In addition to estimated concentrations of imidacloprid in leaves or needles, the exposure assessment for herbivorous insects feeding on treated trees requires estimates of insect food consumption, which 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 they may consume vegetation at a rate of about 0.6 of their body weight per day (Reichle et al. 1973, pp. 1082 - 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 - 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).

For imidacloprid, the actual amount of leaves or needles that an insect might ingest may be overestimated, perhaps substantially so. As discussed in Section 4.1.2.4.2.2, there is robust literature indicating that imidacloprid may lead to a suppression of food consumption. As the insect consumes the contaminated vegetation, it would likely become intoxicated (sicken), resulting in a decreased rate of food consumption. This is an extremely common occurrence in toxicity bioassays and is likely to occur in the field. The overestimation of dose, however, has a minimal impact on the risk characterization, as discussed further in Section 4.4.2.4.

The proportion of the insect's diet that is contaminated is another factor that may be important in some site-specific applications of imidacloprid. In some cases, it may not be reasonable to assume that 100% of the diet is contaminated. For the current risk assessment, the assumption is

made that 100% of the diet is contaminated and lesser rates of dietary contamination are discussed qualitatively in the risk characterization (Section 4.4.2.4).

4.2.3.3. Exposure to Contaminated Nectar

Risks to honeybees foraging for nectar are assessed using the approach taken in the Forest Service risk assessment on dinotefuran (SERA 2009a). The following discussion of the basic method is taken from SERA (2009a), and estimated concentrations of imidacloprid in nectar (discussed further below) are taken from the analysis by Dively and Kamel (2012). The analyses are implemented in Worksheet G10 of the workbooks that accompany the current risk assessment—i.e., Attachments 1 through 4—with differing estimated concentrations of imidacloprid in nectar, based on the different application methods, which are discussed below following the description of the general methods used in the exposure assessment.

4.2.3.3.1 General Method

Prompted by concerns raised in a Tier 1 analysis for imidacloprid conducted by the Forest Service (Appleton 2008), the basic approach taken in the current risk assessment and the Forest Service risk assessment on dinotefuran (SERA 2009) is conceptually similar to the 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). As discussed in Section 4.1.2.4.2.2, the most sensitive endpoint for honeybees is colony death during overwintering. Consequently, the dose-response assessment for honeybees (Section 4.3.2.4.1) is based on the honeybee colony rather than worker bees or other subgroups of honeybees. In that respect, the dose to the nectar forager may be viewed as the route of entry for the honeybee colony.

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 imidacloprid 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 - 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 - 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 used 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 - 344) mg/day. In the worksheets for this exposure scenario (i.e., G10 in the attachments), these values are converted to units of kg nectar per day by dividing mg/day by 1,000,000 mg/kg.

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 imidacloprid consumed by the bee could be the same whether the exposure is based on nectar consumption or honey consumption.

Another uncertainty in the amount of contaminated nectar that a foraging honeybee might consume involves the proportion of the plants that are contaminated in the area in which the honeybee forages. For broadcast applications, this factor is inconsequential as it seems reasonable to assume that 100% of the plants would be contaminated. A discussed in Section 2, however, the Forest Service will not apply imidacloprid in broadcast applications. The more focused application methods used by the Forest Service—i.e., tree and soil injections and bark applications—could and probably would generally result in a highly uneven distribution of imidacloprid over the general area in which the applications occur. This uncertainty is addressed in the exposure assessments by using nominal application rate—i.e., 0.4 lb a.i./acre—in the workbooks that accompany this risk assessment. While some plants might be exposed at higher rates—e.g., plants in the area of a soil injection—other plants might be subject to much lower or negligible levels of contamination—e.g., plants not in the area of a soil injection. The use of the nominal application rate in terms of 0.4 lb a.i./acre is intended to reflect average exposures to imidacloprid from foraging over the course of an entire day.

4.2.3.3.2. Concentrations of Imidacloprid in Nectar

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), the possible imidacloprid concentrations in nectar associated with the various application methods under consideration are much less certain. As reviewed by Blacquiere et al. (2013, p. 981, column 2), imidacloprid has been monitored in nectar at concentrations of about 2 - 20 µg/kg (ppb). These monitoring data for nectar, like the water monitoring data discussed in Section 3.2.3.4.5, are not associated with defined applications of imidacloprid and cannot be used to estimate differing concentrations of imidacloprid in nectar associated with the various application methods covered in the current risk assessment. Three studies, however, are available in which concentrations of imidacloprid in nectar are associated with defined applications – i.e., Dively and Kamel (2012), Byrne et al. (2013), Krischik et al. (2007), and Larson et al. 2015.

The study by Dively and Kamel (2012) provides estimates of imidacloprid in nectar following defined applications of imidacloprid to pumpkin, as a surrogate for the cucurbit crop group. In this study, imidacloprid was applied by bedding drench at an application rate of 0.03 kg a.i./ha and in transplant water at application rates of 0.281 and 0.422 kg a.i./ha. About 5 weeks after application (during flowering), levels of imidacloprid were determined in nectar, pollen, and leaves. Two sets of applications were conducted, one in 2009 and the other in 2010, but levels of imidacloprid in leaves were assayed only in 2010. The data from Dively and Kamel (2012) are summarized in a custom worksheet (G11). This worksheet is included in each of the attachments immediately following Worksheet G10 and the specific uses of these data are discussed in the following section for different application methods – i.e., Section 4.2.3.3.3, Exposures of Bees for Different Application Methods.

The imidacloprid residues in nectar and pollen were substantially higher in 2009 than in 2010. As discussed in Dively and Kamel (2012, p. 4452), this difference appears to be due to atypically hot and dry weather during 2010. For the current risk assessment, only residues for 2009 are used. This approach is only modestly conservative in that the average residues in nectar are only about 20% higher in 2009 than in 2010 (the orange shaded cells in Worksheet G11). Normalized for application rate, the residues for transplant water treatment are virtually identical for the low and high application rates—i.e., the green shaded cells in Worksheet G011. At the lower application rate, the nectar residue rate is 30 (16 - 45) ng/g (ppb) per lb a.i./acre. At the high application rate, the nectar residue rate is 29 (13 - 47) ng/g (ppb) per lb a.i./acre. For the exposure assessments involving application methods other than tree injection, the average of the two sets of values is used—i.e., 29 (14 - 46) ng/g (ppb) per lb a.i./acre [the blue shaded cells in Worksheet G11]. These rates are used in preference to the data from bedding tray drench, because the application rates of about 0.28 and 0.42 kg a.i./ha for transplant water applications are closer to the application rates considered in the current risk assessment (i.e., a maximum rate of 0.4 lb a.i./acre), compared with the very low rate of 0.03 kg a.i./ha used in the bedding tray drench study.

The data from Dively and Kamel (2013) are similar to studies by Byrne et al. (2013) following applications to citrus trees and Krischik et al. (2007) following applications to buckwheat. The study by Byrne et al. (2013) involved treating citrus trees (orange trees or tangerine trees) by soil drench applications at rates 0.56 kg a.i./acre (≈0.5 lb a.i./acre) or 1.12 kg a.i./acre (≈1 lb a.i./acre). At 0.5 lb a.i./acre, average residues in nectar were about 8.3 to 12.81 ng/mL (Table 2 of Byrne et al. 2013), corresponding to residue rates of about 16.6 to 49.62 µg/L (ppb) per lb a.i./acre. These rates are similar to the rates derived from Dively and Kamel (2012) as discussed above – i.e., 29 (14 - 46) ng/g (ppb) per lb a.i./acre.

The study by Krischik et al. (2007) involved the soil treatment of potted buckwheat plants at rates of 0.014 g a.i./pot (the labeled application rate) and 0.028 g a.i./pot (twice the labeled application rate). Note that the treatment rates given in the paper are 1.4 g and 2.8 g formulation/pot using a 1% a.i. formulation of imidacloprid (i.e., Marathon 1% G). Each pot has a surface area of 10.5 cm^2 (Krischik et al. 2007, p. 1239). The application rate of 0.014 g a.i./pot is equivalent to about 118.96 lb a.i./acre [(0.014 g ÷ (453.59 g/lb)) ÷ (10.5 cm^2 ÷ 2.471 x 10^{-8} cm^2/acre)]. At this application rate, the average residue of imidacloprid in the nectar of treated flowers was 6,550 ppb (Krischik et al. 2007, Table 2, all replicates combined) and the corresponding residue rate is about 55 ppb per lb a.i./acre [6,550 ppb ÷ 118.96 lb a.i./acre ≈ 55.05 ppb/lb a.i./acre]. At the higher application rates (equivalent to about 237.92 lb a.i./acre), the average residue was 12,270 ppb, with a corresponding residue rate of about 52 ppb per lb a.i./acre [12,270 ppb ÷ 237.92 lb a.i./acre ≈ 51.57 ppb per lb a.i./acre]. Despite the substantial difference in application rates between the study by Krischik et al. (2007) and the studies by Dively and Kamel (2013) and Byrne et al. (2013), the residue rates from Krischik et al. (2007) are similar to the upper bound rates from Dively and Kamel (2013) – i.e., 46 ppb per lb a.i./acre – and Byrne et al. (2013) – i.e., 49.62 µg/L (ppb) per lb a.i./acre.

The study by Larson et al. (2015) involved foliar spray applications of turf with flowering weeds (i.e., clover) at application rates of 0.45 kg a.i./acre (≈0.4014 lb a.i./acre) conducted both in June

and August. Each application was followed by daily irrigation of the plots. Nectar from the clover flowers was assayed at 1 day after application prior to mowing of the turf and at 13 days after application following several mowings of the turf – i.e., the turf was mowed every three days. At one day following application, average monitored residues in nectar were 5493 ng/g (June application) and 6588 ng/g (August application). These monitored levels correspond to residue rates of about 13,700 ppb per lb/acre [5493 ng a.i./g nectar ÷ 0.4014 lb a.i./acre ≈ 13,684.6 ng a.i./g nectar per lb/acre] and 16,400 ppb per lb/acre [6588 ng a.i./g nectar ÷ 0.4014 lb a.i./acre ≈ 16,412.56 ng a.i./g nectar per lb/acre]. These residue rates in nectar are higher than the upper bound rates from Dively and Kamel (2013) – i.e., 46 ppb per lb a.i./acre – by factor of about 300 [13,700 ppb per lb/acre ÷ 46 ppb per lb/acre ≈ 297.8261] to 360 [16,400 ppb per lb/acre ÷ 46 ppb per lb/acre ≈ 356.5217]. Following mowing, however, the rates in nectar were much lower – i.e., 8.4 ng a.i./g nectar following the June application and 26 ng a.i./g nectar following the August application. These residue correspond to residue rates of about 21 ppb per lb/acre [8.4 µg a.i./g nectar ÷ 0.4014 lb a.i./acre ≈ 20.9 ppb per lb/acre] to 65 ppb per lb/acre [26 µg a.i./g nectar ÷ 0.4014 lb a.i./acre ≈ 64.77 ppb per lb/acre]. The average of these two rates is about 43 ppb per lb/acre, virtually identical to the upper bound rates from Dively and Kamel (2013) – i.e., 46 ppb per lb a.i./acre. It seems only modestly speculative to suggest that the initial high levels of imidacloprid in nectar monitored by Larson et al. (2015) reflect the direct contamination of the flowers following foliar application. The much lower post-mowing levels monitored by Larson et al. (2015), which are consistent with the rates from Dively and Kamel (2013), probably reflect uptake of imidacloprid from contaminated soil, similar to the types of exposure in the study by Dively and Kamel (2013).

In addition to the studies on residues of imidacloprid in nectar, discussed above, data are also available on residues in whole flowers (Krischik et al. 2015; USDA/APHIS 2003). In tropical milkweed (*Asclepias curassavica*) grown in potted soil treated at labelled rates and twice the labelled rates, residues from whole flowers of milkweed plants were about 6,000 ppb (labelled rate) and 10,400 ppb (twice labeled rate). These concentrations of imidacloprid in whole flowers are similar to the residues in nectar for Krischik et al. (2007) as discussed above. Much lower concentrations – i.e., a maximum of 130 ppb – were noted in whole flowers trees (6 Norway maple, 5 silver maple, 1 sugar maple and 8 horsechestnut) at 10 to 12 months following tree injection with imidacloprid (USDA/APHIS 2003, p. 8). These studies are noted for the sake of completeness but are not as relevant to the exposure assessment for bees as the studies discussed above on residues in nectar.

4.2.3.3.3. Exposures of Bees for Different Application Methods

4.2.3.3.3.1. Tree Injection

Tree injection is the most focused application method for imidacloprid and is the least likely to result in significant exposures to foraging bees so long as bees are not involved in the pollination of the tree and do not forage on the tree. In this respect, the injection of hemlock and ash trees to not appear to pose an identifiable source of exposure to bees and exposure assessments for the tree injection of hemlock and ash are not developed.

As discussed in Section 4.2.3.2.1, however, programs for the control of the Asian longhorned beetle, a pest species of concern to the Forest Service, may entail injections of maple trees (Kreutzweiser et al. 2008a). While bees do not appear to be involved in the pollination of maple trees, bees may forage on the flowers of maple trees (Batra 1985; USDA/NRCS 2006).

Consequently, the injection of maple trees appears to be a route of exposure for bees that should be evaluated and this exposure scenario is detailed in Worksheet G10 of the Excel workbook for tree injection (Attachment 1). Worksheet G10 is a custom worksheet designed to accommodate the data on imidacloprid as discussed below.

Levels of imidacloprid in maple nectar are not addressed in the available data. As discussed in Section 4.2.3.2.1 and summarized in Table 30, Ugine et al. (2013) provide data on the residues of imidacloprid in maple foliage following tree injection—i.e., 13.79 (6.16 - 49.17) µg/g (ppm). These investigators observed that the residues from small trees treated at 0.220 g/inch DBH were indistinguishable from the residues from large trees treated at the rate of 0.220 g/inch DBH. This observation suggests that the application instructions on the product labels for imidacloprid will lead to concentrations in maple leaves of about 13.79 (6.16-49.17) µg/g. In other words, the application instructions are designed to provide equi-effective residues of imidacloprid in the trees.

As illustrated in the study by Dively and Kamel (2012) and detailed in Worksheet G11 [region shaded in light red], the concentration of imidacloprid in nectar will be lower than the concentration in foliage. Despite reservations in using the relative concentrations of imidacloprid in nectar and pumpkin foliage, these data are the best available in terms of estimating concentrations in nectar based on concentrations in foliage. Consequently, the ratios of concentrations of imidacloprid in nectar and foliage are used in Worksheet G10 of attachment to estimate the concentrations of imidacloprid that might be found in maple nectar following a tree injection. As detailed in Worksheet G10, the estimated dose to the honey bee is about 2.6 (0.83-17) mg/kg bw. Note that these estimates are not based on application rates in units of lb a.i./acre or g a.i./DBH. The estimates of the imidacloprid concentration in nectar simply assume that the maple tree is treated with an effective rate of imidacloprid.

Note also that this exposure assessment applies specifically to maple trees. Given the similarities in the exposure rates for citrus trees – i.e., i.e., the study by Byrne et al. (2013) as discussed in Section 4.2.3.3.2. – the rates for pumpkin from Dively and Kamel (2012), the exposure rates derived above for maple may be reasonably applied to the injection of other species of flowering trees.

The potential exposures of bees to imidacloprid following injection of other tree species must be addressed on a case-by-case basis depending on the available data. Another qualification to the exposure assessment for maple involves application timing. If injections are made after flowering in maple, exposures of bees to imidacloprid for the treatment year could be negligible. Studies on the long-term fate of imidacloprid in maple have not been identified. The potential for significant levels of exposure to bees in the year following treatment is discussed further in the risk characterization.

4.2.3.3.3.2. Soil Injection

Compared with tree injection, soil injection is a less focused application method in that the pesticide is injected into soil surrounding the tree. Consequently, exposures associated with soil injection may involve nectar from contaminated trees as well as nectar from other flowering

vegetation in the treated area. Thus, the exposure scenario for soil injection is relevant to the treatment of any species of tree.

As discussed in Section 4.2.3.3.2 and detailed in Worksheet G11 of the attachments to this risk assessment, the Dively and Kamel (2012) study is used to derive residue rates in nectar of 29 (14 - 46) ng/g (µg/kg or ppb) per lb a.i./acre. For example, the expected concentration in nectar for an application rate of 0.4 lb a.i./acre (the maximum labelled rate for imidacloprid) would be about 11.6 (5.6 - 18.4) ng/g (µg/kg or ppb).

As discussed at the start of Section 4.2.3.3.2, Byrne et al. (2013) provide data following soil applications to citrus trees that yield residue rates of about 16.6 to 49.62 µg/L (ppb) per lb a.i./acre, very similar to the rates from Dively and Kamel (2012). Given the similarities in these rates, residue rates in nectar of 29 (14 - 46) ng/g (µg/kg or ppb) per lb a.i./acre from the study by Dively and Kamel (2012) are entered into Worksheet A01 of the Excel workbook for soil injection (Attachment 2). These rates are used in the exposure assessment for bees foraging on nectar as detailed in Worksheet G10. Given the similarities in the exposure rates from Dively and Kamel (2012) for pumpkin and Byrne et al. (2013) for citrus trees, this exposure scenario may encompass exposures associated with nectar from flowering trees as well as nontarget vegetation.

4.2.3.3.3.3. Bark Application

Bark applications are similar to tree injection in that imidacloprid is applied directly to the tree. Unlike tree injection, however, the assumption is made that the application efficiency to the tree is 90% and 10% of the imidacloprid is lost to surrounding vegetation (Section 2). Thus, the functional off-site application rate for bark application is taken as one-tenth of the nominal application rate. In the Excel workbook for bark application (Attachment 3), the off-site application rate is taken as 0.04 lb a.i./acre.

No data are available on residues in nectar following bark applications. As with soil injection (Section 4.2.3.3.3.2), the concentration in nectar is estimated using the residue rates of 29 (14 - 46) ng/g (ppb) per lb a.i./acre (Dively and Kamel 2012). As with the residues rates for contaminated vegetation (Section 4.2.3.2.2), the residue rates for bark applications are reduced by a factor of 10—i.e., 2.9 (1.4 - 4.6) ng/g (ppb) per lb a.i./acre.

The calculations for the concentration of imidacloprid in nectar are implemented in Worksheet A01 of the Excel workbook for bark application (Attachment 3), and details of the exposure scenario are given in Worksheet G10. Note that in the WorksheetMaker workbooks, the residues rates for nectar are expressed in units of ppm (mg/kg per lb a.i./acre)—i.e., 0.0029 (0.0014 - 0.0046) mg/kg per lb a.i./acre.

4.2.3.3.3.4. Foliar Application

As discussed in Section 2, the current risk assessment does not support foliar applications of imidacloprid, and the Forest Service does not anticipate using foliar applications of this pesticide. Nonetheless, foliar applications of imidacloprid are considered in this risk assessment as a contrast to more focused application methods.

As with soil injection (Section 4.2.3.3.3.2), the concentration in nectar following soil application is estimated using the residue rates of 29 (14 - 46) ng/g (ppb) per lb a.i./acre (Dively and Kamel 2012). As discussed in Section 4.2.3.3.2 (Concentrations of Imidacloprid in Nectar), the study by Larson et al. (2015) clearly indicates that foliar applications of imidacloprid could lead to initial levels of imidacloprid in nectar that are higher than the rates from Dively and Kamel (2012), which are based on soil treatments, by factors of about 300 to 360. As derived in Section 4.2.3.3.2, the residue rates from the study by Larson et al. (2015) range from about 13,700 to 16,400 ppb per lb a.i./acre for an average rate of about 15,000 ppb per lb a.i./acre. These higher rates are used in the exposure assessment for bees following foliar applications of imidacloprid – i.e., 15,000 (13,700 to 16,400) ppb per lb a.i./acre.

The calculations for the concentration of imidacloprid in nectar are implemented in Worksheet A01 of the Excel workbook for foliar application (Attachment 4), and details of the exposure scenario are given in Worksheet G10. Note that in the WorksheetMaker workbooks, the residues rates for nectar are expressed in units of ppm (mg/kg per lb a.i./acre)—i.e., 15 (13.7 – 15.4) mg/kg per lb a.i./acre.

4.2.3.4. Concentrations in Soil

As discussed in Section 4.1.2.4.3, toxicity data are available on earthworm and soil arthropods. The GLEAMS modeling discussed in Section 3.2.3.4 provides estimates of soil concentration as well as estimates of off-site movement (runoff, sediment, and percolation). Based on the GLEAMS modeling, imidacloprid concentrations in clay, loam, and sand soil textures over a broad range of rainfall rates are summarized in Appendix 10 for soil injection and Appendix 11for broadcast applications. Table 2 in each of these appendices gives the estimated concentration of imidacloprid in the top 12 inches of the soil column at a normalized application rate of 1 lb/acre. Table 3 in these appendices gives the corresponding values for the top 36 inches of soil. Analogous to the approach taken with water contamination rates (Table 11), a summary of the modeled soil concentrations is presented in Table 31. Note that the concentrations in this table are given in units of mg imidacloprid/kg soil (ppm). As indicated in Appendices 10 and 11, the concentrations for clay soil textures are somewhat higher than those for loam, and only the estimates for clay soil textures are given in Table 31. The impact of soil type is discussed further in the risk characterization for soil invertebrates (Section 4.4.2.4.3).

4.2.3.5. Contact with Contaminated Surfaces

As summarized in Appendix 3 and discussed in Section 4.1.2.4, toxicity studies involving the exposure of invertebrates to various types of surfaces contaminated with imidacloprid are available. Insects are likely to come into contact with imidacloprid 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 associated with field exposures are not available. Consequently, the potential risks of exposure from contact with imidacloprid contaminated surfaces are discussed qualitatively in Section 4.4.2.4.4.

4.2.4. Terrestrial Plants

Terrestrial plants, particularly trees treated with imidacloprid, will certainly be exposed to imidacloprid in any application that is effective in the control insect pests on trees. Several different exposure assessments could be made for terrestrial plants, which are typically made for herbicides, including, direct spray, spray drift, runoff, wind erosion, and the use of contaminated

irrigation water. For imidacloprid, however, the development of such exposure assessments would serve no purpose. As discussed in Section 4.1.2.4 (Hazard Identification for Terrestrial Plants), there is no basis for asserting that imidacloprid will cause adverse effects in terrestrial plants. While some damage to crops has been noted following agricultural applications of imidacloprid, the damage appears to be related to adjuvants rather than imidacloprid. Thus, no formal exposure assessment is conducted for terrestrial plants.

4.2.5. Aquatic Organisms

An assessment of the effects of imidacloprid 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 11 and discussed in Section 3.2.3.4.6.

4.3. DOSE-RESPONSE ASSESSMENT

4.3.1. Overview

Table 32 summarizes the toxicity values used in the ecological risk assessment. The derivation of each of these values is discussed in the following subsections. Available toxicity data support separate dose-response assessments in seven groups of organisms: terrestrial mammals, birds, terrestrial invertebrates, 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.

As with many insecticides, the most sensitive groups of organisms are terrestrial and aquatic invertebrates. The information on the toxicity of imidacloprid to both groups of invertebrates has expanded significantly since the previous Forest Service risk assessment (SERA 2005). The data on terrestrial invertebrates are adequate to derive dose-response assessments for honeybee colony health, phytophagous insects, insects subject to direct spray or drift, and soil invertebrates. Honeybee colony health is by far the most sensitive endpoint. Based on four studies by three separate groups of investigators, the estimate of the NOAEC for bee colony health is 0.000095 mg/kg bw with adverse effects on overwintering at doses of about a factor of 4 higher than the NOAEC. Estimates of NOAECs for other species of terrestrial invertebrates are 0.00023 mg/kg bw for phytophagous insects and 0.0059 mg/kg bw for direct spray of a sensitive species of insect. While assessments of exposure to aquatic invertebrates are not directly comparable to those of terrestrial invertebrates, some aquatic invertebrates are clearly, highly sensitive to imidacloprid. Ephemeroptera is the most sensitive group of aquatic invertebrates in terms of both acute and chronic toxicity, and *Daphnia magna*, a common test species, is among the least sensitive species.

Other groups of organisms are much less sensitive to imidacloprid. There is no basis for asserting that terrestrial plants are likely to be harmed by imidacloprid, and no formal dose-response assessment for terrestrial plants is developed. Birds and mammals are highly tolerant of imidacloprid, relative to terrestrial invertebrates. For example, the acute NOAEC in birds (3 mg/kg bw) is a factor of over 30,000 above the NOAEC for bee colony health [3 mg/kg bw ÷ 0.000095 ≈ 31,578]. Similarly, aquatic vertebrates are much less sensitive than aquatic invertebrates. For example, the NOAEC for sensitive species of fish is a factor of nearly 80,000 higher than the NOAEC for sensitive species of aquatic invertebrates [25 mg/L ÷ 0.000325 mg/L ≈79,923].

4.3.2. Toxicity to Terrestrial Organisms

4.3.2.1. Mammals

In characterizing risk to mammalian wildlife, Forest Service risk assessments generally use the NOAELs which serve as the basis for the acute and chronic RfDs from the human health risk assessment. This approach is maintained in the current risk assessment on imidacloprid. As discussed in Section 3.3, the dose-response assessment for human health is unchanged from the previous Forest Service risk assessment (SERA 2005). Consequently, the dose-response assessment for mammals remains unchanged.

As discussed in Section 3.3.2, the acute RfD of 0.14 mg/kg bw is based on a LOAEL of 42 mg/kg from the acute neurotoxicity screening studies in rats (Sheets 1994a,b, MRID 43170301). This LOAEL is based on decreased measures of locomotion in female rats. The LOAEL is divided by an uncertainty factor of 3, yielding an approximated NOAEL of 14 mg/kg. Thus, 14 mg/kg is used as the acute NOAEL for mammals.

As discussed in Section 3.3.3, the chronic RfD of 0.057 mg/kg bw/day is based on a NOAEL of 5.7 mg/kg bw/day from the chronic feeding study in rats by Eiben and Kaliner (1991, MRID 42256331), and this NOAEL is used to characterize risks associated with longer-term exposures of mammalian wildlife to imidacloprid.

4.3.2.2. Birds

As summarized in Appendix 2 and discussed in Section 4.1.2.2, toxicity studies involving the acute and longer-term toxicity of imidacloprid to birds are numerous. In general, Forest Service risk assessments typically defer to the U.S. EPA/OPP on study selection, unless there is a compelling reason to do otherwise. For characterizing risks to birds, the most recent EPA ecological risk assessment (U.S. EPA/OPP/EFED 2007a) uses the acute dietary LC_{50} of 1536 ppm (Toll 1990b, MRID 42055310, summarized in Table A2-2 of the current risk assessment) to characterize risks associated with acute exposures and the reproductive NOAEC of 36 ppm (Toll 1991b, MRID 42055312, summarized in Table A2-3 of the current risk assessment) to estimate risks associated with longer-term exposures. Both of these studies were conducted on bobwhite quail. Their use for risk characterization by EPA is noted in a tabular summary of risk quotients in U.S. EPA/OPP/EFED (2007a, p. 25).

As summarized in Appendix 2, Table A2-2, the acute dietary LC_{50} in quail of 1536 ppm from (Toll 1990b, MRID 42055310) corresponds to a dose of about 460.8 mg a.i./kg bw. This acute dietary LD_{50} in quail is higher than the gavage LD_{50} of 41 mg a.i./kg bw in house sparrows (Stafford 1991, MRID 42055309) by factor greater than 10 [$460.8 \div 41 \approx 11.239$]. U.S. EPA/OPP/EFED (2007a, p. 25) notes the apparently higher sensitivity of the house sparrow, relative to quail, but does not specifically address the decision to use of the quail LC_{50} rather than the sparrow LD_{50}.

Reasons that the EPA used the dietary toxicity study in quail rather than the gavage study in sparrows may be that bolus gavage dosing will generally lead to higher blood levels of a toxicant relative to dietary exposures and that dietary studies relative to gavage studies may more realistically approximate plausible environmental exposures to imidacloprid. Nonetheless, these considerations do not exclude the possibility of species differences in sensitivity to imidacloprid. The concern for the potentially greater sensitivity of sparrows (Passeriformes) relative to quail (Galliformes) is augmented by the early study by Schafer and Brunton (1979, Table 4, p. 167) which noted that sparrows are significantly ($p<0.05$) more sensitive than to quail in bioassays of 36 pesticides as well as the study by Hill (1971) which noted that sparrows were more sensitive than quail in bioassay of four mosquito larvicides. In a more recent review of the toxicity of pesticides to birds, Mineau et al. (1996) have noted that smaller birds are commonly more sensitive to pesticides than larger birds. The Mineau review, however, does not offer specific comparisons of sensitivity between quail and sparrows. As discussed in Section 4.1.2.2.5, the study by Hallman et al. (2014) has implicated neonicotinoids as a potentially causative factor in the declines of bird populations in the Netherlands but these declines may not be direct effects on

birds but reductions in insect populations. Hallman et al. (2014, Table 1, p. 2) do specifically note declines in tree sparrow populations associated with imidacloprid applications but the effect was not statistically significant (p= 0.1211). While these studies cannot be used to assert that sparrows are clearly more sensitive than quail to imidacloprid, these studies raise sufficient concern that the gavage LD_{50} for house sparrows from the study by Stafford (1991) may reflect a true species sensitivity rather than simply a difference in the mode of administration relative to the dietary study in quail by Toll (1990b). Consequently, the current Forest Service risk assessment bases the dose-response assessment for acute exposures on the sparrow as the potentially most sensitive species of bird on which data are available.

Following standard practice in Forest Service risk assessments, NOAECs are used rather than LD_{50} values. As summarized in Appendix 2, Table A2-2, Stafford (1991, MRID 42055309) reports a NOAEC of 3 mg a.i./kg bw with a LOAEL of 12 mg a.i./kg bw, based on clinical signs of neurotoxicity (i.e., ataxia, hypo-reactivity, loss of flight, diarrhea, and immobility). The LOAEL of 12 mg a.i./kg bw corresponds to an HQ of 4, which is used to characterize risks associated with acute exposures of birds to levels of imidacloprid above the NOAEL (Section 4.4.2.2.). No studies from the open literature impact the selection of the acute NOAEL for birds (Appendix 2, Table A2-1 and Table A2-2).

The reproductive NOAEC of 36 ppm in quail from the study by Toll (1991b, MRID 42055312) provides the lowest (i.e., most conservative) NOAEC from the registrant-submitted studies. As summarized in Appendix 2, Table A2-3, this NOAEC corresponds to a dose (NOAEL) of about 2.52 mg/kg bw. This dose is only modestly lower than the acute NOAEL of 3 mg/kg bw, also in bobwhite, discussed above. The proximity of the acute NOAEL to the longer-term NOAEL is not unusual. As discussed in Section 3.1.3.3, the pharmacokinetics of imidacloprid in mammals suggests that body burden in mammals will increase by only about a factor of 1.11 in longer-term exposures, relative to single doses. The ratio of the acute to chronic NOAELs in birds is very similar to this factor from mammals—i.e., 3 mg a.i./kg bw (acute NOAEL) ÷ 2.52 mg/kg bw (chronic NOAEL) ≈ 1.19.

The open literature studies from Spain by Lopez-Antia et al. (2013, 2015) note LOAELs above the longer-term NOAEC of 2.52 mg/kg bw/day from Toll (1991b, MRID 42055312). Lopez-Antia et al. (2013) observed increased mortality in partridge as well as decreased chick survival after 10-day doses of about 31.9 mg/kg bw/day. Lopez-Antia et al. (2015) observed decreases in body weight in partridge as well as other signs of sublethal toxicity at a dose of about 8.8 mg/kg bw/day.

An open literature study from India (Balani et al. 2011) reports a LOAEL in white leghorn chickens following 28 day exposures at a dose of 1.25 mg/kg bw/day. The LOAEL is characterized as a significant decrease in blood glucose levels as well as biochemical indicators of liver damage (e.g., increase in serum glutamic oxaloacetic transaminase). In addition, Balani et al. (2011) report a substantial decrease (82%) in total leucocyte count at a dose of 2.5 mg/kg bw/day. While the Balani et al. (2011) study is acknowledged, it is not used in the dose-response assessment because it does not specify the source and purity of the imidacloprid or whether the test material was technical grade imidacloprid or an imidacloprid formulation. Another study from the Indian literature (Pandey and Mohanty 2015) reports effects on the thyroid in a species

of finch. While this study appears to have been well-conducted, it involved only a small number of birds (n=8) and only a single dose – i.e., a dose-response relationship was not demonstrated.

4.3.2.3. Reptiles and Amphibians (Terrestrial-Phase)

As discussed in Section 4.1.2.3, the toxicity data on reptiles and terrestrial-phase amphibians are limited. The study by Cordone (2015) in a lizard indicated an acute oral NOAEC for gross signs of neurotoxicity of 21.5 mg/kg bw, which is substantially higher than the acute NOAEC of 3 mg/kg bw in sensitive species of birds (Section 4.3.2.2). Also in the study by Cordone (2015), a subchronic LOAEC of 10 mg/kg bw was noted based on change in sperm and plasma hormone levels. An NOAEC, however, was not determined but the LOAEC of 10 mg/kg bw is substantially higher than the estimated chronic NOAEC of 2.52 mg/kg bw/day in birds (Section 4.3.2.2). This limited information supports the standard practice of EPA in using data on birds to characterize potential risks in terrestrial phase amphibians.

4.3.2.4. Terrestrial Invertebrates

4.3.2.4.1. Honeybees

As discussed in Section 4.1.2.4.2.2, the most sensitive endpoint for honeybees involves hive mortality during overwintering. As illustrated in Figure 8 and summarized in Table 33, concern for the impact of imidacloprid on colony overwintering in bees is supported by four studies conducted by three independent groups of investigators (Dively et al. 2015; Faucon et al. 2005; Lu et al. 2014). Taken together, these studies form a reasonably consistent pattern indicating no adverse effects on colony overwintering at imidacloprid concentrations of 5 ppb or less and an increase in colony mortality during overwintering at concentrations of 20 ppb and greater. As summarized in Table 21 and discussed in Section 4.1.2.4.2.2, the NOAEC of 5 ppb corresponds to a NOAEL of about 0.011 ng/bee and the LOAEL of 20 ppb corresponds to a dose of about 0.043 ng/bee based on the well documented dose estimates from Dively et al. (2015).

Notwithstanding the reasonably clear NOAECs of 5 ppb and LOAECs of 20 ppb and greater for overwintering of bee colonies, several limitations in the data are noteworthy. The only study to demonstrate a clear and compelling dose-response relationship is the 2009 study by Dively et al. (2015). The 2010 study by Dively et al. (2015) evidenced high control mortality (three of seven hives) and identical mortalities of four of seven hives in the 5, 20, and 100 ppb exposure groups. As discussed by Dively et al. (2015), the high control mortality may be attributable to abnormally high temperatures that resulted in overfeeding during the winter months. Nonetheless, the uniform responses (4/7) in the imidacloprid treated hives at concentrations of 5, 20, and 100 ppb diminish confidence in imidacloprid as a causative agent. Using regression modelling, Dively et al. (2015, p. 18) note that the pooled results for 2009 and 2010 fail to demonstrate a significant dose-response relationship. As part of the current risk assessment, the pooled data from 2009 and 2010 were analyzed using the more general Cochran-Armitage Trend Test in U.S. EPA's Benchmark Dose Software (U.S. EPA 2015), and a significant dose-response relationship was noted (p=0.0136). The study by Lu et al. (2012) also fails to note a significant dose-response relationship in terms of hive survival during overwintering. Notably, the type of dose-response relationship observed in the study by Lu et al. (2012) is consistent with a dose selection in which all of the doses elicited a maximum or near maximum response. Notwithstanding the lack of a dose-response relationship, the rate of hive failure in the pooled data from all imidacloprid treated hives (15/16) relative to the control hives (1/4) is statistically

significant using the Fisher Exact Test (p=0.012416). Lastly, the failure of Faucon et al. (2005) to note a dose-response relationship is consistent with the data from Dively et al. (2015) indicating that Faucon et al. (2005) used doses that were too low to elicit hive mortality during overwintering.

Another reservation with the studies on colony overwintering is that the longer-term exposure studies failed to note remarkable adverse effects prior to overwintering, which is not consistent with some shorter-term studies. As summarized in Table 21, shorter-term studies (i.e., Boily et al. 2013; Dechaume Moncharmont et al 2003; Boily et al. 2013; Tan et al. 2012, 2014; Williamson et al. 2014) report adverse effects in bees at doses in the range of the longer-term studies on overwintering (Dively et al. 2015; Faucon et al. 2005; Lu et al. 2012, 2014). In some cases, the failure to note adverse effects prior to overwintering in the longer-term studies may be due to differences in the endpoints that were assayed in the shorter-term studies compared with the longer-term studies. For example, Boily et al. (2013) note that a dose of 0.08 ng/bee caused an increase in AChE activity as well as signs of hyperactivity in bees. The studies on overwintering did not assay AChE activity, and it is not clear if the relatively subtle signs of hyperactivity noted by Boily et al. (2013) would have been noted in the long-term studies on overwintering. In other cases, the failure of the overwintering studies to note adverse effects prior to overwintering is inconsistent with some of the short-term studies. For example, Boily et al. (2013) report a 10-day LD_{50} of 0.227 ng/bee/day. Substantial mortality, however, was not observed by Dively et al. (2015) at a dose of 0.2 ng/bee/day nor by Lu et al. (2014) at a dose of 0.74 ng/bee/day in bees prior to overwintering.

The apparent inconsistencies in the overwintering studies and some of the shorter-term toxicity studies cannot be explained conclusively. Nonetheless, as discussed in Section 4.1.2.4.2.1, substantial (i.e., factor of 10 or higher) variability in the sensitivities of different populations of honeybees to imidacloprid is well documented. While clearly speculative, it is possible that difference in sensitivities among the bee populations in the short-term and longer-term studies could account for some of the apparent discrepancies between the adverse effects observed in the shorter-term studies and the lack of adverse effects prior to overwintering at similar doses in the longer-term studies.

While the inconsistencies of the overwintering studies with some of the shorter-term toxicity studies add uncertainties to the dose-response assessment and subsequent risk characterization for bees (Section 4.4.2.4.1), the consistencies among the longer-term studies by Dively et al. (2015), Faucon et al. (2005), and Lu et al. (2012,2014) are striking. In addition, no studies are available that contradict the LOAECs from Dively et al. (2015) and Lu et al. (2012, 2014). In other words, no studies are available that demonstrate successful overwintering of bee colonies exposed to imidacloprid at concentrations of 20 ppb or greater. Consequently, risks to honeybees are characterized at the level of the colony using the NOAEC of 0.011 ng/bee for overwintering from Dively et al. (2015). The LOAEC of 0.043 ng/bee, also from Dively et al. (2015) corresponds to an HQ of about 4 [0.043 ng/bee ÷ 0.011 ≈ 3.91], which is used to further characterize exposures above the NOAEC (Section 4.4.2.4.1).

The risks to bees are characterized in Worksheet G10 of the attachments to this risk assessment, and these worksheets require dose estimates in units of mg/kg bw/day rather than ng/bee. The

studies on overwintering do not provide information on the body weights of the bees. Consequently, the body weight of 116 mg from Winston (1987) is used as the average body weight for a worker bee. This is a standard approach used in Forest Service risk assessments (SERA 2014a). Thus, the NOAEC of 0.011 ng/bee is expressed as 0.000095 ng/mg bw [0.011 ng/bee ÷ 116 mg ≈ 0.00009483 ng/mg bw], which is equivalent to a dose of about 0.000095 mg/kg bw.

As discussed in Section 4.1.2.4.2.1.2, bumblebees appear to be as sensitive as the honeybee to imidacloprid; however, some species of bees from the family Megachilidae may be more sensitive than honeybees. Longer-term studies on Megachilidae and other families of bees are not available, and potential risks to these other families of bees are addressed qualitatively in the risk characterization (Section 4.4.2.4.1).

4.3.2.4.2. Phytophagous Insects

As discussed in Section 4.1.2.4.2.1.1 and illustrated in Figure 4, bees are the most extensively studied group of terrestrial invertebrates. Data suggest that other groups of insects (e.g., Coleoptera) may be somewhat, but not remarkably, less sensitive than bees to imidacloprid. In the absence of more extensive data on the other groups of insects, sublethal studies in bees (Table 20) are used as a surrogate for other sensitive groups of terrestrial invertebrates. This is the standard approach used in EPA ecological risk assessments, including the EPA's most recent assessments on imidacloprid (U.S. EPA/OPP/EFED 2007a, 2008a).

The chronic data on bees discussed in the previous section are highly specific to bee colonies, and, therefore, not directly relevant to assessing risks in other groups of terrestrial invertebrates. The most sensitive nonlethal endpoint other than colony failure during overwintering is the LOAEL of 0.08 ng/bee, associated with signs of neurotoxicity—i.e., an increase in AChE activity and hyperactivity (Boily et al. 2013). Normalizing for body weight, this LOAEL corresponds to a dose of 0.00069 mg/kg bw [0.08 ng/bee ÷ 116 mg ≈ 0.00068966 ng/mg bw or mg/kg bw]. Using an uncertainty factor of 3 to approximate a NOAEL, the estimated NOAEL of phytophagous insects is 0.00023 mg/kg bw. This dose is only modestly higher than the NOAEL of 0.000095 mg/kg bw used for honeybee colony health [0.00023 mg/kg bw ÷ 0.000095 mg/kg bw ≈ 2.4211].

In the absence of appropriate data on sublethal effects, acute mortality data are sometimes used to assess risks to herbivorous insects. As summarized in Table 18, the lowest acute oral LD_{50} is 3.7 ng/bee from the study by Cole (1990, MRID 42273003) in honeybees. As indicated in Appendix 2, Table A2-1, the LOAEL from this study is 1.5 ng/bee—i.e., a dose associated with 20% mortality. While a dose of 1.5 ng/bee was reported as a NOAEL for mortality (Nauen et al 2001), the report by Nauen et al (2001) does not reduce concern for the mortality seen at this dose in the study by Cole (1990, MRID 42273003). Again, using an uncertainty factor of 3, the NOAEL would be estimated at 0.5 ng/bee or about 0.0043 mg/kg bw [0.5 ng/bee ÷ 116 mg/bee ≈ 0.00431 ng/mg bw]. This dose is a factor of about 20 above the NOAEL based on sublethal toxicity [0.0043 mg/kg bw ÷ 0.00023 mg/kg bw ≈ 18.69]. While this higher NOAEL based on lethality is not used explicitly for risk characterization, the factor of 20 is used in Section 4.4.2.4.2 to elaborate the risk characterization for phytophagous insects.

4.3.2.4.3. Direct Spray

As illustrated in Figure 4 and discussed in Section 4.1.2.4.2.1.1, there many topical LD_{50} values for imidacloprid. Honeybees along with *Bombus impatiens* and a solitary bee (*Nannotrigona perilampoides*) are among the most sensitive species. Cole (1990, MRID 42273003) reports a LOAEL of 25 ng/bee, corresponding to a dose of about 0.21 ng/mg bw, based on 20% mortality. This LOAEL is not appropriate as the basis for a dose-response assessment because several of LC_{50} values for topical application are below 0.21 ng/mg bw (Table 16).

As also summarized in Table 16, the lowest topical LD_{50} is 0.059 ng/mg bw for a sensitive population of Siphonaptera (fleas)—i.e., the most sensitive population of *Ctenocephalides felis* in the study by Rust et al. (2014) using technical grade imidacloprid. In the absence of a NOAEL from this study, the LD_{50} is divided by 10 to approximate an NOAEL of 0.0059 ng/mg bw. This approach to estimating a NOAEL from an LD_{50} is consistent with EPA's variable level-of-concern method, as detailed in SERA (2014a, Section 4.3.2).

4.3.2.4.4. Soil Invertebrates

Information on the toxicity of imidacloprid to soil invertebrates is robust (Section 4.1.2.4.3), and soil invertebrates will undoubtedly be exposed to imidacloprid in some types of applications—e.g., soil injection. The most extensively studied group of soil invertebrates are earthworms (Appendix 2, Table A2-10). As with other groups of invertebrates, LC_{50} values for earthworms are highly variable, ranging from about 0.77 mg/kg soil (*Eisenia fetida* in the study by Chen et al. (2014b) to about 25 mg/kg soil (*Eisenia andrei* in the study by Alves et al. 2013).

Relatively few soil invertebrate studies report NOAECs. The most sensitive endpoint appears to be sperm malformations from the Luo et al. (1999) in *Eisenia foetida*. The NOAEC for this endpoint is 0.1 mg/kg soil with a LOAEC of 0.2 mg/kg soil. Other species of worms appear to be at least somewhat more tolerant. Dittbrenner et al. (2010) reports an NOAEC of 0.2 mg/kg soil in *Lumbricus terrestris*, based on increases in body weight at 0.66 mg/kg soil and decreases in body weight at 2 mg/kg soil. Several studies indicate either altered burrowing behavior or changes in reproductive parameters at concentrations greater than 1 mg/kg soil (Dittbrenner et al. 2011; Fernandez-Gomez et al. 2011).

For the current risk assessment, the NOAEC of 0.1 mg/kg soil is used for the risk characterization of sensitive species of earthworms. Risks to more tolerant species are addressed further in the risk characterization for soil invertebrates (Section 4.4.2.4.4).

4.3.2.5. Terrestrial Plants (Macrophytes)

There is no indication that imidacloprid will damage terrestrial plants (Section 4.1.2.5). Consequently, no dose-response assessment is developed or is appropriate for this group of organisms.

4.3.2.6. Terrestrial Microorganisms

There is little information suggesting that imidacloprid will substantially impact terrestrial microorganisms (Section 4.1.2.5). Transient changes in microbial populations were noted at soil concentrations as low as 1 mg/kg soil with a NOAEC of 0.1 mg/kg soil (Cycon et al. 2013). A protracted effect on soil microbial populations was noted only at concentrations of 10 mg/kg soil (Cycon et al. 2013). In terms of a functional impact on litter degradation by soil

microorganisms, Kreutzweiser et al. (2008b) noted no adverse effects on soil microorganisms at concentrations of up to 1400 mg/kg soil.

While a formal dose-response assessment is not developed for terrestrial microorganisms, risks to this group of organisms are characterized qualitatively in Section 4.4.2.6.

4.3.3. Aquatic Organisms

4.3.3.1. Fish

The data on the toxicity of imidacloprid to fish are sparse. As with terrestrial organisms, imidacloprid appears to be much less toxic to aquatic vertebrates than to aquatic invertebrates (as discussed further in Section 4.3.3.3). Consequently, the dose-response assessment for fish is uncomplicated.

The most recent EPA ecological risk assessment (U.S. EPA/OPP/EFED 2007a, p. 21) classifies imidacloprid as *practically non-toxic to fish* on an acute basis and uses an LC_{50} of 83 ppm for rainbow trout (the indefinite LC_{50} of >83 mg/L from Bowman and Bucksath 1990b, MRID 42055315) to characterize risk for acute exposures. For longer-term exposures, the EPA risk assessment uses the NOAEC of 1.2 mg/L in rainbow trout (Cohle and Bucksath 1991, MRID 42055320).

For acute toxicity, the Forest Service prefers to use NOAECs rather than LC_{50} values. As summarized in Appendix 4, Table A4-1, the NOAEC in the study by Bowman and Bucksath 1990b, MRID 42055315) on rainbow trout is 42 mg a.i./L. While this could be a reasonable basis for the dose response assessment for sensitive species of fish, another indefinite LC_{50} of >105 mg/L in bluegills (Bowman and Bucksath 1990a, MRID 42055314) is associated with a somewhat lower NOAEC of 25 mg a.i./L. Because both of the LC_{50} values are indefinite, these studies cannot be used to suggest that one species is more sensitive than the other. Consequently, the somewhat lower NOAEC of 25 mg a.i./L in bluegill is used in the current Forest Service risk assessment to characterize risks to potentially sensitive species of fish following acute exposures. Based on the study by Tisler et al. (2009) with both technical grade imidacloprid as well as a Confidor formulation (Appendix 4, Table A4-1), zebra fish appear to be the most tolerant species with definitive LC_{50} values greater than 200 mg a.i./L. NOAECs, however, are not available from this study. Consequently, the acute NOAEC of 58.2 mg a.i./L in sheepshead minnow (Ward 1990a, MRID 42055318) is used for presumably tolerant species of fish.

For longer-term exposures, the NOAEC of 1.2 mg/L in rainbow trout is adopted from the EPA risk assessment U.S. EPA/OPP/EFED (2007a). Because rainbow trout appear to be among the more sensitive species of fish, this NOAEC is applied to sensitive rather than tolerant species. Risks associated with longer-term exposures of potentially more tolerant species are not quantified but are addressed qualitatively in the risk characterization (Section 4.4.3.1).

4.3.3.2. Amphibians (Aquatic-phase)

The most recent EPA ecological risk assessments of imidacloprid do not specifically discuss the effects of imidacloprid on aquatic-phase amphibians. Following common practice in EPA risk assessments, fish are used as surrogates to characterize risks to aquatic phase amphibians (U.S.

EPA/OPP/EFED 2007a, p. 9; U.S. EPA/OPP/EFED 2008a, p. 11). As discussed in Section 4.3.3.2, the EPA classifies imidacloprid as practically nontoxic to fish on an acute basis, and the definitive 96-hour LC_{50} values in fish range from 163 mg a.i./L (Ward 1990a, MRID 42055318) to 241 mg a.i./L (Tisler et al. 2009).

As discussed in Section 4.1.3.2, two of the studies on aquatic-phase amphibians were either conducted with formulations not used in the United States or were conducted outside of the United States without clearly indicating the source or purity of the imidacloprid (Channing 1998; Perez-Iglesias et al. 2014). These studies are not considered for the dose-response assessment.

Of the remaining studies, the lowest reported 96-hour LC_{50} is 82 mg/L for *Rana limnocharis* tadpoles from the study by Feng et al. (2004). This study used technical grade imidacloprid (>95% purity) and reports an NOAEC for mortality of 16.7 mg/L. While this study is well documented, an NOAEC for mortality is a marginal endpoint for the dose-response assessment. A much higher 48-hour LC_{50} of 388.5 mg a.i./L is reported for *Pseudacris triseriata* (Howard et al. 2003; Julian 2000); however, this LC_{50} is associated with a much more sensitive NOAEL of 3.89 mg a.i./L, based on delayed metamorphosis at a concentration of 39.9 mg a.i./L. This study involved a Merit 75% a.i. formulation. As summarized in Table 2, Merit 75 WP is representative of formulations that might be used in Forest Service programs. Consequently, the NOAEC of 3.89 mg a.i./L is used in the current risk assessment to characterize short-term risks in sensitive species of aquatic-phase amphibians.

The dose-response assessment for acute exposures of more tolerant species is based on the NOAEC of 16.7 mg a.i./L in *Rana limnocharis* (Feng et al. 2004). As noted above, this NOAEC is based on mortality, and, therefore, may be viewed as marginal for risk characterization. As discussed further in Section 4.4.3.4 (risk characterization for aquatic-phase amphibians), this marginal NOAEC has no substantial impact on this risk assessmentm because upper bound estimates of potential exposures are substantially below the NOAECs for both sensitive and tolerant species.

No longer-term studies on the toxicity of imidacloprid to aquatic-phase amphibians were identified in the available literature on imidacloprid. Consequently, no dose-response assessment is developed for longer-term exposures. Following the approach used by EPA (discussed above), risks associated with longer-term exposures of aquatic-phase amphibians to imidacloprid are characterized using fish as a surrogate.

4.3.3.3. Aquatic Invertebrates

As discussed in Section 4.1.3.3, the information on the acute and chronic toxicity of imidacloprid to aquatic invertebrates is unusually robust and detailed. Notwithstanding the large amount of data, the dose-response assessment is reasonably simple and unambiguous.

The lowest toxicity values used for risk characterization in the most recent EPA ecological risk assessment, U.S. EPA/OPP/EFED (2007a, p. 24), are an acute EC_{50} of 0.037 mg a.i./L (mysid shrimp from Ward 1990b, MRID 42055319) and a chronic NOAEC of 0.0006 mg a.i./L in midge larvae (Gagliano 1991, MRID 42256304). Both of these registrant-submitted studies involved technical grade imidacloprid. A NOAEC was not identified in the acute study by Ward (1990b, MRID 42055319). Following standard practice in Forest Service risk assessments, the acute

EC_{50} of 0.037 mg a.i./L would be divided by a factor of 20 to approximated an NOAEC of about 0.0019 mg a.i./L [0.037 mg a.i./L ÷ 20 = 0.00185 mg a.i./L] (SERA 2014a, Section 4.3.2).

4.3.3.3.1. Acute Toxicity

Forest Service risk assessments typically defer to the U.S. EPA in the selection of toxicity studies used in the dose-response assessment, unless there is a compelling reason to do otherwise. As discussed in Section 4.1.3.3.1 and illustrated in Figure 6, the extensive open literature on imidacloprid indicates that mysids are not a particularly sensitive to imidacloprid. The most sensitive group of aquatic invertebrates is Ephemeroptera. As summarized in Table 22 and detailed further in Appendix 6, Table A6-6, the most sensitive species of Ephemeroptera is *Cloeon dipterum*, with an acute EC_{50} of 0.00177 mg a.i./L and a corresponding EC_{10} of 0.000325 mg a.i./L, based on immobility (Roessink et al. 2013). An EC_{10} may be treated as a functional NOAEC (U.S. EPA 2012). The bioassay by Roessink et al. (2013) in *Caenis horaria* involved an unspecified soluble concentrate formulation of imidacloprid and yielded a 96-hour EC_{50} of 0.00177 mg a.i./L. This EC_{50} is only modestly lower than the EC_{50} of 0.00848 mg a.i./L in another species of Ephemeroptera using analytical grade imidacloprid—i.e., *Baetis rhodani* in the study by Beketov and Liess (2008). Consequently, the use of the EC_{10} of 0.000325 mg a.i./L does not seem overly protective and is used in the current risk assessment for the risk characterization of sensitive species of aquatic invertebrates.

As also illustrated in Figure 6, branchiopods, including daphnids, other Cladocera, and *Artemia* are clearly among the most tolerant aquatic invertebrates. The highest reported EC_{50} is 361.23 mg a.i./L from the study by Song et al. (1997) using a species of *Artemia*. This study, however, does not provide an NOAEC. In addition, only a single bioassay is available on *Artemia*. The next most tolerant species is *Daphnia magna*, for which a number of bioassays are available. The study by Young and Hicks (1990, MRID 42055317) reports an EC_{50} of 85 mg a.i./L for technical grade imidacloprid and a corresponding NOAEC of 42 mg a.i./L. An added benefit in using this study in the dose-response assessment is that the study was submitted to and reviewed by the U.S. EPA. Consequently, the NOAEC of 42 mg a.i./L in *Daphnia magna* is used for the risk characterization of tolerant species of aquatic invertebrates.

4.3.3.3.2. Chronic Toxicity

As with acute toxicity, Ephemeroptera are clearly the most sensitive taxonomic order of aquatic invertebrates. The study by Roessink et al. (2013) provides two similar EC_{10} values for immobilization following a 28-day period of exposure—i.e., 0.000024 mg a.i./L for *Caenis horaria* and 0.000033mg/L for *Cloeon dipterum*. These toxicity values are substantially below the NOAEC of 0.006 mg a.i./L for midge larvae used in the 2007 risk assessment conducted by EPA. For the current risk assessment, the NOAEC of 0.000024 mg a.i./L is used to characterize risks associated with longer-term exposures of sensitive species of aquatic invertebrates to imidacloprid.

Based on the available data, *Daphnia magna* is clearly the least sensitive species in terms of the chronic toxicity of imidacloprid (Figure 7). As summarized in Table 25, the average chronic NOAEC for Daphnia magna is 1.13 mg a.i./L, a factor of over 40,000 higher than the corresponding value for Ephemeroptera. For the current risk assessment, the average NOAEC of 1.13 mg a.i./L is used to characterize risks associated with longer-term exposures of tolerant species of aquatic invertebrates to imidacloprid.

4.3.3.4. Aquatic Plants

4.3.3.4.1. Algae

The U.S. EPA/OPP/EFED (2007a, p. 24) uses the NOAEC of 10 mg a.i./L for *Scenedesmus subspicatus* (Heimbach 1989, MRID 42256374) to characterize risks associated with exposures to algae. This toxicity value is cited in the EPA risk assessment (p. 24) as a definitive EC_{50}; however, the toxicity value is actually a NOAEC and is more correctly cited in the EPA risk assessment (p. 43) as an indefinite EC_{50} of >10 mg a.i./L.

The more recent open literature on imidacloprid includes an EC_{50} of 116 mg a.i./L with a corresponding EC_{10} of 5.6 mg a.i./L in *Desmodesmus subspicatus*, a species of green algae. While this study was conducted outside of the United States, it is well documented and uses a Confidor 200 SL formulation from Bayer. The EC_{10} of 5.6 mg a.i./L is used in the current risk assessment as a modestly more conservative estimate of a functional NOAEC for sensitive species of algae.

Kungolos et al. (2009) report the highest indefinite EC_{50}—i.e., >1000 mg/L for *Selenastrum capricornutum* using a Confidor formulation. It is not clear, however, if this toxicity value is expressed as a formulation or as the active ingredient. The next highest indefinite EC_{50} is >600 mg a.i./L, also for *Selenastrum capricornutum* using a Confidor formulation (Daam et al. 2013). This indefinite EC_{50} is consistent with the NOAEC of 119 mg a.i./L for *Selenastrum capricornutum* using technical grade imidacloprid (Gagliano and Bowers 1991, MRID 42256374). *Selenastrum capricornutum* is clearly a tolerant species of algae, and the NOAEC of 119 mg a.i./L is used to characterize risk for tolerant species of algae.

4.3.3.4.2. Aquatic Macrophytes

The only data on aquatic macrophytes is the 7-day EC_{50} of 740 mg a.i./L in *Lemna minor* for the inhibition of frond numbers using a Confidor formulation of imidacloprid (Daam et al. 2013). In the absence of additional information, the EC_{50} is divided by 20 to approximate an NOAEC of 37 mg a.i./L [740 ÷ 20 = 37]. This approach to estimating a NOAEC from an EC_{50} is consistent with EPA's level-of-concern method, as discussed in SERA (2014a, Section 4.3.2). Because no information is available on other species of aquatic macrophytes, the estimated NOAEC is applied to tolerant species, and risks to potentially sensitive species are not addressed quantitatively but are discussed qualitatively in the risk characterization (Section 4.4.3.4.2).

4.4. RISK CHARACTERIZATION

4.4.1. Overview

The toxicity data on and exposure estimates for imidacloprid support quantitative risk characterizations in mammals, birds, terrestrial insects as well as other invertebrates, fish, aquatic invertebrates, and aquatic plants. Risk characterizations for reptiles and amphibians are not possible because of the lack of toxicity data. For terrestrial plants, the lack of data regarding end points of concern precludes a quantitative risk characterization. The organisms at greatest risk are the invertebrates, both terrestrial and aquatic.

Among the terrestrial invertebrates, risks to honeybees and phytophagous insects exceed the level of concern substantially (HQ=1) for all application methods of concern in Forest Service programs—i.e., tree injection, soil injection, and bark application (Table 34). Risks to honeybees are characterized at the level of the colony or hive rather than the individual. The only substantial qualification to the risk characterization for honeybees concerns tree injection for which risks vary according to tree type. If maple trees are injected with effective doses of imidacloprid, adverse effects on honeybees foraging on the maple flowers appear to be high — HQs of 27,166 (8,754 - 180,390). Risks to honeybees following the injection of ash and hemlock are less certain because of a lack of information indicating that honeybees forage on these trees. The risks associated with other types of exposures (e.g., nest building) on ash or hemlock cannot be characterized. The available information of the distribution of imidacloprid in hemlock, ash, and maple suggests that residue levels in flowering trees may vary substantially. Risks to bees foraging on treated maple are clear; however, the risks are less certain with respect to other tree species. For soil injection and bark application, risks to honeybees are associated primarily with the contamination of flowering nontarget vegetation. HQs exceed the level of concern for both soil injection [HQs = 203 (58 - 575)] and bark application [HQs = 20 (6 - 57)].

Risks to phytophagous insects are also substantial (Table 36). For tree injection, the HQs exceed the level of concern across the range of estimates with all lower bounds of the HQs exceeding the level of concern—i.e., lower bound HQs range from 78 to 16,174. For tree and soil injection, HQs differ substantially for hemlock (lowest HQs), ash (intermediate HQs), and maple (highest HQs). For bark application, the HQs vary according to the type of vegetation that might be contaminated. Nonetheless, as with tree injection, all of the lower bounds of the HQs for bark application exceed the level of concern—i.e., lower bounds range from 334 to 3130.

Risks to aquatic invertebrates are highly variable among groups of aquatic invertebrates. For tolerant groups of aquatic invertebrates, adverse effects are unlikely even in the event of an accidental spill. For sensitive groups of aquatic invertebrates, the risk characterization is much more severe (Table 37). At both the central estimates and upper bounds of the HQs, there is a clear difference among the application methods considered by the Forest Service. Bark applications pose the lowest risk with acute HQs of 2 (0.0002 - 12) and chronic HQs of 12 (0.0003 - 135). Soil injections pose substantially higher risks with acute HQs of 16 (0.001 - 209) and chronic HQs of 140 (0.008 - 800). These HQs are all based on toxicity data for Ephemeroptera, the taxonomic order of aquatic invertebrates most sensitive to imidacloprid. While HQs would be lower for less sensitive groups of aquatic invertebrates, the groups that appear to be at risk (HQs>1) include Ostracoda, Annelida, midges and other Diptera, Hemiptera, Amphipoda, Trichoptera, Mysida, Megaloptera, and one species of Cladocera (*Ceriodaphnia*

dubia). A major limitation in the risk assessment for aquatic invertebrates is that exposures associated with tree injection are not quantified, except for accidental spills. Risks associated with non-accidental exposures following tree injection would most likely involve water contamination secondary to leaf fall from treated trees. Given the high HQs for sensitive species of aquatic invertebrates with respect to other application methods, risks to some sensitive species of aquatic invertebrates following tree injection cannot be dismissed. Whether adverse effects might be noted in aquatic invertebrates following tree injection depends greatly on the volume of water contaminated by falling leaves and the total number of leaves transported to the body of water.

None of the application methods under consideration by the Forest Service—i.e., tree injection, soil injection, and bark application—pose risks to mammals, and risks to birds are limited to bark applications. All avian HQs of concern (HQ>1) are limited to the consumption of contaminated vegetation or contaminated insects. As with other HQs associated with bark application, the magnitude of the HQ is related to the assumed application efficiency of imidacloprid to bark. The current risk assessment uses an application efficiency of 90% with 10% of the imidacloprid lost to nontarget vegetation. Greater application efficiencies would lead to lesser risk. Nonetheless, some of the upper bound HQs for birds following bark applications are greater than 10, and it seems unlikely that these HQs could be reduced below the level of concern (HQ=1) by feasible application efficiencies (i.e., >99%).

The risk characterization for imidacloprid focuses on the potential for direct toxic effects. Nonetheless, there is a potential for secondary effects in virtually all groups of nontarget organisms. Terrestrial applications of any effective insecticide, including imidacloprid, are likely to alter insect and other invertebrate populations within the treatment area. This alteration could have secondary effects on terrestrial or aquatic animals and plants, including changes in food availability and habitat quality. These secondary effects may be beneficial to some species and detrimental to others; moreover, the magnitude of secondary effects is likely to vary over time. In the case of imidacloprid, an analysis of bird populations suggests that adverse effects on terrestrial invertebrates may reduce populations of insectivorous birds.

4.4.2. Terrestrial Organisms

4.4.2.1. Mammals

The HQs for mammals are given in Worksheet G02a of the attachments to this risk assessment. For the application methods to be used in Forest Service programs, there is no basis for asserting that mammals will be adversely affected by imidacloprid, based on the exposure assessments developed in Section 4.2.2. None of the HQs for tree or soil injection exceed the level of concern (HQ=1). For bark applications, the highest HQ is 1.4, which is the upper bound of HQs associated with the accidental direct spray of a small mammal. As discussed in the dose-response assessment (Section 4.3.2.1), the estimated NOAEL for mammals is a factor of 3 below a LOAEL based on changes in locomotion. Thus, while an HQ of 1.4 is a concern, it is not clearly or necessarily associated with overt effects in mammals. For directed foliar applications, several of the acute HQs for the consumption of contaminated vegetation exceed the level of concern in both central estimates and upper bounds. These HQs, however, do not impact the assessment of the more focused application methods to be used in Forest Service programs.

As in the previous Forest Service risk assessment on imidacloprid (SERA, 2005) and the Forest Service risk assessment on dinotefuran (SERA 2009a), a plausible exposure scenario that is not standard in Forest Service risk assessments involves porcupines (*Erethizon dorsatum*) which preferentially consume the inner bark, small twigs, and buds of eastern hemlock trees. In any of the application methods used to control the hemlock wooly adelgid, imidacloprid will enter the sap of the hemlock tree, distributing to leaves and branches. This distribution of the pesticide could result in unintended exposures for the porcupine. As summarized in Table 30, the highest concentration of imidacloprid monitored in hemlock foliage is about 0.2 mg/kg twigs and foliage (Dilling et al. 2010, Table 2). As in the risk assessment on dinotefuran (SERA 2009a), it is assumed that a porcupine might consume 20% of its bodyweight in inner bark, small twigs, and buds from hemlock trees. Accordingly, the dose to the porcupine would be about 0.04 mg a.i./kg bw [0.2 mg a.i./kg twigs and foliage x 0.2 food/body weight]. Based on the chronic NOAEL of 5.7 mg/kg bw, the HQ for the porcupine would be about 0.007 [0.04 mg a.i./kg bw ÷ 5.7 mg/kg bw ≈ 0.007012], below the level of concern by a factor of over 140 [1÷0.007≈142.86].

4.4.2.2. Birds

The HQ values for birds are given in Worksheet G02b of the attachments to this risk assessment. For tree and soil injections, plausible exposures and risks are likely to be negligible. None of the exposure levels associated with these application methods approaches a level of concern.

For bark applications (Attachment 3), the risk characterization is much more severe. Although HQs for exposures to contaminated water do not exceed the level of concern, all acute exposure scenarios associated with the consumption of contaminated vegetation exceed the level of concern at the upper bounds (upper bound HQs of up to 23), and the central estimates of the HQs are above the level of concern for the consumption of broadleaf foliage (HQ=3), tall grass (HQ=2), and short grass (HQ=5). For the chronic exposure scenarios, only two of the upper bound HQs exceed the level of concern—i.e., upper bound HQs of 2 for broadleaf vegetation and HQs of 4 for short grass.

As discussed in the exposure assessment, these HQs may be viewed as conservative in that HQs are based on the assumption that 100% of the diet is contaminated and that 10% of imidacloprid applied to the bark is lost to surrounding vegetation. For bark applications, however, it does not seem unreasonable to assume that 100% of the diet is contaminated because most of the pesticide which leaches from the bark will accumulate in a relatively small area around the treated tree. In this small area, the actual amount of accumulated pesticide will be greater than the nominal offsite average application rate. Thus, the assumption that 100% of the diet is contaminated is based on the implicit average of higher residues in the areas close to the treated trees and lower residues in areas further from the treated trees.

The assumption of 10% loss of pesticide from the treated bark may be viewed as conservative. As discussed in Section 2.4.3, the value of 10% is an upper bound estimate from Onken (2009). Cowles (2009) suggests that rates of 5% or less could be achieved. In any specific application, losses of less than 10% could be used if justified by site-specific or program-specific considerations. Nonetheless, some of the HQs are sufficiently high that reasonable alternative assumptions of loss would not impact the qualitative characterization of risk. For example, the upper bound acute HQ associated with residues that would be similar to those on tall grass is 10.

For the HQ to reach the level of concern (HQ=1), requires that the offsite loss be 1% and the application efficiency to the bark be 99%.

As with mammals, certain species of birds not considered explicitly in most Forest Service risk assessments may be at increased risk. For example, hummingbirds could be exposed to imidacloprid in both the consumption of small insects (explicitly covered in Worksheet F09c of the attachments) and the consumption of contaminated nectar (not explicitly covered in the worksheets). While the potential for such exposures is acknowledged, this type of consideration is the basis for modeling likely food items (such as fruit) as well as less likely food items (such as short grass) (SERA 2014a, Section 4.2.2.3). Clearly, many species of birds will not consume substantial amounts of grasses; nonetheless, grasses and other the food groups from Fletcher et al. (1994) are considered for birds in an attempt to encompass the large variety of items that birds might consume. Although several of the HQs for birds associated with bark applications are a concern, these HQs are substantially below the HQs for foliar applications (Attachment 4).

As discussed in Section 4.1.2.2.5, Hallman et al. (2014) suggest that imidacloprid may be associated with declines in populations of insectivorous birds in the Netherlands secondary to adverse effects on terrestrial invertebrates. As discussed further in Section 4.4.2.4, terrestrial invertebrates may be adversely affected by imidacloprid.

A simple interpretation of the HQs discussed above is that neither tree nor soil injections of imidacloprid are likely to pose a substantial or even detectable risk to birds, based on the quantitative exposure assessments. Bark applications, particularly those involving many trees in the same area, could lead to harmful exposures over both short and longer-term periods following treatment.

4.4.2.3. Reptiles and Amphibians (Terrestrial-Phase)

No explicit or quantitative risk characterization is developed for reptiles or terrestrial-phase amphibians because the available toxicity data do not support a dose-response assessment (Section 4.3.2.3). Within the reservations discussed in Section 4.1.2.3, the current Forest Service risk assessment is consistent with the most recent EPA ecological risk assessment on imidacloprid (U.S. EPA/OPP/EFED 2007a) and uses birds as a surrogate for reptiles and terrestrial-phase amphibians (Section 4.4.2.2).

4.4.2.4. Terrestrial Invertebrates

4.4.2.4.1. Honeybees

The hazard quotients for honeybees are summarized in Table 34. These HQs are based on the NOAEL of 0.000095 mg/kg bw for colony health from Dively et al. (2015), as summarized in Table 31 and discussed in Section 4.3.2.4.1. This NOAEL is derived from the NOAEC of 5 ppb for the concentration of imidacloprid in the diet of foraging bees. This NOAEC is supported by a similar study conducted by Faucon et al. (2005). In addition to the NOAEC, adverse effects on colony health were observed at dietary concentrations of 20 ppb and higher (Dively et al. 2015; Lu et al. 2012, 2014).

4.4.2.4.1.1. Tree Injection

The highest HQs are associated with the tree injection of maples—i.e., HQs of 27,166 (8,754 - 180,390). As summarized in Table 30, the exposure assessment is based on the study by Ugine et al. (2013) which reports concentrations of imidacloprid in maple foliage—i.e., 13.79 (6.16 - 49.17) µg/g—at day 150 following the injection of Norway maple. Kreutzweiser et al. (2008a) report somewhat lower concentrations of imidacloprid in sugar maple leaves—i.e., 11 (6.4 - 18.5) µg/g—at 35 days after injection. In terms of potential impacts on honeybees, levels of imidacloprid in foliage are not directly relevant, and the study by Dively and Kamel (2012) is used to estimate concentrations in nectar. As discussed in Section 4.2.3.3.3.1, the study by Dively and Kamel (2012) involved levels of imidacloprid in the nectar and foliage of pumpkin. The use of an adjustment factor to estimate concentrations in maple adds obvious and substantial uncertainty to the estimated HQs. In addition, as noted in Section 4.2.1, the exposure assessment for nectar foraging bees on treated maple assumes that 100% of the diet is contaminated. In most cases, this assumption will overestimate exposures. Nonetheless, given the extraordinarily high HQs for bees associated with the injection of maple trees, the qualitative risk characterization is reasonably clear and unambiguous. While honeybees may not be involved in the pollination of maple, they do forage on some species of maple during the spring (Batra 1985; USDA/NRCS 2006). If honeybees were to actively forage on maple treated by injection with imidacloprid, concern for colony health during overwintering would be high if injections were made prior to flowering. As discussed in Section 4.2.3.3.3.1, long-term studies on the fate of imidacloprid in maple are not available. Given the magnitude of the HQs, there appears to be a potential for adverse effects in bees if exposures were to occur in the year following tree injection. In other words, residues on maple would need to diminish by a factor of over 180,000 in order for the estimated exposure to drop below the level of concern.

Despite the apparently high risk to honeybees posed by the injection of maple trees with imidacloprid, risks following the injection of ash, hemlock, and other species of trees with imidacloprid are not characterized quantitatively. Bees associate with various species of trees in terms of hive locations and incidental foraging. Information on the likelihood and intensity of honeybee exposure to imidacloprid from tree injection to species other than maple is not addressed in the available literature. Given the extreme risk characterization for the injection of maple trees, residual concern for the injection of other species of trees is warranted in the absence of data indicating that such injections will not be likely to result in the exposure of honeybees to toxicologically significant amounts of imidacloprid.

4.4.2.4.1.2. Soil Injection

The HQs for soil injection are 203 (58 - 575). As discussed in Section 4.2.3.3.3, these HQs are based directly on the study by Dively and Kamel (2012) concerning residues of imidacloprid in pumpkin nectar, and the same exposure assessment methods are used for both soil injection and foliar application. As discussed in Section 4.2.3.3.3.2, there is a concern that this approach may underestimate honeybee exposures in the area of treated trees because of the number of injection sites around the treated tree. Even for soil injections adhering to the 0.4 lb a.i./acre application rate, the functional application rate in the area of the treated tree will be higher than the nominal average application rate of 0.4 lb a.i./acre. This concern, however, is offset by the fact that bees

foraging at a greater distance from the treated tree will be exposed to lesser amounts of imidacloprid.

Unlike the case with tree injection, honeybee exposure from soil injection or bark application (discussed further below) is likely to be associated with nontarget vegetation—i.e., flowering plants in the vicinity of the treated tree. Thus, the risk characterization applies to the treatment of all species of trees treated by soil injections of imidacloprid.

As discussed in Section 4.3.2.4.1, bee exposures equivalent to an HQ of 4 are associated with colony death during overwintering. Thus, while the HQs associated with soil injection are less than those associated with tree injection, the risk characterization is essentially identical. If bees forage on flowering plants in the area of trees treated with imidacloprid by soil injection, adverse effects on colony overwintering could be expected. The HQs are sufficiently high—i.e., 203 (58 - 575)—that uncertainties associated with the proportion of the diet that might be contaminated would not have a substantial impact on risk characterization.

4.4.2.4.1.3. Bark Application

The HQs for bark application are 20 (6 - 57), about a factor of 10 below those for soil injection and foliar application. As discussed in Section 4.2.3.3.3.3, this difference is a result of using an application efficiency to the tree bark of 90% and an off-site loss to nontarget vegetation of 10%. Unlike the case with maple tree injection or soil injection, the lower HQs for bark application could be impacted by reasonable assumptions concerning the proportion of the bee diet that is contaminated. For example, the treatment of a single high value tree in an area not otherwise contaminated with imidacloprid or other neonicotinoids might warrant the assumption that only 10% of the material foraged by a worker bee would be contaminated. In this situation, the functional application rate would also be less, and possibly much less, than 0.4 lb a.i./acre, and this reduced application rate would further reduce potential risk. Thus, in limited programs involving sparse bark treatments of imidacloprid, program-specific conditions could result in HQs for bee colonies that are below the level of concern.

4.4.2.4.1.4. Foliar Application

The HQs for foliar application are about 105,000 (57,000 – 190,000). These HQs are substantially higher than the corresponding HQs for soil injection – i.e., 203 (58 - 575). As discussed in Section 4.2.3.3.3.4, the higher exposures for foliar application are based on the study by Larson et al. (2015) which involved foliar applications to turf with measures of the concentration of imidacloprid in the nectar of flowering clover shortly after application – i.e., the direct spray of the flowering clove. As also discussed in Section 4.2.3.3.3.4, levels of imidacloprid in the nectar of flowering clover from the study by Larson et al. (2005) were comparable to levels associated with soil applications once the lawn had been mowed and repeatedly irrigated. Thus, the high HQs for foliar applications are applicable to nectar levels that may be seen shortly after foliar applications in which flowers are directly sprayed. Over more prolonged periods of time, imidacloprid will wash off into soil and levels of imidacloprid in the nectar flowering plants would probably be closer to those associated with soil applications of imidacloprid (Section 4.4.2.4.1.2).

4.4.2.4.1.5. Uncertainties

As noted in Section 4.3.2.4.1, the dose-response assessment for bees is based on honeybee colonies involving exposure periods of several months. Some shorter-term studies suggest that populations of honeybees may differ in sensitivity to imidacloprid by an order of magnitude. While risks to honeybees are apparent, the extent to which the risk characterization for honeybees is applicable to other groups of bees is unclear. As discussed in Section 4.1.2.4.2.1 (Variations in Sensitivity), honeybees are among the most sensitive species of terrestrial invertebrates but data on other types of bees – i.e., stingless bees (Megachilidae) – are variable with some studies suggesting that Megachilidae are more sensitive and other studies suggesting that Megachilidae may be somewhat less sensitive. In addition, no data are available on the sensitivity of Andrenidae (ground nesting bees) to imidacloprid. As discussed in the meta-analysis by Arena and Sgolastra (2014) on bioassays of a large number of pesticides in different groups of bees, the difference in sensitivity between honeybees and other species of bees may exceed a factor of 1000 – i.e., other types of bees being up to 1000 times less sensitive than honeybees to over 1000 more sensitive than honeybees to various pesticides. The possible differences in sensitivity combined with differences in the foraging radius and methods of exposure between honeybees and other types of bees lead to substantial uncertainty in the application of the risk characterization for honeybees to other species/families of bees.

The studies used in the dose-response assessment for bees (i.e., Dively et al. 2015; Faucon et al. 2005; Lu et al. 2012, 2014) all involve exposures of bees to relatively constant levels of imidacloprid in the diet over a period of months. This type of constant exposure is not likely to occur in the field. For example, maple trees injected with imidacloprid may be an important source of exposure for foraging bees in early spring; however, the exposures will not be maintained throughout the summer and into fall. In other cases, exposures to imidacloprid from contaminated nontarget vegetation are likely to be variable and possibly shift from one plant species to another in the treated area over the course of a single season. It is beyond the scope of the current generic risk assessment to attempt to elaborate further. In the assessment of a site-specific application, these factors could be considered further depending on the timing and extent of the applications and the native vegetation in the treated area. As with considerations of inter- and intra-species variability, exposure factors in a site-specific assessment would need to differ substantially from the exposure assessments developed in the current risk assessment in order for the risk characterization to be altered qualitatively.

While the risk assessment for honeybees is focused on contaminated nectar or nectar/pollen mixtures in the exposure assessment, contaminated propolis is another potential source of exposure for honeybees as well as other types of bees. The term *propolis* is used to designate resins harvested by bees from various plant species and then used to cover openings or cracks within the nest or to line the nest cavity. Resin from poplar trees is a common source of propolis in temperate climates but resins used for propolis may also be harvested from pine, birch, elm, alder, beech, horse-chestnut, willow, and palm species (Simone-Finstrom and Spivak 2010; Toreti et al. 2013; Wollenweber and Buchmann 1997). Resins could be contaminated with imidacloprid following tree treatments but no studies have been encountered on the concentrations of imidacloprid in propolis or levels of exposure of bees to imidacloprid associated with contaminated propolis. Consequently, it is unclear if contaminated propolis is a significant or only minor route of exposure of bees to imidacloprid. Given the design of the

whole colony studies used in the dose-response assessment (Section 4.3.2.4.1), it does not seem likely that these studies encompassed exposures to contaminated propolis.

Another potential source of uncertainty involves the basic approach used in the risk assessment for bees. Following the approach used in the Forest Service risk assessment on dinotefuran (SERA 2009a), the current risk assessment adopts a method developed for the French Ministry of Agriculture (Alix and Vergnet 2007; Halm et al. 2006; Rortais et al. 2005). As detailed in Section 4.2.3.3.1, this method is based on considerations of the concentration of imidacloprid in nectar as well as the activity levels and metabolic requirements of worker bees foraging for nectar. Using this method, the risk characterization is based on an estimated dose in units of mass per bee (e.g., mg/kg bw/day) as well as estimated exposures expressed in the same units. It should be noted, however, that the NOAECs on which the dose-response assessment is based involves colony level responses rather than simply the response of the foraging bee. Thus, the longer-term exposures to different groups of bees within the hive are implicitly considered.

Much of the literature concerning the potential impact of imidacloprid on bees simply compares imidacloprid concentrations in nectar to imidacloprid concentrations in the diet of bees and their associated effects. For example, imidacloprid concentrations in the bee diets used by Dively et al. (2015) are intended to represent seed-treated crops (5 ppb), field doses for other crops (20 ppb), and "*worst-case*" field exposures (100 ppb). Implicit in these comparisons is a risk quotient based on concentrations—i.e., the concentration of imidacloprid in nectar in the field divided by experimental NOAECs. Examples of concentration-based HQs are given in Table 35. The upper portion of Table 35 summarizes the estimated concentrations of imidacloprid in nectar associated with the injection of maple trees, soil injection, and bark application. The lower portion of this table gives the HQs calculated as the estimated concentration in nectar divided by the experimental NOAEC of 5 ppb from Dively et al. (2015) and Faucon et al. (2005).

For the injection of maple trees, the concentration-based HQs are consistent with the dose-based HQs, indicating that adverse effects on colony overwintering would be expected. For soil injection, the HQs [2.3 (1.1 - 3.7)] lead to a more nuanced risk characterization in that an HQ of 4 corresponds to a clear LOAEC—i.e., the 20 ppb concentrations from Dively et al. (2015) and Lu et al. (2012). For bark applications, all of the concentration-based HQs are below the level of concern, leading to a clear difference from the dose-based HQs.

The concentration-based HQs in Table 35 are presented solely for the sake of transparency and are not intended as an alternative to the dose-based HQs given in Table 34. As with the risk assessments for mammalian wildlife and birds, it is important to recognize that laboratory diets tend to be higher in calories than environmental food sources; accordingly, dose estimates based on caloric requirements are preferable to a direct comparison of pesticide concentrations in lab chow to pesticide concentrations in environmental media. Considerations of the caloric requirements of the animal and the calories in dietary commodities are used in all Forest Service risk assessments for mammals and birds (SERA 2014a, Section 4.2.2.3). The extension of this method to honeybees seems both reasonable and appropriate.

The risk characterization for honeybees is somewhat atypical in that risks are characterized at the level of the hive or colony rather than the individual organism. As discussed above, there are

several uncertainties associated with this approach. As summarized in Table 32, the estimated NOAEL for effects on colony overwintering is 0.000095 mg/kg bw, which is lower than the NOAEL for an individual bee (i.e., 0.00023 mg/kg bw) by a factor of about 2.4 [0.00023 mg/kg bw ÷ 0.000095 mg/kg bw ≈ 2.421]. Given the magnitude of the HQs for bees, using the modestly higher NOAEL of 0.00023 mg/kg bw for the individual bee instead of the NOAEL of 0.000095 mg/kg bw for colony overwintering would not have a substantial impact on the risk characterization.

The various processes involved in exposures to different groups of bees within a colony (e.g., Rortais et al. 2005; Dively et al. 2015) are not explicitly addressed in the colony level HQs derived in the current risk assessment. A single application of imidacloprid may lead to a single or short-term exposure for adult bees harvesting contaminated nectar or pollen and then subsequently lead to longer-term exposures throughout development of the next generation. This type of exposure is not addressed by studies of single short term exposure in adult bees. Nonetheless, a benefit of using colony level responses in the derivation of HQs is that the longer-term exposures to imidacloprid within the colony are encompassed at least implicitly.

Lastly, the longer-term studies on overwintering may be viewed as field studies in the sense that exposures occurred in the field rather than the laboratory. Nonetheless, the studies involved relatively controlled field exposures to imidacloprid rather than exposures associated with forestry applications of imidacloprid. The HQs for bees suggest that field applications of imidacloprid associated with forestry programs have the potential to adversely affect colony overwintering. Field studies explicitly involving the impact of forestry applications on bee colony health, including overwintering, would be useful in refining the risk characterization for bees.

4.4.2.4.2. Phytophagous Insects

The hazard quotients for phytophagous insects are summarized in Table 36. As discussed in Section 4.3.2.4.2, these HQs are based on the most sensitive nonlethal endpoint for insects other than colony failure—i.e., LOAEL for neurotoxicity of 0.08 ng/bee from the study by Boily et al. (2013) in honeybees. As discussed in Section 4.1.2.4.2.1.1 and illustrated in Figure 4, some insects may be somewhat but not remarkably less sensitive than honeybees, and the toxicity data on honeybees is more robust than the corresponding data on the toxicity of imidacloprid to phytophagous insects. Using a toxicity value for the honeybee as a surrogate toxicity value for phytophagous insects may seem somewhat conservative.

As discussed in Section 4.3.2.4.2, an HQ of 3 may be associated with a mild LOAEL (hyperactivity) and an HQ of 20 could be associated with mortality.

4.4.2.4.2.1. Tree and Soil Injection

The HQs for phytophagous insects vary substantially according to the species of trees that might be treated with imidacloprid—i.e., 565 (78 - 1913) for hemlock, 4804 (261 - 12,243) for ash, and 79,130 (16,174 - 468,696) for maple. These vast differences in the HQs for various types of trees are based on well documented studies, as summarized in Table 30 and discussed in Section 4.2.3.2.1.

Given the extensive data on the toxicity of imidacloprid to insects, the well documented data on residues in trees following tree and soil injection, and the magnitude of the HQs, the risk characterization is reasonably simple and unambiguous. Insects foraging on trees treated with imidacloprid will be exposed to lethal doses.

Insect lethality would be delayed for some time after either tree or soil injection because of the time required for uptake and translocation of imidacloprid to foliage. Given the magnitude of the HQs, mortality could be seen long before peak levels of imidacloprid occur in foliage.

This risk characterization is limited to the insects that will feed on the treated trees. The species most likely to be impacted will vary with the species of tree that is treated and the types of insects in the treated area.

4.4.2.4.2.2. Bark Application

As summarized in Table 36, the HQs for bark application range from over 300 (the lower bound for contaminated fruit) to over 90,000 (the upper bound for contaminated short grass).

Unlike tree and soil injection, the exposure assessments for bark application are based on standard residue rates (Table 12) and the assumption that 10% of the imidacloprid nominally applied to the bark will be deposited on nontarget vegetation. The residues rates used are the standard rates proposed by U.S. EPA/EFED (2001, p. 44) as adopted from Fletcher et al. (1997); furthermore, these rates are consistent with monitoring data on imidacloprid (Section 3.2.3.7). The other major difference between bark application and injection applications is that exposures following bark application do not depend on the species of tree treated.

As with tree and soil injection, the risk characterization for bark application is reasonably simple. Insects feeding on nontarget vegetation incidentally contaminated during a bark application will be exposed to lethal levels of imidacloprid.

4.4.2.4.2.3. Uncertainties

Despite uncertainties in both the exposure assessment and dose-response assessment, the magnitude of the HQs might suggest that these uncertainties are inconsequential to the risk characterization. Nonetheless, other field studies suggest caution in the interpretation of the HQs (Appendix 4, Table A4-14). While some field studies support the assessment of adverse effects on phytophagous insects (Dilling et al. 2009; James and Vogele 2001; Peck 2009), other field studies note either no effects or only transient effects on predatory insects and other predatory arthropods (Kilpatrick et al. 2005; Kunkel et al. 1999). A limitation in the field studies, however, is that they do not involve forestry applications of imidacloprid.

As with the risk characterization for honeybees (Section 4.4.2.4.1), some potential routes of exposure are not quantitatively considered in the current risk assessment. For example, Hoffmann and Castle (2012) have found toxic levels of imidacloprid (i.e., up to 4.1 mg/L) in exudate from cantaloupe following agricultural applications of imidacloprid. Similarly, Larson et al. (2015) found much lower levels of imidacloprid (i.e., ≈23-88 µg/kg) in exudates from grasses following applications of imidacloprid to turf. As summarized in Attachment 4 (foliar applications), the maximum concentration of 4.1 mg/L from Hoffmann and Castle (2012) is in

the range of concentrations estimated in fruit following agricultural foliar applications of imidacloprid – i.e., 1.28 to 6 mg a.i./L. Again, however, the high HQs for phytophagous insects suggest that a quantitative consideration of contaminated plant exudate (i.e., guttation) would not fundamentally alter the risk characterization for insects that feed on treated plants.

4.4.2.4.3. Direct Spray of Insects

Direct spray scenarios apply only to bark applications, again under the assumption that 10% of the imidacloprid nominally applied to the bark is lost to nontarget areas and could be deposited on nontarget invertebrates (e.g., Section 4.4.2.4.2.2).

The HQs for this scenario are given in Worksheets G09 of Attachment 3 (bark application) and Attachment 4 (foliar applications). While the HQs are highly variable depending on assumptions of foliar interception, most of the HQs are substantially above the level of concern—e.g., from 2 to 465 for bark applications at distances of up to 50 feet from the application site.

The interpretation of these HQs is simple. Imidacloprid is highly toxic to insects and other arthropods. If a sensitive species of terrestrial invertebrate is accidentally sprayed with a field solution of imidacloprid, the animal will die. Nonetheless, direct spray would occur only during application and only incidentally to unintended loss from the bark to be treated. Relative to the effects on honeybees and phytophagous insects, this exposure scenario is not a major concern, because relatively few organisms would be impacted over a brief period of time.

4.4.2.4.4. Soil Invertebrates

Quantitative risk characterizations (i.e., HQs) are not developed for soil invertebrates in Forest Service risk assessments (SERA 2014a); however, the data on imidacloprid support a semi-quantitative assessment.

The soil concentrations of imidacloprid associated with soil injection, bark application, and foliar application is summarized in Table 31, and more extensive details about of soil concentrations of imidacloprid are provided in Appendix 8 (Table A8-2 and A8-3) for soil injection and Appendix (Table A9-2 and A9-3) for foliar application. All of these estimates are expressed in units of mg/kg soil per lb a.i. applied. The highest soil contamination rate is 0.4 mg a.i./kg soil per lb a.i. applied. Thus, at the maximum application rate of 0.4 lb a.i./acre, the anticipated maximum concentration of imidacloprid in soil is about 0.16 mg a.i./kg soil.

As discussed in Section 4.3.2.4.4, the earthworm is most sensitive species of soil invertebrates, with a LOAEL of 0.2 mg a.i./kg soil for sperm malformations observed in *Eisenia foetida* (Luo et al. 1999). This LOAEL is close to the maximum concentration in soil of 0.16 mg a.i./kg soil; thus, adverse effects in some species of earthworms cannot be completely ruled-out, based on the upper bound estimates of exposure. Longer-term studies in earthworms note no adverse effects on reproduction at concentration below 1 mg/kg soil (Dittbrenner et al. 2011; Fernandez-Gomez et al. 2011). Based on the longer-term studies, it appears that adverse effects on earthworms are unlikely or would be, at most, transient.

4.4.2.5. Terrestrial Plants

The risk characterization for imidacloprid is unchanged from the previous Forest Service risk assessment (SERA 2005). No quantitative risk assessment to terrestrial plants is made. As

discussed in Section 4.1.2.4, imidacloprid is not phytotoxic under conditions of normal use. In addition, imidacloprid has been extensively tested in both the laboratory and field studies for efficacy in the protection of terrestrial plants from insect pests. If imidacloprid were toxic to plants at applications rates used to control the pest species, the available data would most likely include reports of phytotoxicity.

4.4.2.6. Terrestrial Microorganisms

As discussed in Section 4.2.3.4 and summarized in Table 31, the highest levels of imidacloprid in soil are associated with soil injection in clay, with a maximum soil concentration rate of 0.4 ppm per lb a.i. applied. Thus, at the maximum application rate of 0.4 lb a.i./acre, the maximum anticipated concentration of imidacloprid in soil would be about 0.16 ppm. As discussed in Section 4.3.2.6, transient changes in soil microbial populations have been noted at 1 ppm and protracted changes in microbial populations have been noted 100 ppm (Cycon et al. 2013). In terms of a functional impact on litter degradation, no effects have been noted on soil microorganisms at concentrations of up to 1400 ppm. While soil microorganisms are not formally incorporated into the workbooks that accompany this risk assessment, there is no basis for asserting that adverse effects on soil microorganisms are likely following applications of imidacloprid.

4.4.3. Aquatic Organisms

4.4.3.1. Fish

As discussed in Section 4.1.3.1, imidacloprid is classified as practically nontoxic to fish, and this classification is reflected in the low HQs for fish. None of the HQs for fish exceed the level of concern (HQ=1). The highest HQ of 0.06 is the upper bound for sensitive species of fish in the exposure scenario involving an accidental spill. This HQ is below the level of concern by a factor of over 16 [1÷0.06≈16.666…]. For non-accidental exposure scenarios, the highest HQs are 0.02 for soil injection (Attachment 2, Worksheet G03), 0.003 for bark applications (Attachment 3, Worksheet G03), and 0.03 for foliar application (Attachment 4, Worksheet G03). All of these HQs are the upper bounds of the HQs for the longer-term exposures of sensitive species of fish and are below the level of concern by factors of 50 for soil injection, about 333 for bark application, and about 33 for foliar application.

Non-accidental exposure scenarios are not developed for tree injection, because general methods for estimating imidacloprid concentrations in surface water are not available. For fish, this limitation is irrelevant. As discussed further below (Section 4.4.3.4), this is not the case for aquatic invertebrates.

4.4.3.2. Amphibians (Aquatic-Phase)

As summarized in Table 32, the acute toxicity values for amphibians are somewhat lower than those for fish—i.e., factors of about 6 for sensitive species [25 mg/L ÷ 3.89 mg/L ≈ 6.427] and 3 for tolerant species [50 mg/L ÷ 16.7 mg/L ≈ 2.994]. As with fish, none of HQs for amphibians approaches a level of concern. The highest acute HQ for amphibians is 0.1, the upper bound for sensitive species following an accidental spill.

Chronic toxicity data on amphibians are not available, and explicit longer-term HQs for amphibians cannot be derived. Using fish as a surrogate for aquatic-phase amphibians (Section 4.3.3.2), lowers concern for longer-term exposures of amphibians to imidacloprid.

4.4.3.4. Aquatic Invertebrates

As discussed in Section 4.3.3.3 and summarized in Table 23 (acute toxicity) and Table 24 (chronic toxicity), the toxicity of imidacloprid varies substantially among different groups and species of aquatic invertebrates. Some species of aquatic invertebrates are as tolerant of exposures to imidacloprid as fish. As with the HQs for fish, HQs for tolerant species of aquatic invertebrates do not exceed the level of concern (HQ=1) even for the accidental spill scenarios.

Other groups of aquatic invertebrates are much more sensitive to imidacloprid. As also discussed in Section 4.3.3.3, the most sensitive taxonomic order of aquatic invertebrate is Ephemeroptera, and the HQs for the most sensitive species of Ephemeroptera (*Cloeon dipterum*) are summarized in Table 3. These HQs are taken from Worksheet G03 of the EXCEL workbooks for soil injection (Attachment 2), bark application (Attachment 3), and directed foliar application (Attachment 4).

The HQs for accidental spills substantially exceed the level of concern, even at the lower bounds for all application methods. As summarized in the G03 worksheets, the concentrations of imidacloprid in water following an accidental spill range from about 0.0076 mg/L (the lower bound for bark application) to 1.6 mg/L (the upper bound for tree injection). As summarized in Table 22, the acute EC_{50} for *Cloeon dipterum* is 0.000123 mg/L, a factor of about 61 below the lower bound concentration for an accidental spill [0.0076 mg/L ÷ 0.000123 mg/L ≈ 61.789]. In the event of an accidental spill of imidacloprid into a small body of water (as detailed in Section 3.2.3.4.1), there is little doubt that substantial mortality would occur in sensitive species of aquatic invertebrates.

The HQs for non-accidental acute exposures are below the level of concern only at the lower bounds of estimated exposures. The central estimates of the HQs are 2 for bark application, 16 for soil injection, and 20 for directed foliar applications. The modest excursion above the NOAEC for bark applications would not necessarily be accompanied by observable mortality. The HQ for soil injection is associated with a peak concentration of 0.0052 mg/L, above the acute EC_{50} for *Cloeon dipterum* by a factor of over 40 [0.0052 mg/L ÷ 0.000123 mg/L ≈ 42.276]. This concentration as well as all of the concentrations associated with upper bound acute HQs would likely be associated with substantial mortality in the most sensitive species of aquatic invertebrates.

As with the acute HQs, the lower bounds of the chronic HQs are below the level of concern. The central estimates of the chronic HQs, however, are substantially above the level of concern—i.e., an HQ of 12 for bark applications and 140 for soil injection. As summarized in Table 32, the chronic toxicity value for Ephemeroptera is 0.000024 mg a.i./L, the 28-day EC_{10} for immobilization of *Caenis horaria* from the study by Roessink et al. (2013). As summarized in Table 24, the EC_{50} for this species is 0.000126 mg a.i./L. The lowest central estimate of the chronic HQs is associated with a concentration of imidacloprid in surface water of 0.00064 mg a.i./L (Worksheet G03 of Attachment 3). This concentration is a factor of about 5 higher than the chronic EC_{50} [0.00064 mg a.i./L ÷ 0.000126 mg a.i./L ≈ 5.079]. This relationship suggests that adverse effects, including mortality, are likely in the most sensitive species of aquatic invertebrates following longer-term exposures to imidacloprid, based on both the central estimates and the upper bounds.

Because of the substantial variability in the sensitivity of aquatic invertebrates to imidacloprid, a further refinement is warranted concerning the groups of aquatic invertebrates most likely to be impacted by imidacloprid. This elaboration may be made at least for acute exposures. As discussed above, the highest HQ for acute exposures is 209, the upper bound HQ associated with soil injection. Table 23 (column 5) summarizes the sensitivity of different species or groups of aquatic invertebrates, relative to Ephemeroptera. The species or groups which are within the range of 209 or less in terms of sensitivity relative to Ephemeroptera include Ostracoda, Annelida, midges and other Diptera, Hemiptera, Amphipoda, Trichoptera, Mysida, Megaloptera, and one species of Cladocera (*Ceriodaphnia dubia*). As discussed in Section 4.1.3.3.1, not all of these groups are well represented in terms of the number of studies that are available on each group, and this general lack of information adds uncertainty to the risk characterization. Nonetheless, as summarized in Table 26, adverse effects on Ephemeroptera, Amphipoda, Trichoptera, and Diptera are supported by several mesocosm studies, particularly the multispecies mesocosm studies by Colombo et al. (2013) and Hayasaka et al. (2012c), neither of which is used directly in the dose-response assessments for aquatic invertebrates.

As discussed in Section 3.2.3.1.2, no explicit exposure assessment is conducted for concentrations of imidacloprid in surface water following tree injection. GLEAMS-Driver does not accommodate tree injection, and other models or methods for estimating concentrations of pesticides in surface water following tree injection were not identified in the available literature. For most groups of organisms, this limitation is not serious because the estimated concentrations of imidacloprid from other less focused application methods, including foliar application, are below the level of concern. For aquatic invertebrates, this is clearly not the case, and most HQs for sensitive species of aquatic invertebrates are substantially above the level of concern (Table 37).

Leaf fall is the most plausible mechanism for the exposure of aquatic invertebrates to imidacloprid following tree injection. As discussed in Section 4.1.3.3, Kreutzweiser et al. (2007, 2008a, 2009) conducted several studies demonstrating that imidacloprid can leach from fallen leaves of trees injected with imidacloprid into stream water. These studies indicate that leaves from trees injected with normal field rates of imidacloprid do not cause adverse effects but that leaves from trees intentionally injected with excessive doses of imidacloprid can harm sensitive species of aquatic invertebrates. These results, however, cannot be used directly in the risk characterization because the results may be an artifact of the experimental designs. For example and as detailed in Appendix 6, Table A6-10, the study by Kreutzweiser et al. (2007) noted no adverse effects in stonefly (*Pteronarcys dorsata*) using leaves from trees treated at the recommended application rate but excessive mortality (≈90%) using leaves from trees treated at a 10-fold higher dose. This study involved adding 12 contaminated ash leaves to 6 liters of water with observations over a 14-day period. If more leaves had been added to the water or if a longer period of exposure period had been used, different results could have been observed. Consequently, given the very high HQs for sensitive species of aquatic invertebrates for other application methods, risks to some sensitive species of aquatic invertebrates following tree injection cannot be dismissed. Whether or not adverse effects might be noted in aquatic invertebrates would depend greatly on the volume of the water that might be contaminated by falling leaves as well as the total number of leaves that would be transported to the water body.

4.4.3.4. Aquatic Plants

4.4.3.4.1. Algae

As summarized in Table 32, some species of algae—i.e., *Desmodesmus subspicatus* from the study by Tisler et al. (2009)—are nearly as sensitive as sensitive species of amphibians to imidacloprid. As with amphibians, none of the HQs for algae approach a level of concern.

4.4.3.4.2. Macrophytes

As discussed in Section 4.3.3.4.2, the only information on the toxicity of imidacloprid to aquatic macrophytes is an EC_{50} in a species of duckweed (Daam et al. 2013). While this single toxicity value may be viewed as tenuous basis for a risk characterization, the low HQs for imidacloprid in algae as well as supporting data from terrestrial plants (Section 4.4.2.5) support the HQs in aquatic macrophytes in suggesting that they are not likely to be directly impacted by imidacloprid.

5. REFERENCES

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

Dino	**References from the 2009 Forest Service risk assessment on dinotefuran (SERA 2009a).**
Emam	**References from the 2010 Forest Service risk assessment on emamectin benzoate (SERA 2010a).**
E-Docket-1	**Registration Review, EPA-HQ-OPP-2008-0844 at www.regulations.gov [n=6].**
Forg	**Abstracts of non-English articles [n=1].**
FS/USDA	**Personal communications from Forest Service and other personnel.**
MRID05	**Registrant studies summarized in 2005 Forest Service risk assessment [n=258].**
PrRv	**References recommended in peer review.**
RA2005	**Open literature studies from 2005 Forest Service risk assessment [n=162].**
Set00	**Preliminary scoping or background documents.**
Set01	**Open access papers from initial TOXLINE search [n=181].**
Set02	**Papers for NAL from initial TOXLINE search [n=154].**
Set03	**References recommended by Dave Bakke [n=7].**
Set04	**Update literature search on January 7, 2015 [n=39]**
Set05	**Sundry citations acquired during preparation of the initial draft [n=20+]**
Set06	**Final update literature search in August 2015.**
Sec	**Summary of citations from a secondary source [n=0].**
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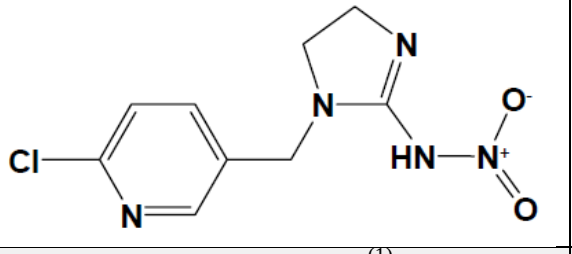
Table 1: Chemical and Physical Properties

Item	Value	Reference[1]
	Identifiers	
Common name:	Imidacloprid	Tomlin 2004
CAS Name	1-[(6-chloro-3-pyridinyl)methyl]-N-nitro-2-imidazolidinimine	Tomlin 2004
CAS No.	138261-41-3 (current) 105827-78-9 (former)	U.S. EPA/OPP/HED 2008a Tomlin 2004
Chemical Group	Chloronicotinyl nitroguanidine	NPIC 2010
Development Codes	BAY NTN 33893	Tomlin 2004
IUPAC Name	1-(6-chloro-3-pyridylmethyl)-N-nitroimidazolidin-2-ylideneamine	Tomlin 2004
Molecular formula	C_9-H_{10}-Cl-N_5-O_2	ChemIDplus 2014
Mechanistic group	4A. Neonicotinoid – Nicotinic acetylcholine receptor (nAChR) agonist	IRAC 2013
EPA PC Code	129099	U.S. EPA/OPP 2010a
Smiles Code	`c1nc(Cl)ccc1CN1\C(=N\[N+]([O-])=O)NCC1`	ChemIDplus 2014
Structure		U.S. EPA/OPP/EFED 2008a
	Chemical Properties(1)	
Density	1.54 g/cm^3	MRID 42734103, Yen and Wendt 1993
Form	Colorless, odorless crystals	Krohn and Hellpointner 2002
	Colorless crystals with weak odor	Tomlin 2004
	Light yellow powder (TGAI?)	Yen and Wendt 1993
Henry's Law Constant	4.0x10^{-12} atm-m^3/mol	U.S. EPA/OPP/EFED 2007, p. 59
Hydrolysis half-lives	Stable at pH 5 to 11	Tomlin 2004
	33.82 to 41.2 days at pH 7 (Confidor formulation) 37.6 days to 44.26 days (Gaucho formulation) `Note: reported halftimes are possibly a combination of hydrolysis and photolysis.`	Sakar et al. 1999
	Stable at pH 5 and 7. 355 days at pH 9.	Yoshida 1989, MRID 42055337
	1.5 % loss in three months at pH 7. 20 days at pH 10.8 and 2.85 days at pH 11.8	Zheng and Liu 1999
K_{ow}	3.7 [Log K_{ow} = 0.57] `Note: The Kow is incorrectly cited in Graebing and Chib (2004) as 0.57, the log Kow.`	Tomlin 2004; U.S. EPA/OPP/EFED 2007a; U.S. EPA/OPP/HED 2007a
	8.3 [Log K_{ow} = 0.92 from HPLC retention]	Nemeth-Konda et al. 2002
Molecular weight (g/mole)	255.664	ChemIDplus 2014
	255.6633	U.S. EPA/OPP/EFED 2007, p. 62
	255.66	U.S. EPA/OPP/EFED 2008a
Melting point	144 °C	Tomlin 2004

<table>
<tr><th>Item</th><th>Value</th><th>Reference[1]</th></tr>
<tr><td>Photolysis</td><td>Estimated environmental half-life of 4.2 hours at pH 7 based on experimental half-life of 57 minutes.</td><td>Anderson 1991, MRID 42256376</td></tr>
<tr><td></td><td>1.2 hours at 290 nm for 4 hours.</td><td>Moza et al. 1998</td></tr>
<tr><td>pK_a</td><td>11.2</td><td>Oliveira et al. 2000</td></tr>
<tr><td>Specific gravity</td><td>1.54</td><td>Tomlin 2004</td></tr>
<tr><td>Vapor pressure</td><td>$4x10^{-7}$ mPa (20 °C)
$9x10^{-7}$ mPa (25 °C)</td><td>Tomlin 2004</td></tr>
<tr><td></td><td>$1.5x10^{-9}$ mm Hg (20 °C)</td><td>Yen and Wendt 1993, MRID 42734103</td></tr>
<tr><td>Water solubility</td><td>610 mg/L</td><td>Krohn and Hellpointner 2002; Tomlin 2004</td></tr>
<tr><td></td><td>510 mg/L</td><td>Yen and Wendt 1993</td></tr>
<tr><td></td><td>695 mg/L</td><td>Riviere et al. 2014</td></tr>
<tr><td></td><td>580 mg/L</td><td>U.S. EPA/OPP/EFED 2008a, p. 18</td></tr>
<tr><td></td><td>Environmental Properties</td><td></td></tr>
<tr><td>Aquatic aerobic metabolism half-lives</td><td>1040 days (half-life)
2x the aerobic soil input value</td><td>U.S. EPA/OPP/EFED 2008a, p. 18</td></tr>
<tr><td></td><td><table><tr><th>Soil</th><th>% O.C.</th><th>Half-life (days)</th></tr><tr><td>Loamy sand</td><td>2.2</td><td>188</td></tr><tr><td>Silt loam</td><td>1.2</td><td>248</td></tr><tr><td>Sandy loam</td><td>1.3</td><td>341</td></tr><tr><td>Sandy loam</td><td>1.4</td><td>660</td></tr></table>EPA gives mean of 359 with 90% upper bound of 520 days. 80% confidence bound recalculated for current risk assessment using a critical value for t of 1.638 (3 d.f.) of 359 (187-531) days.</td><td>U.S. EPA/OPP/EFED 2008a, p. 50. Summary of several MRIDs.</td></tr>
<tr><td>Aquatic anaerobic half-lives</td><td>27 days, sediment</td><td>Fritz and Hellpointner 1991, MRID 42256378</td></tr>
<tr><td>Aqueous photolysis</td><td>39 days</td><td>U.S. EPA/OPP/EFED 2007, p. 18 based on MRIDs 42256376; 42256377</td></tr>
<tr><td></td><td>28 hours (pond mesocosms)</td><td>Colombo et al. 2013</td></tr>
<tr><td></td><td>43 minutes (a.i.)
126 minutes (Confidor formulation)
Experimental</td><td>Wamhoff and Schneider 1999</td></tr>
<tr><td>Bioconcentration in fish (BCF)</td><td>None expected due to low k_{ow}. Testing requirement waived.</td><td>U.S. EPA/OPP/EFED 2008a, p. 6</td></tr>
<tr><td></td><td>0.97 to 1.5 L/kg (zebra fish)</td><td>Ding et al. 2004</td></tr>
<tr><td></td><td>7.35 (Gammarus pulex)</td><td>Ashauer et al. 2010</td></tr>
<tr><td>Foliar/vegetation half-lives</td><td>2.35 to 2.95 days (grape leaves)</td><td>Arora et al. 2009</td></tr>
<tr><td></td><td>1.98 and 3.3 days (fruits)</td><td>Banerjee et al. 2012</td></tr>
<tr><td></td><td>2.45 to 2.67 days (tea leaves)</td><td>Hou et al. 2013</td></tr>
<tr><td></td><td>3-3.5 days (eggplant)
3.4-4.3 days (cabbage)
4.3-5 (mustard)</td><td>Mukherjee and Gopal 2000</td></tr>
<tr><td></td><td>9.8 days (turf)</td><td>Lin 1992a; MRID 42256307</td></tr>
<tr><td></td><td>9 days (turf)</td><td>Toll and Fischer 1993 MRID 42737101</td></tr>
<tr><td></td><td>1.17 days (turf)</td><td>Lin 1992d; MRID 42556101</td></tr>
</table>

<table>
<tr><th>Item</th><th>Value</th><th>Reference[1]</th></tr>
<tr><td>Foliar/vegetation half-lives (continued)</td><td>60 hours [2.5 days] (tomato fruit)
61.92 hours [≈2.6 days] (tomato leaves)</td><td>Romeh et al. 2009</td></tr>
<tr><td></td><td>4.5 days (turf)</td><td>Toll 1994, MRID 43472301</td></tr>
<tr><td></td><td>2.10–3.98 days (fresh flowers and buds)</td><td>Wu et al. 2012</td></tr>
<tr><td>Soil Sorption, K_{oc} /K_d</td><td>K_{oc}: 178 (132 to 256) ml/g [mean and range]
Working Note: 178 days used by EFED for modeling.</td><td>U.S. EPA/OPP/EFED 2008a, p. 6</td></tr>
<tr><td></td><td>Greater binding at lower concentrations: Koc of 77 at half of water solubility and 411 at field application rate.</td><td>Cox et al. 1997</td></tr>
<tr><td></td><td><table><tr><th>Soil</th><th>K_d</th><th>K_{oc}</th></tr><tr><td>Fine sand</td><td>0.52</td><td>179</td></tr><tr><td>Fine sandy loam</td><td>0.4</td><td>98</td></tr><tr><td>Sandy loam</td><td>3.4</td><td>487</td></tr><tr><td>Silt loam</td><td>5.7</td><td>228</td></tr><tr><td>Silty clay</td><td>3.1</td><td>231</td></tr><tr><td>Silty clay loam</td><td>11.4</td><td>288</td></tr><tr><td>Silty clay loam</td><td>4.8</td><td>454</td></tr></table>Soil sorption is concentration dependent (greater at lower concentrations) and OC is major factor in sorption.</td><td>Cox et al. 1998a,b</td></tr>
<tr><td></td><td>Salt water sediment: 0.28-0.62</td><td>Felsot and Ruppert 2002</td></tr>
<tr><td></td><td><table><tr><th>Soil</th><th>K_d</th></tr><tr><td>Low humus sandy soil</td><td>3.59</td></tr><tr><td>Silt</td><td>2.39</td></tr><tr><td>Silty clay</td><td>1.36</td></tr></table></td><td>Fritz 1988, MRID 42055338</td></tr>
<tr><td></td><td>Calcium Montmorillonite K_d 6.86
Humic acid K_d 247 at 1:200
Humic acid K_d 326 at 1:100
Binding to clay inhibited by humic acid (competitive)</td><td>Liu et al. 2002</td></tr>
<tr><td></td><td>Kd 1.43, Ko/c 209.6 in clay alluviation (0.68 % OC)</td><td>Nemeth-Konda et al. 2002</td></tr>
<tr><td></td><td>Kd 4.82 on Day 0 and 15.6 on Day 100 in sandy loam (1.8%OC)
Kd 2.24 on Day 0 and 8.6 on Day 100 in silt loam (0.9% OC)
Greater binding (decreased leaching) over time.</td><td>Oi 1999</td></tr>
<tr><td></td><td><table><tr><th>Soil</th><th>K_d</th><th>K_{oc}</th></tr><tr><td>Clay</td><td>11.3</td><td>779</td></tr><tr><td>Clay</td><td>5.18</td><td>186</td></tr><tr><td>Loamy sand</td><td>0.55</td><td>158</td></tr><tr><td>Sand</td><td>1.18</td><td>203</td></tr><tr><td>Sandy clay loam</td><td>10.8</td><td>620</td></tr><tr><td>Sandy loam</td><td>16.9</td><td>227</td></tr></table>Higher sorption with decreasing concentrations.</td><td>Oliveira et al. 2000</td></tr>
<tr><td></td><td><table><tr><th>Soil</th><th>K_d</th><th>K_{oc}</th></tr><tr><td>Sand</td><td>0.956</td><td>411</td></tr><tr><td>Loamy sand</td><td>1.02</td><td>292</td></tr><tr><td>Silt loam</td><td>4.18</td><td>277</td></tr><tr><td>Loam</td><td>3.45</td><td>296</td></tr></table></td><td>Williams et al. 1992a, MRID 42520801
Williams et al. 1992b, MRID 42520802</td></tr>
</table>

Item	Value	Reference[1]
Soil half-life, aerobic	520 days [90% upper bound confidence limit]	U.S. EPA/OPP/EFED 2007 based on MRIDs 45239301, 45239302, and 42073501
	22.5% degradation in 25 days No degradation in sterile soil.	Liu et al. 2011
	First-order rates of 0.008 to 0.004 day^{-1}. [i.e., half-lives of ≈173-346 days]	Cycon et al. 2013
Soil half-life, anaerobic	Halftime of > 1 year in anaerobic soil with no light.	Anderson et al. 1991 MRID 42073501
Soil dissipation half-lives	Half-times of 79 to 196 days. No mobility below 0 to 10 cm (3.9 inches). Bare loam to sandy loam, OM 1.36 to 3.82%.	Bachlechner 1992, MRID 42734101
	55-280 days (7 soils)	Dalkmann et al. 2012
	12 days (bare soil) 107 days (turf)	Rice et al. 1991a, MRID 42256379
	40.9 days (from groundnut fields)	Singh and Singh 2005a
	33 days	Toll and Fischer 1993 MRID 42737101
	7 days (bare soil) 61 days (turf)	Rice et al. 1991b, MRID 42256380
	53 days (tomatoes)	Rice et al. 1991c, MRID 42256381
	39 (27,8-44.9) days (Conifer formulation) 40.7 (35.8-46.3) days (Gaucho formulation)	Sarkar et al. 2001
	40.9 days	Singh and Singh 2005a
	3.55-5.17 days	Wu et al. 2012
Soil photolysis half-life	460 hours (19 days) in moist soil 830 hours (34.6 days) in dry soil [bi-phasic pattern]	Graebing and Chib 2004
	38.9 days	Yoshida 1990, MRID 42256377

[1] There a many sources of information on some standard values – e.g., molecular weight. In general, only two sources as cited for each value. More than two sources are cited only to highlight apparent discrepancies.

See Section 2.2.2 for discussion.

Table 2: Representative Formulations

Formulation, Supplier, EPA Registration Number, Label Date	Composition/ Characteristics	Application Information, Methods and Rates[2]
Marathon 60 WP OHP Inc. EPA Reg. No. 432-1361-59807 March 2007	Powder packets, 60% a.i., 20 g per packet Inert: Crystalline silica at 0.912%	Foliar Broadcast: one packet per 2900-3850 ft^2. [≈0.3 to 0.4 lb a.i./acre]. At least 2 gallons of water/1000 ft^2 [≈87 gallons/acre]. Soil Injection: one packet per 8 to 16 inches of trunk diameter [0.75 to 1.5 g a.i./inch]. …*sufficient water to inject an equal amount of solution in each hole*. Soil Drench: One packet per 3000 ft^2. [≈0.38 lb a.i./acre]
Marathon II OHP Inc. EPA Reg. No. 432-1369-59807 June 2008	Liquid, 21.4% a.i. (w/w), 2 lbs a.i./gallon [≈240 mg a.i./mL]. Inerts: None specified.	Foliar Spray: 13 to 17 mL formulation/1000 ft^2. At least 2 gallons water/1000 ft^2. [≈0.30 to 0.39 lb a.i./acre; At least ≈87 gallons/acre.] Soil Injection: 3-6 mL (0.1 to 0.2 fl. oz.) per inch DBH [0.72 to 1.4 g a.i./inch DBH]. *Mix required dosage in sufficient water to inject an equal amount of solution in each hole.* Soil Drench: 50 mL formulation/3000 ft^2. [≈0.38 lb a.i./acre]
Merit 2F Bayer Environ. Sci. EPA Reg. No. 432-1312 Sept. 2006	Liquid, 21.4% a.i. (w/w), 2 lbs a.i./gallon [≈119.8mg/mL]. Inerts: Glycerine/Glycerol (CAS No. 56-81-5).	Foliar Spray: 14 to 17 mL formulation/1000 ft^2. At least 2 gallons water/1000 ft^2. [≈0.32 to 0.39 lb a.i./acre; At least ≈87 gallons/acre.] Soil Injection: 3-6 mL (0.1 to 0.2 fl. oz.) per inch DBH [0.72 to 1.4 g a.i./inch DBH]. *Mix required dosage in sufficient water to inject an equal amount of solution in each hole.* Soil Drench: Rates identical to soil injection. 10 gallons of water/1000 ft^2 [435.6 gallons/acre]. Basal Bark Application [4]: NYS FIFRA 2(ee) recommendation dated 9/23/2013. Application rates of 3 to 6 mL per inch of trunk diameter (D.B.H.) for the control of HWA.
Merit 75 WP Bayer Environ. Sci. EPA Reg. No. 432-1314 April 2013	Wettable powder, 75% a.i. (w/w). 1.4 g formulation per teaspoon, 1.05 g a.i./teaspoon. Inerts: None specified.	Foliar Spray: 3-4 teaspoons formulation per 1000 ft^2. At least 2 gallons of water per 1000 ft^2. [0.3 to 0.4 lb a.i./acre. At least ≈87 gallons/acre.] Soil Injection: 0.7 to 1.4 teaspoons formulation per inch DBH. [0.735 to 1.47 g a.i./inch DBH]. *Mix required dosage in sufficient water to inject an equal amount of solution in each hole.* Soil Drench: Rates identical to soil injection. 10 gallons of water/1000 ft^2 [435.6 gallons/acre].
Imicide J.J. Mauget Co. EPA Reg. No. 7946-16 Dec. 2010	Liquid, 10% a.i. (w/w/), 110.7 mg a.i./mL Available in 2, 3, 4, 8, 12, and 16 mL capsules. Inerts: Tetrahydrofurfuryl alcohol (% N.S.)	Tree Injection: Volume of formulation used is highly variable and dependent on size of tree and severity of infestation. See product label for additional details. No dilution specified on label. Applied as is.
IMA-jet ArborJet EPA Reg No. 74578-1 Jan. 2011	Liquid, 5% a.i. (w/w) Specific gravity: 1.07 g/mL (53.5 mg a.i./mL) Inerts: None specified.	Tree Injection only. Adelgids and several other species: 2.0 – 8.0 mL per inch of cumulative trunk diameter at breast height. Asian longhorned beetle: 4.0 – 8.0 mL per inch of cumulative trunk diameter at breast height. Use restricted to USDA supervision. 8 mL/injection site (428 mg a.i. or ≈0.000944 lb /injection site). No dilution specified on label. Applied as is.

[1] The % inerts is taken from product labels. Additional information on inerts is taken from Material Safety Data Sheets.

[2] Unless otherwise noted, application rates are for trees for the control of adelgids. All formulations are specifically labelled for adelgid control.

[3] The 2013 EPA label for Merit 2.5 G specifies the control of "Aldegids". This appears to be a typographical error and should be "Adelgids".

[4] FIFRA 2(ee) labels are also available for Lesco Bandit 2F Insecticide [EPA Reg. No. 432-1312] and PrimeraOne Imidacloprid 2F Insecticide [EPA Reg. No. 83100-6-88975] for the control of HWA.

Table 3: Worker Exposure Rates Used in EPA Risk Assessments

Scenario	No clothing[1]	Single Layer, No gloves[1]	Single layer, Gloves[1]	Inhalation[1]
1. Dry flowable, open mixing and loading	1.1	0.066	0.066	0.00077
2. Granular, open mixing and loading	0.032	0.0084	0.0069	0.0017
3. All liquids, open mixing and loading	**3.1**	**2.9**	**0.023**	**0.0012**
4. Wettable powder, open mixing and loading	6.7	3.7	0.17	0.04342
5. Wettable powder, water soluble bags	0.039	0.021	0.0098	0.00024
6. All liquids, closed mixing and loading			0.0086	0.000083
7. Aerial-fixed wing, enclosed cockpit/liquid[2]	0.0050	0.0050	0.0022	0.000068
8. Aerial-fixed wing, enclosed cockpit/granular	0.0044	0.0017	0.0017	0.0013
9. Helicopter application, enclosed cockpit		0.0019	0.0019	0.0000018
10. Aerosol application	480	190	81	1.3
11. Airblast application, open cockpit	2.2	0.36	0.24	0.0045
12. Airblast application, enclosed cockpit			0.019	0.00045
13. Groundboom applications, open cab[2]	0.046	0.014	0.014	0.00074
14. Groundboom applications, enclosed cab	0.010	0.0050	0.0051	0.000043
15. Solid broadcast spreader, open cab, AG	0.039	0.0099		0.0012
16. Solid broadcast spreader, enclosed cab, AG	0.0021	0.0021	0.0020	0.00022
17. Granular bait dispersed by hand			71	0.47
18. Low pressure handwand	25	12	7.1	0.94
19. High pressure handwand	13	1.8	0.64	0.079
20. Backpack applications	680			0.33
21. Hand gun (lawn) sprayer			0.34	0.0014
22. Paintbrush applications	260	180		0.280
23. Airless sprayer (exterior house stain)	110	38		0.830
24. Right-of-way sprayer	1.9	1.3	0.39	0.0039
25. Flagger/Liquid	0.053	0.011	0.012	0.00035
26. Flagger/Granular	0.0050			0.00015
27. WP or liquid/open pour/airblast/open cab	26			0.021
28. WP or liquid/open pour/airblast/closed cab	0.88	0.37	0.057	0.0013
29. Liquid or DF /open pour/ground boom/closed cab	0.22	0.089	0.029	0.00035
30. Granule/open pour/belly grinder	210	10	9.3	0.062
31. Push type granular spreader		2.9		0.0063
32. Liquid/open pour/low pressure handwand	110	100	0.43	0.030
33. WP/open pour/low pressure handwand			8.6	1.1
34. Liquid/open pour/backpack			2.5	0.03
35. Liquid/open pour/high pressure handwand			2.5	0.12
36. Liquid/open pour/garden hose end sprayer	34			0.0095
37. Liquid/open pour/termiticide injection			**0.36**	**0.0022**

[1] All rates are in units of mg/lb a.i. handled.

[2] The entries shaded in bold are discussed in the risk assessment.

Source: Keigwin 1988

See Sections 3.2.2.1.1 (tree injection) and 3.2.2.1.2 (soil injection) for discussion.

Table 4: Bark Applications - Derivation of Worker Exposure Rates

Item	Value	Reference/Note	Row
Reference Chemical	Triclopyr-BEE	Section 3.2.2.1.3.	2
First-order dermal absorption rate coefficient for reference chemical (hour^{-1}) [ka_{Ref}]	0.0031	SERA 2014b	3
Occupational Exposure Rates for Reference Chemical			4
Central Estimate	0.001	SERA 2014b, Table 14	5
Lower 95% Prediction Bound	0.0001	SERA 2014b, Table 14	6
Upper 95% Prediction Bound	0.02	SERA 2014b, Table 14	7
Subject Chemical	Imidacloprid		8
First-order dermal absorption rate coefficient for subject chemical (hour^{-1}) [ka_P]	0.0015	Section 3.1.3.2.2	9
$ka_P \div ka_{Ref}$	0.48387097		10
Occupational Exposure Rates for Subject Chemical (Imidacloprid)			11
Central Estimate	0.00048387	SERA 2014b, Eq. 22	12
Lower 95% Prediction Bound	0.00004839	SERA 2014b, Eq. 22	13
Upper 95% Prediction Bound	0.00967742	SERA 2014b, Eq. 22	14

See Section 3.2.1. for discussion.

Documentation for Table: The above table implements the adjustment of worker exposure rates based dermal absorption rates. The table uses MS Word "fields" rather than macros.

- Determine the first-order dermal absorption rate coefficient for the chemical under review. See SERA 2014a, Section 3.1.3.2.2.
- Select the reference chemical. See SERA 2014b, Section 4.1.6.1.
- Fill in the information on the reference chemical in the upper section of the above table.
- Fill in the first-order dermal absorption rate coefficient for the chemical under review in the Value column of Row 9 in the above table.
- Update the estimated values for ration of the k_a values and the occupational exposure rates for the chemical under review – i.e., the green shaded cells in the above table. The simplest way to update these fields is to select each of the 4 green shaded cells (one at a time and in order), press the right mouse button, and select 'Update field'.

Table 5: Backpack Applications - Derivation of Worker Exposure Rates

Item	Value	Reference/Note	Row
Reference Chemical	Triclopyr-BEE	Section 3.2.2.1.3.	2
First-order dermal absorption rate coefficient for reference chemical ($hour^{-1}$) [ka_{Ref}]	0.0031	SERA 2014b	3
Occupational Exposure Rates for Reference Chemical			4
Central Estimate	0.01	SERA 2014b, Table 14	5
Lower 95% Prediction Bound	0.002	SERA 2014b, Table 14	6
Upper 95% Prediction Bound	0.06	SERA 2014b, Table 14	7
Subject Chemical	Imidacloprid		8
First-order dermal absorption rate coefficient for subject chemical ($hour^{-1}$) [ka_P]	0.0015	Section 3.1.3.2.2	9
$ka_P \div ka_{Ref}$	0.48387097		10
Occupational Exposure Rates for Subject Chemical (Imidacloprid)			11
Central Estimate	0.00483871	SERA 2014b, Eq. 22	12
Lower 95% Prediction Bound	0.00096774	SERA 2014b, Eq. 22	13
Upper 95% Prediction Bound	0.02903226	SERA 2014b, Eq. 22	14

See Section 3.2.1. for discussion.

Documentation for Table: The above table implements the adjustment of worker exposure rates based dermal absorption rates. The table uses MS Word "fields" rather than macros.

- Determine the first-order dermal absorption rate coefficient for the chemical under review. See SERA 2014a, Section 3.1.3.2.2.
- Select the reference chemical. See SERA 2014b, Section 4.1.6.1.
- Fill in the information on the reference chemical in the upper section of the above table.
- Fill in the first-order dermal absorption rate coefficient for the chemical under review in the Value column of Row 9 in the above table.
- Update the estimated values for ration of the k_a values and the occupational exposure rates for the chemical under review – i.e., the green shaded cells in the above table. The simplest way to update these fields is to select each of the 4 green shaded cells (one at a time and in order), press the right mouse button, and select 'Update field'.

Table 6: Summary of Exposure Scenarios for the General Public

	Attachment:	1	2	3	4	
Scenario	**Person**	**Tree Injection**	**Soil Injection**	**Bark**	**Foliar**	**Worksheet**
Accidental Acute						
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[1]	■	■	■	■	D08b
Non-Accidental Acute						
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[1]		■	■	■	D09d
Chronic/Longer Term						
Contaminated Fruit	Female			■	■	D04a
Contaminated Vegetation	Female			■	■	D04b
Water consumption	Male		■	■	■	D07
Fish consumption	Male		■	■	■	D09a
Fish consumption	SP[1]		■	■	■	D09b

[1] Subsistence populations

Table 7: 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.

Table 8: Input Parameters for Fields and Waterbodies Used in Gleams-Driver Modeling

Field Characteristics	Description	Pond Characteristics	Description
Type of site and surface (FOREST)	Mixed forest	Surface area	1 acre
Treated and total field areas	10 acres	Drainage area:	10 acres
Field width	660 feet	Initial Depth	2 meters
Slope	0.1 (loam and clay) 0.05 (sand)	Minimum Depth	1 meter
Depth of root zone	36 inches	Maximum Depth	3 meters
Cover factor	0.15	Relative Sediment Depth	0.01
Type of clay	Mixed		
Surface cover	No surface depressions		

Stream Characteristics	Value
Width	2 meters
Flow Velocity	6900 meters/day
Initial Flow Rate	710,000 liters/day

Application, Field, and Soil Specific Factors [1]	Code[3]	Clay	Loam	Sand
Percent clay (w/w/):	CLAY	50%	20%	5%
Percent silt (w/w/):	SILT	30%	35%	5%
Percent sand (w/w/):	N/A	20%	45%	90%
Percent Organic Matter:	OM	3.7%	2.9%	1.2%
Bulk density of soil (g/cc):	BD	1.4	1.6	1.6
Soil porosity (cc/cc):	POR	0.47	0.4	0.4
Soil erodibility factor (tons/acre):	KSOIL	0.24	0.3	0.02
SCS Runoff Curve Number [2]:	CN2	83	70	59
Evaporation constant (mm/d):	CONA	3.5	4.5	3.3
Saturated conductivity below root zone (in/hr):	RC	0.087	0.212	0.387
Saturated conductivity in root zone (in/hr)	SATK	0.087	0.212	0.387
Wilting point (cm/cm):	BR15	0.28	0.11	0.03
Field capacity (cm/cm):	FC	0.39	0.26	0.16

[1] The qualitative descriptors are those used in the QuickRun window of Gleams-Driver. Detailed input values for the soil types are given in the sub-table below which is adapted from SERA (2007b, Tables 2 and 3). All fields are run for about 6 months before the pesticide is applied in early summer.

[2] From Knisel and Davis (Table H-4), *Clay*: Group D, Dirt, upper bound; *Loam*: Group C, woods, fair condition, central estimate; *Sand*: Group A, meadow, good condition, central estimate.

[3]Codes used in documentation for GLEAMS (Knisel and Davis 2000) and Gleams-Driver (SERA 2007a)

Table 9: Chemical parameters used in Gleams-Driver modeling

Parameter	Values	Note/Reference
Halftimes (days)		
Aquatic Sediment	27	Fritz and Hellpointner 1991, MRID 42256378
Foliar	2 to 10	Note 1
Soil	359 (188-660)	Note 2
Water	718 (376-1320)	Note 3
Soil $K_{o/c}$, mL/g	178 (132 to 256)	Note 4
Sediment K_d, mL/g	4.8 (0.4-16.9)	Note 5
Water Solubility, mg/L	580	U.S. EPA/OPP/EFED 2008a, p. 18
Foliar wash-off fraction	0.5	Default assumption. A much lower value (≈0.06) reported by Thuyet et al. (2012) for turf.
Fraction applied to foliage	0.5/0.01/0	Note 6
Depth of Soil Incorporation (cm)	1/1/15	Note 7
Application Date	June 1	Note 8

Notes

Number	Text
1	Range of values from MRID and open literature studies. See Table 1.
2	Average and range of values from U.S. EPA/OPP/EFED 2007a. See Table 1. Modelled with triangular distribution. This is modestly more conservative than the upper 90% confidence limit of 520 days used by U.S. EPA/OPP/EFED 2007a (p. 18) in PRZM/EXAMS modelling.
3	No data. Used 2x soil values per U.S. EPA/OPP/EFED 2007a (p. 18) in PRZM/EXAMS modelling.
4	Mean and range from U.S. EPA/OPP/EFED 2008a, p. 6. Central estimate consistent with U.S. EPA/OPP/EFED 2007a, p.18 inputs for PRZM/EXAMS modeling.
5	Mean and range from Cox et al. 1998a,b; Fritz 1988; Oliverira et al. 2000; and Williams et al. 1992a,b. See Table 1.
6	For foliar broadcast applications, a standard value of 0.5 used for foliar as a default. For soil surface treatments, foliar deposition will be minimal. For soil injection, no foliar deposition will occur.
7	For liquid broadcast or soil surface treatments, an incorporation depth of 1 cm is used (Knisel and Davis 2000). For soil injection or drench, a depth of 15 cm (about 6 inches) is used.
8	Taken from Spring application timing in Cowles et al. 2006 for the control of HWA. Application timing may be highly variable – e.g., September in Eisenback et al. 2014.

Table 10: Summary of Modeled Concentrations in Surface Water

Scenario/Source	Peak Concentrations (ppb or µg/L per lb/acre)	Long-Term Average Concentrations (ppb or µg/L per lb/acre)
Direct Spray and Spray Drift (coarse droplets)		
Pond, Direct Spray (Section 3.2.3.4.2) [1]	112	N/A
Pond, drift at 25 feet (Section 3.2.3.4.2) [1]	0.933	N/A
Stream, Direct Spray (Section 3.2.3.4.2) [1]	91.3	N/A
Stream, drift at 25 feet (Section 3.2.3.4.2) [1]	0.76	N/A
Soil Injection (Appendix 8), clay and loam		
Pond, Section 3.2.3.4.4	13.1 (0.0012-169) [7]	8.4 (0.0005-48) [7]
Stream, Section 3.2.3.4.4	2.4 (0.0023-23.5) [7]	0.3 ($1.4x10^{-5}$-3.7) [7]
Directed Foliar Application (Appendix 9) , clay and loam		
Pond, Section 3.2.3.4.4	15.7 (0.002-95) [7]	6.9 (0.00016-81) [7]
Stream, Section 3.2.3.4.4	13.3 (0.007-78) [7]	0.2 (0.000021-1.93) [7]
Directed Foliar Application (Appendix 9), sandy soil		
Pond, Section 3.2.3.4.4	59.3 ($7x10^{-6}$-264)	26.2 ($2.3x10^{-6}$-122)
Stream, Section 3.2.3.4.4	9.63 ($1.4x10^{-5}$-37)	1.26 ($7.0x10^{-8}$ - 5.8)
EPA Modeling		
PRZM/EXAMS (peanuts) [2]	21.5	15.6
PRZM/EXAMS (soybeans) [3]	27.1	20.9
GENEEC (blackberries) [4]	45.9	43.6
FIRST (tree nuts) [5]	71.8	30.6
FIRST (citrus) [6]	72.0	34.4
SCIGROW (Ground water) [6]	4.18	

[1] Applies only to broadcast. The estimate for bark applications is lower by a factor of 10.
[2] U.S. EPA/OPP/EFED (2007a), p. 22. Modeling based on a cumulative application rate of 0.38 lb a.i./acre over a 52 day period.
[3] U.S. EPA/OPP/EFED (2007a), p. 22. Modeling based on a cumulative application rate of 0.14 lb a.i./acre over a 52 day period.
[4] U.S. EPA/OPP/EFED (2007a), p. 23. Modeling based on a single application at 0.5 lb a.i./acre.
[5] U.S. EPA/OPP/HED (2007a), p. 45, Table 5.1.8. Modeling based on application rate of 0.5 lb a.i./acre.
[6] U.S. EPA/OPP/HED (2010a), p. 24, Table 5.2.1. Modeling based on maximum application rate of 0.5 lb a.i./acre.
[7] For composites of clay and loam soils, the central estimate is the approximate average of the means for the runs with clay and loam soils. The lower bound is the lowest of the nonzero 25th percentiles for clay and loam soil. The upper bound is the highest of the maximum values for clay and loam soils.

See Section 3.2.3.4 for discussion.

Table 11: Concentrations in surface water used in this risk assessment

Soil Injection, clay or loam	**Peak WCR[1]**	**Longer-term WCR[1]**
Central	0.013	0.0084
Lower	0.0000012	0.0000005
Upper	0.17	0.048
Bark Application, clay or loam [2]	**Peak WCR[1]**	**Longer-term WCR[1]**
Central	0.0016	0.00069
Lower	0.0000002	0.000000016
Upper	0.0095	0.0081
Foliar Application, clay or loam	**Peak WCR[1]**	**Longer-term WCR[1]**
Central	0.016	0.0069
Lower	0.000002	0.00000016
Upper	0.095	0.081
Any applications to sandy soils	**Peak WCR[1]**	**Longer-term WCR[1]**
Central	0.059	0.026
Lower	0.000000007	0.0000000023
Upper	0.264	0.122

[1] WCR (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.

[2] Rates for bark applications are taken as 10% of the rates for foliar application.

See Section 3.2.3.4.6 for discussion

Table 12: Estimated residues in food items per lb a.i. applied

Standard Values [1]

Food Item	Central [2]	Lower [2]	Upper [2,3]
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

Note: Residue rates for bark applications are taken as 1-10th the rates give above. See Section 3.2.3.7 for discussion.

Experimental Values for Imidacloprid

Vegetation	Application Rate (lb/acre)	Initial Residue (mg a.i./kg vegetation)	Residue Rate	Reference
Grape Leaves	0.36	9.44	26.22	Arora et al. 2009 [4]
Grape Leaves	0.36	9.84	27.33	Arora et al. 2009 [4]
Grape Leaves	0.71	18.49	26.04	Arora et al. 2009 [4]
Grape Leaves	0.71	14.85	20.92	Arora et al. 2009 [4]
Potato foliage	0.5	2	4.00	Lin 1992d
Potato foliage	0.5	4	8.00	Lin 1992d
Tea shoots, fresh	0.027	3.47	128.52	Hou et al. 2013 [6]
Tea shoots, fresh	0.053	7.11	134.15	Hou et al. 2013 [6]
Tomato	0.075	1.2	16.00	Banerjee et al. 2012[5]
Turf	0.5	40	80.00	Lin 1992a
Turf	0.5	45	90.00	Lin 1992a
Turf	0.5	42	84.00	Toll 1994

[1] Concentration given in units of ppm (mg agent/kg food) per lb a.i./acre.
[2] U.S. EPA/EFED 2001, p. 44 as adopted from Fletcher et al. (1997).
[3] Central values × (Central Value ÷ Upper Value).
[4] Application rates specified as 400 g/ha or 0.4 kg/ha (lower rate) and 800 kg/ha or 0.8 kg/ha (higher rate). 1 kg/ha ≈ 0.8922 lb/acre.
[5] Application rate specified as 84 g/ha or 0.084 kg/ha [0.084 kg/ha x 0.8922 lb/acre ≈ 0.075 lb/acre. Initial residues read from Figure 1 of publication.
[6] Application rates specified as 30 g/ha and 60 g/ha. Converted as above to lb/acre.

See Section 3.2.3.7 for discussion.

Table 13: Summary of HQs for Workers

Tree Injection

		Central	Lower	Upper
Accidental/Incidental				
Contaminated Gloves, 1 min.	Worker	1E-02	5E-03	2E-02
Contaminated Gloves, 1 hour	Worker	0.6	0.3	**1.1**
Spill on Hands, 1 hour	Worker	5E-02	2E-02	0.1
Spill on lower legs, 1 hour	Worker	0.1	6E-02	0.3
General Exposures				
	Acute	2E-05	8E-06	6E-05
	Chronic	5E-05	2E-05	2E-04

Soil Injection

Accidental/Incidental				
Contaminated Gloves, 1 min.	Worker	2E-03	2E-04	2E-02
Contaminated Gloves, 1 hour	Worker	0.1	1E-02	0.9
Spill on Hands, 1 hour	Worker	1E-02	1E-03	0.1
Spill on lower legs, 1 hour	Worker	3E-02	3E-03	0.3
General Exposures				
	Acute	6E-04	2E-04	2E-03
	Chronic	2E-03	4E-04	4E-03

Bark Application

Accidental/Incidental				
Contaminated Gloves, 1 min.	Worker	2E-03	2E-04	2E-02
Contaminated Gloves, 1 hour	Worker	0.1	1E-02	0.9
Spill on Hands, 1 hour	Worker	1E-02	1E-03	0.1
Spill on lower legs, 1 hour	Worker	3E-02	3E-03	0.3
General Exposures				
	Acute	6E-03	2E-04	0.2
	Chronic	2E-02	5E-04	0.6

Directed Foliar Applications

Accidental/Incidental				
Contaminated Gloves, 1 min.	Worker	4E-05	1E-05	2E-04
Contaminated Gloves, 1 hour	Worker	3E-03	7E-04	1E-02
Spill on Hands, 1 hour	Worker	2E-04	6E-05	1E-03
Spill on lower legs, 1 hour	Worker	6E-04	1E-04	3E-03
General Exposures				
	Acute	6E-02	4E-03	0.7
	Chronic	0.2	1E-02	**1.7**

See Section 3.4.2 for discussion.
Source: Worksheets E02 of Attachments 1-4.

Table 14: Summary of Selected HQs for the General Public

Tree Injection
No HQs of concern.

Soil Injection -- Accidental

Scenario	Receptor	Central	Lower	Upper
Water consumption (spill)	Child	1E-01	2E-03	**1.2**
Fish consumption (spill)	Subsistence Populations	5E-02	2E-03	0.1

Bark Application – Accidental

Direct Spray of Child, whole body	Child	0.5	4E-02	**4**
Direct Spray of Woman, feet and lower legs	Adult Female	5E-02	4E-03	0.4
Water consumption (spill)	Child	1E-01	2E-03	**1.2**

Foliar Application – Acute

Contaminated Fruit	Adult Female	3E-02	2E-02	0.5
Contaminated Vegetation	Adult Female	0.5	3E-02	**4**

NOTE: Includes only HQs that approach of exceed a level of concern.

See Section 3.4.3 for discussion.
Source: Worksheets E04 of Attachments 1-4.

Table 15: Comparative Toxicity of Imidacloprid and Its Metabolites

Study	Decourtye et al. 2003	Nauen et al 2001	Suchail et al. 2001	Nauen et al. 1999
Species	*Apis mellifera*	*Apis mellifera*	*Apis mellifera*	*Bemisia tabaci*
Endpoint	Oral 48-h LD_{50}, ng/bee	Oral 48-h LD_{50}, ng/bee	Oral 48-h LD_{50}, ng/bee	Oral 48-LC_{50} mg/L
Imidacloprid	30.6	41	57	0.24
Olefin		<36	28	0.025
4-hydroxy				0.15
5-hydroxy	153.5	>49	258	2.4
di-hydroxy			>1000	>60
Urea		>99,500		>60
6-chloronicotinic acid		121,500		
Relative Toxicity[1]				
Olefin		**>1.14**	**2.04**	**9.6**
4-hydroxy				**1.6**
5-hydroxy	0.199348534	<0.83	0.22	0.1
di-hydroxy			<0.057	<0.004
Urea		<0.00041		<0.004
6-chloronicotinic acid		<0.00034		

[1] Toxicity value for imidacloprid ÷ corresponding value for metabolite. Values greater than 1 indicated that the metabolite is more toxic than imidacloprid.

Table 16: Topical LD_{50} Values in Terrestrial Invertebrates

Species	Hrs	Type[1]	LD_{50} (ng)	BW[2] (mg)	LD_{50} (µg/g bw)	Reference [Note]
Bees [Hymenoptera]						
Apis mellifera	48	TGAI	78	116	0.672	Cole 1990
Apis mellifera	24	TGAI	17.9	116	0.154	Iwasa et al. 2004
Apis mellifera	48	TGAI	21.21	116	0.183	Di Prisco et al. 2013
Apis mellifera	48	TGAI	62.4	116	0.538	Nauen et al. 2001
Apis mellifera	48	Provado 1.6F	200	116	1.724	Biddinger et al. 2013
Apis mellifera	48	SC200	59.7	116	0.515	Schmuck et al. 2001
Apis mellifera	48	WS70	242.6	116	2.091	Schmuck et al. 2001
Bombus impatiens	72	NOS	20	150	0.133	Marletto et al. 2003
Osmia cornifrons	48	Provado 1.6F	3800	160	23.75	Biddinger et al. 2013
Nannotrigona perilampoides	24	NOS	1.1	8.2	0.134	Valdovinos-Nunez et al. 2009
Diptera						
Aedes aegypti	24	NOS	2.05	2.91	0.705	Riaz et al. 2013[3]
Aedes aegypti	24	NOS	2.5	2.91	0.859	Riaz et al. 2013[3]
Siphonaptera						
Ctenocephalides felis	24	TGAI	0.02	0.34	0.059	Rust et al. 2014[3]
Ctenocephalides felis	24	TGAI	0.19	0.34	0.559	Rust et al. 2014[3]
Coleoptera						
Laricobius nigrinus	144	TGAI	1.8	0.75	2.4	Eisenback et al. 2010
Sasajiscymnus tsugae	144	TGAI	0.71	0.39	1.82	Eisenback et al. 2010
Hippodamia convergens	48	TGAI	NR	NR	0.7	Kaakeh et al. 1996
Hemiptera						
Myzus persicae	N.S.	TGAI	0.28	0.48	0.58	Puinean et al. 2010 [4]
Myzus persicae	N.S	TGAI	7.775	0.48	16.2	Puinean et al. 2010 [4]
Blattodea						
Blattella germanica	24	TGAI	266	78	3.41	Sims and Appel 2007

[1] TGAI: Technical grade; WG70 and SC200 formulations.

[2] *Apis mellifera* from Winston (1987, p.54), *Bombus impatiens* from Franklin et al. (2004), *Aedes aegypti* from Christophers (1960, p. 393), *Ctenocephalides felis* from Khokhlova et al.(2002), *Myzus persicae* from Cabral et al. (2006), Blattella germanica from Grigolo et al. (1991, p. 191). *Osmia cornifrons* approximated from weights of from *Osmia cornuta* in Bosh and Vicens (2002). All other body weights from the toxicity studies.

[3] Only the most sensitive and tolerant populations included.

[4] Data on only two populations are given.

See Appendix 3 for study details.
See Figure 4 for illustration.
See Section 4.1.2.4.2.1.1 for discussion.

Table 17: LC_{50} Values in Terrestrial Invertebrates for Spray/Immersion

Species (Family)	Duration (hours)	Exposure[1]	Agent	LC_{50} (mg/L)	Reference [Note]
Bees					
Apis mellifera (Apidae)	24	Spray	TGAI	22	Bailey et al. 2005
Bombus impatiens (Apidae)	48	Spray	TGAI	32.2	Scott-Dupree et al. 2009
Megachile rotundata (Megachilidae)	48	Spray	TGAI	1.7	Scott-Dupree et al. 2009
Osmia lignaria (Megachilidae)	48	Spray	TGAI	0.7	Scott-Dupree et al. 2009
Other Hymenoptera					
Diadegma insulare (wasp)	24	Spray	Provado 2F	2	Hill and Fosler 2000 [2]
Trichogramma cacoeciae (wasp)	24	Spray	Confidor 200	1.25	Saber 2011
Hemiptera					
Hyaliodes vitripennis, nymphs	24	Spray	Admire	2.3	Bostanian et al. 2001
Hyaliodes vitripennis , adults	24	Spray	Admire	1.1	Bostanian et al. 2001
Nilaparvata lugens	48	Spray	NOS	40	Bullangpoti et al. 2007
Agonoscena pistaciae	24	Dip 2s	Confidor	138.21	Amirzade et al. 2014
Aphis pomi	72	Dip 2s	Admire	0.38	Lowery et al. 2005
Aphis pomi	72	Dip 2s	Admire	1.46	Lowery et al. 2005
Aphis spiraecola	72	Dip 2s	Admire	6.9	Lowery et al. 2005
Aphis spiraecola	72	Dip 2s	Admire	3.08	Lowery et al. 2005
Arachnids					
Pardosa pseudoannulata	24	Dip 20s	TGAI	40.44	Chen et al. 2012

[1] For immersion or dip assays, the duration of the immersion or dip in seconds is specified by a number followed by an "s" after the word "Dip".

[2] Based on the application volume given in Hill and Fosler (2000), the LC_{50} corresponds to an application rate of about 0.00048 kg a.i./ha – i.e., 2 mg/L x 240 liter/ha = 0.00048 kg/ha ≈ 0.000428 lb/acre.

See Appendix 3 for study details.
See Figure 5 for illustration.
See Section 4.1.2.4.2.1.2 for discussion.

Table 18: Oral LD_{50} values in bees

Species	Agent	Oral LD_{50} (ng/bee)[1]	Oral LD_{50} (µg/g bw)[2]	Reference
Apis mellifera	TGAI	3.7	0.032	Cole 1990
Apis mellifera	TGAI	41	0.35	Nauen et al 2001
Apis mellifera	TGAI	57	0.49	Suchail et al. 2001
Apis mellifera	TGAI	30.6	0.26	Decourtye et al. 2003
Apis mellifera [Africanized]	TGAI	80.9	0.70	de Almeida Rossi et al. 2013
Apis mellifera	WS70	11.6	0.10	Schmuck et al. 2001
Apis mellifera	SC200	21.2	0.18	Schmuck et al. 2001
Bombus impatiens	Formulation (NOS)	20	0.13	Marletto et al. 2003
Melipona quadrifasciata	Brazilian Formulation (700 g a.i./L)	23.54	2.9 [3]	Tom et al. 2015

[1] All LD_{50} values are based on 48-hour observations except for Bombus impatiens, which is based on 72 hour observations.
[2] See Table 16 for body weights used to estimate doses in units of µg/g bw.
[3] Based on an estimated body weight of 8 mg from Contrera et al. (2006).

See Appendix 3 for study details.
See Section 4.1.2.4.2.1.3 for discussion.

Table 19: Matched Leaf Uptake Bioassays in Hymenoptera and Hemiptera

Organism	Description [Order: Family, common name]	LC_{50}, g a.i./L (95% Confidence Interval)
Aphytis melinus	Hymenoptera: Aphelinidae, parasite of the California Red Scale	0.246 (0.089-0.465)
Encarsia formosa	Hymenoptera: Aphelinidae, parasitoid of whitefly	0.980 (0.267-1.53)
Eretmocerus eremicus	Hymenoptera: Aphelinidae, parasitic wasp of whitefly	1.93 (1.33-2.67)
Gonatocerus ashmeadi	Hymenoptera: Mymaridae, fairyfly	2.63 (1.56-4.16)
Orius insidiosus	Hemiptera: Anthocoridae, insidious flower bug	2.78 (1.42-4.26)
Geocoris punctipes	Hemiptera: Geocoridae, big eyed bug`	5.18 (2.33-10.02)

Data from Prabhaker et al. (2011)
See Appendix 4 for study details.
See Section 4.1.2.4.2.1.3 for discussion.

Table 20: Sublethal Studies in Bees Based on Concentrations of Imidacloprid

Species	Endpoint/Duration	NOAEC[1] (ppb)	LOAEC[1] (ppb)	References
Honeybees, field	Single hive exposure, multiple parameters	0.00355		Belien et al. 2009
B. terrestris	14 days, brood production	0.1	1	Laycock et al. 2012 [4]
B. terrestris audax	14 days, brood production	0.15	1.44	Laycock and Cresswell 2013 EC_{10} and EC_{50}
Honeybees, field	15-days, increase expression of P450 genes		2	Derecka et al. 2013
B. terrestris	11 weeks, foraging and colony performance	2	3.7	Mommaerts et al. 2010
Honeybees, field	32 (Faucon) or 81 (Dively) days , hive survival	5		Faucon et al. 2005; Dively et al. 2015
B. terrestris	2 weeks[1], colony weights and queen production [3]		6	Whitehorn et al. 2012
B. terrestris	2 weeks, nectar foraging[3]	6		Feltham et al. 2014
B. terrestris	2 weeks, pollen foraging[3]		6	Feltham et al. 2014
Honeybees, mesocosm	4-days, foraging activity		6	Colin et al. 2004
B. terrestris	4 weeks, pollen foraging and worker production		10	Gill et al. 2012
B. terrestris	11 weeks, colony health	10	20	Scholer and Krischik 2014
Honeybees	12 to 13 weeks, hive death [2]		≥20	Lu et al. 2012; Dively et al. 2015
Honeybees, field	39-days, colony health	20		Schmuck et al. 2001[4]
B. terrestris	11 weeks, reproduction	20	37	Mommaerts et al. 2010 EC_{50} rather than LOAEL
Honeybees	2-days, foraging behavior	5	55	Teeters et al. 2012
Honeybees, mesocosm	10 days, foraging activity		24	Decourtye et al. 2004
Honeybees	7-days, T-tube maze behavior		48	Han et al. 2010b ng/g pollen
Honeybees, mesocosm	4-days, foraging		48	Ramirez-Romero et al. 2005
Honeybees, mesocosm	24-hours, foraging		100	Bortolotti et al 2003
Honeybees, field	Single feeding, foraging and behavior	50	100	Yang et al. 2008
Apis mellifera carnica	3-days, foraging behavior	11.5	115	Schneider et al. 2012[4] Concentration in nectar
Honeybees	13 weeks, hive death [2, 4]		135	Lu et al. 2014
Honeybees, field	Retrospective on depopulated hives.		377	Pareja et al. 2011 ppb in honeycombs

[1] NOAEC and LOAEC values given in ppb sucrose unless otherwise specified in last column.
[2] Colony death noted only in post-exposure overwintering period.
[3]Exposures included 6 ppb in pollen and 0.7 ppb in nectar.
[4] Studies also measured ingested dose in units of ng/insect. See Table 21.
Note: All studies on *Bombus* species are mesocosm or field studies unless otherwise specified.

See Appendix 3 for details of studies.
See Section 4.1.2.4.2.2 for discussion.

Table 21: Sublethal Studies in Invertebrates Based on Doses of Imidacloprid

Species	Endpoint/Duration	NOAEC[1] (ng/organism /day)	LOAEC[1] (ng/organism /day)	References
Honeybees, field	84-Days exposure, hive overwintering[3, 4]	0.011		Dively et al. 2015
Honeybees, field	84-Days exposure, hive overwintering[3, 4]		0.043	Dively et al. 2015
Honeybees, field	10-day, AChE increase, hyperactivity		0.08	Boily et al. 2013
Honeybees	30-40 day survival		0.08-0.16	Dechaume Moncharmont et al 2003
Honeybees, field	84-Days exposure, hive overwintering[3, 4]		0.2	Dively et al. 2015
Honeybees, field	10-day, lethality, LD_{50}		0.227	Boily et al. 2013
Hemiptera: Miridae, *Apolygus lucorum*	Short-term **topical**, reproductive effects		0.38	Tan et al. 2012
Apis ceranae	Short-term (hours), feeding inhibition	0.27	0.39	Tan et al. 2014
Honeybees	1-day, neurotoxicity		0.4	Williamson et al. 2014
B. terrestris, mesocosm	14 days, brood production [2, 4]	< 0.1	≈ 0.7	Laycock et al. 2012
Honeybees, field	91 days, hive overwintering [3, 4]		0.74	Lu et al. 2014
Honeybees	4-days, proboscis extension response		1.3	Williamson and Wright 2013
Apis mellifera carnica	3-days, foraging behavior[4]	0.14	1.4	Schneider et al. 2012
Honeybees, field	39-days, colony health[4]	0.52		Schmuck et al. 2001
Honeybees	11-day survival	0.97		Decourtye et al. 2003
Honeybees, field	Single feeding, foraging and behavior	≈0.9	≈1.82	Yang et al. 2008
Honeybees	10-day brain pathology	1.6	8.09	de Almeida Rossi et al. 2013

[1] NOAEC and LOAEC values in units of ng/organism.
[2] Doses read graphically from Figure 2a of Laycock et al. 2012. The estimated LOAEL can be read reasonably well but the NOAEL is unclear.
[3] Exposures in spring/summer. No apparent effects until overwintering.
[4] Studies also express exposures as concentrations and are also summarized in Table 20.

See Appendix 3 for details of studies.
See Section 4.1.2.4.2.2 for discussion.

Table 22: Details of Acute Toxicity Values for Aquatic Invertebrates

Group/Species	Hr	LC_{50} (mg/L)	EC_{50} (mg/L)	Reference	Agent
Cladocera					
Daphnia magna	48		97.0	Loureiro et al. 2010	TGAI
Daphnia magna	48		11.822	Sanchez-Bayo & Goka 2006a	TGAI
Daphnia magna	48		10.44	Song et al 1997	TGAI
Daphnia magna	48		56.6	Tisler et al. 2009	TGAI
Daphnia magna[1]	48		85.0	Young & Hicks 1990	TGAI
Daphnia magna	48		84.0	Daam et al. 2013	Form.
Daphnia magna	48		64.6	Kungolos et al. 2009	Form.
Daphnia magna	48		96.5	Pestana et al. 2010	Form.
Daphnia magna	48		90.68	Pestana et al. 2010	Form.
Daphnia magna	48		30.0	Tisler et al. 2009	Form.
Daphnia magna	48		43.265	Hayasaka et al. 2012b	Form.
Daphnia pulex	48		36.872	Hayasaka et al. 2012b	Form.
Ceriodaphnia dubia	48	0.00207		Chen et al. 2010[6]	Form.
Ceriodaphnia dubia	48		0.57162	Hayasaka et al. 2012b	Form.
Ceriodaphnia reticulata	48		5.55	Hayasaka et al. 2012b	Form.
Moina macrocopa	48		45.27	Hayasaka et al. 2012b	Form.
Chydorus sphaericus[3]	48		2.209	Sanchez-Bayo & Goka 2006a	TGAI
Amphipoda					
Hyalella azteca [1]	96	0.526	0.055	England & Bucksath 1991	TGAI
Gammarus pulex	96		0.00534[5]	Agatz et al. 2014	TGAI
Gammarus pulex	96		0.131	Ashauer et al. 2011	TGAI
Gammarus pulex	96	0.27		Beketov & Liess 2008	TGAI
Gammarus roeseli	96		0.0142	Bottger et al. 2012 (6 mm)	TGAI
Gammarus roeseli	96		0.0019	Bottger et al. 2012 (9 mm)	TGAI
Gammarus roeseli	96		0.028	Bottger et al. 2012 (11 mm)	TGAI
Gammarus roeseli	96		0.125	Bottger et al. 2012 (6 mm, 17°C)	TGAI
Gammarus fossarum	48	0.8	0.07[2]	Lukancic et al. 2010a,b	Form.
Gammarus pulex	96	0.316	0.0183	Roessink et al. 2013	Form.
Midges (Chironomus)					
Chironomus tentans [1]	96	0.069[4]		Gagliano 1991	TGAI
Chironomus tentans	96		0.00575	Stoughton et al. 2008	TGAI
Chironomus dilutus	96	0.00265		Leblanc et al. 2013	Form.
Chironomus riparius	96		0.01294	Pestana et al. 2009a (cues)[7]	Form.
Chironomus riparius	96		0.01406	Pestana et al. 2009a (no cues)	Form.
Chironomus tentans	96		0.0054	Stoughton et al. 2008	Form.

Group/Species	Hr	LC_{50} (mg/L)	EC_{50} (mg/L)	Reference	Agent
Other Diptera					
Aedes aegypti	48	0.044		Song et al 1997	TGAI
Simulium vittatum	48	0.0081		Overmyer et al. 2005	TGAI
Simulium latigonium	96	0.00373		Beketov & Liess 2008	TGAI
Chaoborus obscuripes	96	0.294	0.284	Roessink et al. 2013	Form.
Aedes taeniorhynchus[3]	48	0.013		Song et al 1997	TGAI
Ostracoda					
Cypretta seurati	48		0.016	Sanchez-Bayo & Goka 2006a	TGAI
Cypridopsis vidua	48		0.003	Sanchez-Bayo & Goka 2006a	TGAI
Ilyocypris dentifera	48		0.003	Sanchez-Bayo & Goka 2006a	TGAI
Ephemeroptera					
Baetis rhodani	48	0.00849		Beketov & Liess 2008	TGAI
Cloeon dipterum	96	0.00668	0.00177	Roessink et al. 2013	Form.
Caenis horaria	96	0.0263	0.00102	Roessink et al. 2013	Form.
Epeorus longimanus	96	0.00065		Alexander et al. 2007	Form.
Isopoda					
Asellus aquaticus	48	8.5	0.8	Lukancic et al. 2010a,b	Form.
Asellus aquaticus	96	0.316	0.119	Roessink et al. 2013	Form.
Hemiptera					
Micronecta sp.	96	0.0282	0.0108	Roessink et al. 2013	Form.
Notonecta sp.	96	>10.0	0.0182	Roessink et al. 2013	Form.
Plea minutissima	96	0.0375	0.0359	Roessink et al. 2013	Form.
Trichoptera					
Sericostoma vittatum	96		0.03586	Pestana et al. 2009a (cues) [7]	Form.
Sericostoma vittatum	96		0.04722	Pestana et al. 2009a (no cues)	Form.
Limnephilidae sp.	96	0.0257	0.00986	Roessink et al. 2013	Form.
Mysida					
Mysidopsis bahia[3]	96	0.0377[4]		Ward 1990b	TGAI
Mysidopsis bahia[3]	96	0.0341		Ward 1990b	TGAI
Mysidopsis bahia[3]	96	0.036		Lintott 1992	Form.
Megaloptera *Sialis lutaria*	96	10.0	0.0506	Roessink et al. 2013	Form.
Annelida *Lumbriculus variegatus*	96		0.0062	Alexander et al. 2007	Form.
Gastropoda *Marias cornuarietis*	336	10.0		Sawasdee & Kohler 2009	TGAI
Anostraca *Artemia* sp. [3]	48	361.23		Song et al. 1997	TGAI
Decapoda Palaemonetes pugio[3]	96	0.3008		Key et al. 2007	TGAI
Bivalvia *M. galloprovincialis*[3]	96	1.8		Dondero et al. 2010	TGAI

[1] Registrant submitted study. [2] 24-hour EC_{50}. [3] Saltwater Species [4] U.S. EPA/OPP/EFED (2007, p. 24) used a Mysid acute EC_{50} of 0.037 to calculated acute RQs for saltwater organisms and an EC_{50} of 0.069 mg/L midges to calculated acute RQs for freshwater species. The reason for the discrepancy in the EC_{50} in midges is not apparent.
[5]Feeding inhibition. [6]Mortality based on heartbeat. [7] With and without predator cues.

See Appendix 6, Tables A6-1 through A6-7 for details of studies. See Section 4.1.3.3.1 for discussion.

Table 23: Summary of Acute Toxicity Values for Aquatic Invertebrates

Average Toxicity Values for Groups of Aquatic Invertebrates

Group	Endpoint	Geometric Mean of Toxicity Value (mg/L)	Number of Values	Relative Sensitivity[2]	Freq (i-.5)÷ Tot[3]
Ephemeroptera	EC_{50}	0.0013	2	1	0.025
Ostracoda	EC_{50}	0.0052	3	4	0.075
Annelida	EC_{50}	0.0062	1	5	0.125
Midges	EC_{50}	0.0087	4	6	0.175
Hemiptera	EC_{50}	0.0192	3	14	0.225
Diptera (other than midges)	LC_{50}	0.0281	5	16	0.275
Amphipoda	EC_{50}	0.0256	9	19	0.325
Trichoptera	EC_{50}	0.0256	3	19	0.375
Ceriodaphnia dubia (Clad.)	EC_{50}/LC_{50}	0.0344	2	26	0.425
Mysida[1]	LC_{50}	0.0359	3	27	0.475
Megaloptera	EC_{50}	0.0506	1	38	0.525
Decapoda[1]	LC_{50}	0.3008	1	224	0.575
Isopoda	EC_{50}	0.3085	2	230	0.625
Bivalvia[1]	LC_{50}	1.8000	1	1,340	0.675
Chydorus sphaericus (Clad.)[1]	EC_{50}	2.2090	1	1,644	0.725
Ceriodaphnia reticulata (Clad.)	EC_{50}	5.5529	1	4,133	0.775
Gastropoda	LC_{50}	10.0000	1	7,442	0.825
Moina macrocopa (Clad.)	EC_{50}	45.2710	1	33,693	0.875
Daphnia sp. (*magna and pulex*)	EC_{50}	47.4688	12	35,328	0.925
Atremia sp. [Anostraca][1]	LC_{50}	361.23	1	268,842	0.975

[1] Saltwater

[2] Toxicity value for group divided by toxicity values for Ephemeroptera (most sensitive group).

[3] The i^{th} observation divided by the total number of observations.

Clad.= Cladocera

See Table 22 for details of data.
See Figure 6 for illustration.
See Section 4.1.3.3.1 for discussion.

Table 24: Overview of Aquatic Invertebrate Chronic Studies

All concentrations in mg/L

Group/ Species	End-point[1]	Days	Pulse	NOAEC	LOAEC	EC_{10}	EC_{50}	Reference	Agent
Cladocera									
D. magna	Rep	21	N	1.8	3.6		7.3	Young and Blake 1990	TGAI
D. magna	Imm	21	N				37.24	Ieromina et al. 2014	TGAI
D. magna	Rep	21	N	1.25	2.5			Jemec et al. 2007	TGAI
D. magna	Rep	21	N				5.5	Pavlaki et al. 2011	TGAI
D. magna	Feed	7	N	0.15	12.0			Agatz and Brown 2013b	TGAI
C. dubia	Rep	8	N		8.093			Chen et al. 2010	Form.
D. magna	Rep	21	N	2.5	5.0			Jemec et al. 2007	Form.
D. magna	Rep	21	N	2.2	4.0			Pestana et al. 2010	Form.
Amphipoda									
G. pulex	Feed	21	Y	0.09				Nyman et al. 2013	TGAI
H. azteca	Surv	10	N	0.00353	0.01195			Stoughton et al. 2008	Form.
H. azteca	Surv	28	N	0.00344	0.01146			Stoughton et al. 2008	Form.
H. azteca	Surv	10	Y	0.01193				Stoughton et al. 2008	Form.
H. azteca	Surv	28	Y	0.00353	0.01193			Stoughton et al. 2008	Form.
G. pulex	Imm	28	N			0.00295	0.0154	Roessink et al. 2013	Form.
Diptera									
C. tentans[3]	Surv	10	N	0.00124			0.00317	Gagliano 1991	
C. tentans	Surv	10	N	0.00117	0.00357			Stoughton et al. 2008	Form.
C. tentans	Surv	28	N	0.00114	0.00346			Stoughton et al. 2008	Form.
C. tentans	Surv	10	Y	0.00347				Stoughton et al. 2008	Form.
C. tentans	Survl	28	Y	0.00347				Stoughton et al. 2008	Form.
Tipula sp[5]	Surv	14	N			0.0162[2]	0.071[2]	Kreutzweiser et al. 2008c	Form.
Megaloptera									
Sialis lutaria	Imm	28	N			0.00128	0.00346	Roessink et al. 2013	Form.
Hemiptera									
P. minutissima	Imm	28	N			0.00203	0.00645	Roessink et al. 2013	Form.
Ephermeropt.									
C. dipterum	Imm	28	N			0.000033	0.000123	Roessink et al. 2013	Form.
C. horaria	Imm	28	N			0.000024	0.000126	Roessink et al. 2013	Form.
P. dorsata [5]	Survl	14	N			0.0208[2]	0.071[2]	Kreutzweiser et al. 2008c	Form.
Mysida									
M. bahia[4]	Surv	28	N	0.0006	0.0013			Ward, 1991 (per EFED)	TGAI

[1] Endpoint Key: Feed=Feeding; Imm=Immobilization; Rep=Reproduction; Surv=Survival
Agent Key: Form.=Formulation; TGAI=Technical grade active ingredient/imidacloprid.
[2] Mesocosm study.
[3] Used by U.S. EPA/OPP/EFED 2007a for RQs in freshwater aquatic invertebrates.
[4] Used by U.S. EPA/OPP/EFED 2007a for RQs in saltwater aquatic invertebrates.
[5] Mesocosm study. *Pteronarcys dorsata* is a Plecoptera rather than Ephemeroptera, both of which are Pterygota sub.

See Appendix 6, Table A6-10 for details of studies. See Section 4.1.3.3.2 for discussion.

Table 25: Summary of Chronic Studies in Aquatic Invertebrates

Group	Duration (Days)	Number of Studies	Concentration (mg/L)	Type of Endpoint	Relative Sensitivity	Freq (i-.5)÷ Tot[1]
Bioassays						
Ephemeroptera	28	2	0.0000281	EC_{10}	1	0.0625
Mysida	28	1	0.0006	NOAEC	21	0.1875
Megaloptera	28	1	0.00128	NOAEC	45	0.3125
Chironomus tentans (Diptera)	28	5	0.00182	NOAEC	65	0.4375
Hemiptera	28	1	0.00203	EC_{10}	72	0.5625
Gammarus pulex	21	1	0.00295	EC_{10}	105	0.6875
Hyalella azteca	28	2	0.00348	NOAEC	124	0.8125
Daphnia magna	7-21	5	1.13	NOAEC	40,213	0.9375
Mesocosm						
Tipula sp (Diptera)	14	1	0.0162	EC_{10}		0.25
Plecoptera	14	1	0.0208	EC_{10}		0.75

[1] The i^{th} observation divided by the total number of observations.

See Table 24 for details.
See Figure 6 for illustration.
See Section 4.1.3.3.2 for discussion.

Table 26: Overview of Aquatic Mesocosm Studies

Type	Species, Group	NOAEC (mg a.i/L)	LOAEC (mg a.i/L) [Basis for LOAEC]	Reference
Artificial Stream	*Baetis rhodani*, Ephemeroptera		0.00097 [Drift]	Beketov and Liess 2008
Artificial Stream	*Gammarus pulex*, Amphipod		0.030 [Drift]	Beketov and Liess 2008
Benthic	Chironomidae, **Ephemeroptera**, Gastropoda	0.0014 (Nom.) 0.0004 (TWA)	0.0032 (Nom.) 0.001 (TWA) [Diversity and Abundance]	Colombo et al. 2013
Rice Paddy	**Coleopteran Ostracods Chironomids**		0.0019 (peak) [Abundance]	Hayasaka et al. 2012a
Rice paddy	Many (178 species) including **Chironomidae, Sarcophagidae, Ephemeroptera, Oligochaeta, and Gastropoda**.	0.049 (peak)[1] 0.001 (TWA) [1]	0.049 (peak)[1] 0.001 (TWA) [1] [Abundance]	Hayasaka et al. 2012c
Artificial Stream, Leaf litter	Plecoptera (1 sp.) Diptera (1 sp.)	0.012 (mortality)	0.135 [mortality]	Kreutzweiser et al. 2007
Artificial Stream, Leaf litter	Plecoptera (1 sp.) Diptera (1 sp.)	0.024 (mortality)	0.048 [mortality]	Kreutzweiser et al. 2008c
Artificial Stream	Amphipoda **Diptera Ephemeroptera Trichoptera**	0.012 [2]	0.012 [sublethal] [2]	Mohr et al. 2012
Mixed, lentic	**Mayfly, Midge, Caddisfly, and Beetles**	0.0176	0.019 [Abundance]	Moring et al. 1992
Mixed, lentic	**Amphipods**	ND	0.002 [Abundance]	Moring et al. 1992
Outdoor Stream mesocosm	**Oligochaetes** Diptera Coleoptera	0.00163	0.0176 [Population density]	Pestana et al. 2009a

Nom.: Nominal
TWA: Time-weighted average.
Most sensitive group(s), basis for LOAEL, given in **bold font**.
[1] Only a single treatment level. Transient effects at Day 56 with recovery by Day 112.
[2] Only one concentration used in study. Sublethal effects in Ephemeroptera (decreases emergence/possible larval death) and Trichoptera (decreased abundance). Increase in abundance of amphipods.

See Appendix 6, Table A6-10, for details.
See Section 4.1.3.3.3 for discussion.

Table 27: Exposure Assessments for Mammals and Birds

	Attachment:	1	2	3	4	
Scenario	**Receptor**[1]	**Tree Injection**	**Soil Injection**	**Bark**	**Foliar**	**Worksheet(s)**
Accidental Acute						
First-order absorption	Mammal (20g)			■	■	F01a
100% absorption	Mammal (20g)			■	■	F01b
Water consumption (spill)	Mammals[2]	■	■	■	■	F02a-d
	Two Birds[3]	■	■	■	■	F02e-f
Fish consumption (spill)	Two Mammals[4]	■	■	■	■	F03a-b
	Raptor	■	■	■	■	F03c
Non-Accidental Acute						
Fruit	Mammals and Bird[5]			■	■	F04a-e
Broadleaf Vegetation	Mammals and Bird[5]			■	■	F05a-e
Tall Grass	Mammals and Bird[5]			■	■	F06a-e
Short Grass	Mammals and Bird[5]			■	■	F07a-e
Contaminated Water	Mammals and Bird[6]		■	■	■	F08a-f
Contaminated Insects	Mammals and Bird[7]			■	■	F09a-c
Contaminated Rodent	Mammal and Bird[8]			■	■	F10a-b
Contaminated Fish	Mammals and Bird[8]		■	■	■	F11a-c
Chronic/Longer Term						
Fruit	Mammals and Bird[5]			■	■	F12a-e
Broadleaf Vegetation	Mammals and Bird[5]			■	■	F13a-e
Tall Grass	Mammals and Bird[5]			■	■	F14a-e
Short Grass	Mammals and Bird[5]			■	■	F15a-e
Contaminated Water	Mammals and Bird[6]		■	■	■	F16a-f
Contaminated Fish	Mammals and Bird[8]		■	■	■	F17a-c

[1] See Table 28 for details of mammalian and avian receptors.
[2] Mammals (20 g, 400 g, 4 kg, and 70 kg).
[3] Small and large bird as detailed in Table 27.
[4] Canid and large carnivore as detailed in Table 27.
[5] Mammals (20 g, 400 g, and 70 kg) and birds (10 g and 4 kg).
[5] Mammals (20 g, 400 g, 4 kg, and 70 kg) and birds (10 g and 4 kg).
[6] Mammals (20 g, 400 g, and 70 kg) and birds (10 g).
[7] Mammal (4 kg canid) and carnivorous bird (640 g).
[8] Mammal s(4 and 70 kg) and fish-eating bird (2.4 g).

See Section 4.2.2 for discussion.
See Attachments 1 through 4 for details.

Table 28: Terrestrial Nontarget Animals Used in Ecological Risk Assessment

MAMMALS [1]

Animal	Representative Species	W[4]	Food Consumption[5]	Water Consumption
Small mammal	Mice	20	$2.514\ W^{0.507}$ [Eq 3-48]	$0.099\ W^{0.9}$ [Eq 3-17]
Larger mammal	Squirrels	400	$2.514\ W^{0.507}$ [Eq 3-48]	$0.099\ W^{0.9}$ [Eq 3-17]
Canid	Fox	5,000	$0.6167\ W^{0.862}$ [Eq 3-47]	$0.099\ W^{0.9}$ [Eq 3-17]
Large Herbivorous Mammal	Deer	70,000	$1.518\ W^{0.73}$ [Eq 3-46]	$0.099\ W^{0.9}$ [Eq 3-17]
Large Carnivorous Mammal	Bear	70,000	$0.6167\ W^{0.862}$ [Eq 3-47]	$0.099\ W^{0.9}$ [Eq 3-17]

BIRDS [2]

Animal	Representative Species	W[4]	Food Consumption[5]	Water Consumption
Small bird	Passerines	10	$2.123\ W^{0.749}$ [Eq 3-36]	$0.059\ W^{0.67}$ [Eq 3-15]
Predatory bird	Owls	640	$1.146\ W^{0.749}$ [Eq 3-37]	$0.059\ W^{0.67}$ [Eq 3-15]
Piscivorous bird	Herons	2,400	$1.916\ W^{0.704}$ [Eq 3-38]	$0.059\ W^{0.67}$ [Eq 3-15]
Large herbivorous bird	Geese	4,000	$1.146\ W^{0.749}$ [Eq 3-37]	$0.059\ W^{0.67}$ [Eq 3-15]

INVERTEBRATES [3]

Animal	Representative Species	W[4]	Food Consumption[5]
Honey bee [7]	*Apis mellifera*	0.000116	≈2 (1.2 to 4)[6]
Herbivorous Insects	Various	Not used	1.3 (0.6 to 2.2)

[1] Sources: Reid 2006; U.S. EPA/ORD 1993.
[2] Sources: Sibley 2000; Dunning 1993; U.S. EPA/ORD 1993.
[3] Sources: Humphrey and Dykes 2008; Reichle et al. 1973; Winston 1987
[4] Body weight in grams.
[5] For vertebrates, based on allometric relationships estimating field metabolic rates in kcal/day for rodents (omnivores), herbivores, and non-herbivores. For mammals and birds, the estimates are based on Nagy (1987) as adapted by U.S. EPA/ORD (1993). The equation numbers refer to U.S. EPA/ORD (1993). See the following table for estimates of caloric content of food items. For herbivorous insects, consumption estimates are based on fractions of body weight (g food consumed/g bw) from the references in Note 3.
[6] For honeybees, food consumption based on activity and caloric requirements. Used only when estimates of concentrations in nectar and/or pollen can be made, which is not the case in the current risk assessment.
[7] A surface area of 1.42 cm2 is used for the direct spray scenario of the honey bee. This value is based on the algorithms suggested by Humphrey and Dykes (2008) for a bee with a body length of 1.44 cm.

See data on food commodities in following table.
See Sections 4.2.2 and 4.2.3.2 for discussion.

Table 29: Diets: Metabolizable Energy of Various Food Commodities

Food Item	Animal Group	Caloric Value [1] (kcal/g bw)	Water Content [2]	Comment/Source(s)
Fruit	Mammals	1.1	0.77	See Footnote 3
	Birds	1.1	0.77	See Footnote 4
Fish	Mammals	4.47	0.70	Water content from Ali et al. (2005).
	Birds	3.87	0.70	Water content from Ali et al. (2005).
Insects	Mammals	4.47	0.70	Water contents from Chapman 1998 (p. 491). Typical ranges of 60-80%.
	Birds	4.30	0.70	Water contents from Chapman 1998 (p. 491). Typical ranges of 60-80%.
Vegetation (NOS)	Mammals	2.26	0.85	See Footnote 5
	Birds	2.0	0.85	See Footnote 5

[1] Metabolizable energy. Unless otherwise specified, the values are taken from U.S. EPA/ORD (1993), Table 3-1, p. 3-5 as adopted from Nagy 1987.

[2] From U.S. EPA/ORD (1993), Table 4-2, p. 4-14 unless otherwise specified.

[3] Based on a gross caloric value of 2.2 kcal/g bw (U.S. EPA/ORD 1993, Table 4-2). An assimilation factor for mammals eating fruit not identified. Use estimate for birds (see below).

[4] Based on a gross caloric value of 2.2 kcal/g bw (U.S. EPA/ORD 1993, Table 4-2) and an assimilation factor for the consumption of fruit by birds of 51% [2.2 kcal/g bw x 0.51 ≈ 1.1 kcal/g bw]

[5] Based on a gross caloric value of 4.2 kcal/g bw for dicot leaves (U.S. EPA/ORD 1993, Table 4-2). For birds, the value is corrected by an assimilation factor for the consumption leaves by birds of 47% [4.2 kcal/g bw x 0.47 = 1.974 kcal/g bw]

See Sections 4.2.2.3 for discussion.

Table 30: Residues in Tree Leaves/Needles

Treatment	Residues in Leaves/Needles (µg/g, ppm)	Residue Rates (µg/g leaves per g/inch DBH applied)	Reference
Norway Maple			
Tree injection, 0.220 g/inch DBH (if DBH<61 cm, Norway maple	13.79 (6.16-49.17)[1] ≈150 DAT.	63 (28-224)	Ugine et al. 2013
Tree injection, 0.440 g/inch DBH (if DBH≥61 cm Norway maple	13.79 (6.16-49.17)[1] ≈150 DAT	31 (14-112)	Ugine et al. 2013
Soil Injection, rate not specified [5]	0.16-6.3 90 DAT	N/A	USDA/APHIS 2003
Green or White Ash			
Stem injection: 0.06 g a.i./cm DBH (low end field rate). 0.1524 g/inch DBH	0.85 About 90 days after treatment.	5.6	Kreutzweiser et al. 2007
Soil Injection: 0.56 g a.i./cm DBH (high end field rate). 1.4224 g/inch DBH	1.28 About 90 days after treatment.	0.90	Kreutzweiser et al. 2007
Soil Injection: 5.6 g a.i./cm DBH (overdose). 14.224 g/inch DBH. **Gross over treatment.**	81.3 About 90 days after treatment.	5.7	Kreutzweiser et al. 2007
Tree injection, 6 mL Imicide (10% a.i.). 110.7 mg a.i./mL x 6 mL = 664.2 mg or 0.6642 g/cm DBH. Rate: ≈0.2214 g/inch	≈0.1 About 105 days after treatment (Figure 2).	0.45	Mota-Sanchez et al. 2009
Tree injection, 6 mL Imicide (10% a.i.). 110.7 mg a.i./mL x 6 mL = 664.2 mg or 0.6642 g/cm Rate: ≈0.166 g/inch	≈0.1 About 105 days after treatment (Figure 2).	0.60	Mota-Sanchez et al. 2009
Eastern Hemlock			
Soil injection, 1 g/inch DBH, near trunk (higher) and under canopy (lower)	0.037 to 0.052 ≈450 DAT	0.037 to 0.052	Cowles et al. 2006[2]
Soil drench, 1 g/inch DBH (NOS)	0.031 ≈450 DAT	0.031	Cowles et al. 2006[2]
Arborject injection, 0.1 g/inch DBH	0.032 ≈450 DAT	0.31	Cowles et al. 2006[2]
Mauget System injection, 0.15 g/inch DBH	0.220 ≈450 DAT	1.5	Cowles et al. 2006[2]
Wedgle System injection, 0.09 g/inch DBH	0.0069 ≈450 DAT	0.078	Cowles et al. 2006[2]
Imicide , 0.056 g a.i./inch DBH	0.19933	3.6	Dilling et al. 2010
Merit 75 WP, soil injection, 1 g a.i./inch DBH	0.18142	0.18142	Dilling et al. 2010
Apple			
Tree Injection, rate not specified in 1 g a.i./inch DBH	0.5-2.2 14 to 42 DAT	N/A	Acimovic et al. 2014
Mixed Species [4]			
Tree Injection, 0.2214 g a.i./inch DBH	1.7 (0.72-12) 90 DAT	7.6 (3.3-54)	USDA/AHPIS 2003

[1] Mean (median-maximum). See Table 1 of paper. Injections made in "spring" (NOS) and leaves sampled in September. Assume about a 5 month period to sampling. No differentiation in monitoring between the two tree sizes.

[2] Applied in October 2002 and between May and June 2003. Note that concentrations give in Table 2 of paper are in ppb rather than ppm. Concentrations above in the current table are given as ppm. Monitoring of needles in August 2003.

[3] Imicide (110.7 mg a.i./mL)3 mL per 15 cm DBH = 0.3321 g/5.9 inches = 0.056 g a.i./inch DBH. Data on fap from twigs and needles. Only maximum concentrations are used. See Table 2 of paper.

[4] Norway, sycamore, sugar and silver maple; poplar; elm; hackberry and mountain ash.

[5] No detectable residues in elm trees.

See Section 4.2.3.2.1 for discussion.

Table 31: Concentrations of Imidacloprid in Soil

Soil Injection, clay	**Top 12 inches**[1]	**Top 36 Inches**[1]
Central	0.4	0.153
Lower	0.35	0.142
Upper	0.51	0.171
Bark Application, clay	**Top 12 inches**[2]	**Top 36 Inches**[2]
Central	0.0291	0.0104
Lower	0.0268	0.0095
Upper	0.037	0.0123
Foliar Application, clay	**Top 12 inches**[1]	**Top 36 Inches**[1]
Central	0.291	0.104
Lower	0.268	0.095
Upper	0.37	0.123

[1] Concentrations in units of mg a.i./kg soil expected at a unit application rate of 1 lb a.i./acre. Data from Appendix 8 (Tables A8-2 and A8-3) for soil in injection and Appendix 9 (Tables A9-2 and A9-3) for broadcast applications.

[2] Rates for bark applications are taken as 10% of the rates for foliar application.

See Section 4.2.3.4 for discussion

Table 32: Summary of toxicity values used in ecological risk assessment

Group/Duration / Organism		Endpoint	Toxicity Value (a.i.)	Reference
Terrestrial Animals				
Acute				
Mammals (including canids)		LOAEL (42 mg/kg bw) ÷ 3	14 mg/kg bw	Section 4.3.2.1.
Birds		Gavage NOAEL	3 mg/kg bw	Section 4.3.2.2
Honey Bee (colony health)		Longer-term oral	0.000095 mg/kg bw	Section 4.3.2.4.1
Phytophagous Insect (oral)		LOAEL ÷ 3	0.00023 mg/kg bw	Section 4.3.2.4.2
Insect (spray)		LD_{50} ÷ 10	0.0059 mg/kg bw	Section 4.3.2.4.3
Soil invertebrates		NOAEC (earthworms)	0.1 mg/kg soil	Section 4.3.2.4.4
Longer-term				
Mammals		Chronic NOAEL (male rats)	5.7 mg/kg bw/day	Section 4.3.2.1
Bird		Reproductive NOAEL	2.52 mg/kg bw/day	Section 4.3.2.2.
Aquatic Animals				
Acute				
Amphibians	Sensitive	NOAEC for delayed development	3.89 mg/L	Section 4.3.3.2
	Tolerant	NOAEC (mortality)	16.7 mg/L	
Fish	Sensitive	NOAEC (mortality), bluegills	25 mg/L	Section 4.3.3.1
	Tolerant	NOAEC (mortality) minnows	50 mg/L	
Invertebrates	Sensitive	EC_{10}, Ephemeroptera	0.000325 mg/L	Section 4.3.3.3
	Tolerant	NOAEC, *Daphnia magna*	42 mg/L	
Longer-term				
Amphibians	Sensitive	No data.	N/A	Section 4.3.3.2
	Tolerant	No data.	N/A	
Fish	Sensitive	Chronic NOAEC in trout	1.2 mg/L	Section 4.3.3.1
	Tolerant	No data	N/A	
Invertebrates	Sensitive	EC_{10}, Ephemeroptera	0.000024 mg/L	Section 4.3.3.3
	Tolerant	NOAEC, *Daphnia magna*	1.13 mg/L	
Aquatic Plants				
Algae	Sensitive	EC_{10}, *Desmodesmus subspicatus*	5.6 mg/L	Section 4.3.3.4
	Tolerant	NOAEC, *S. capricornutum*	119 mg/L	Section 4.3.3.4
Macrophytes	Sensitive	No data.	N/A	Section 4.3.3.4
	Tolerant	EC_{50} ÷ 20, *Lemna minor*	37	Section 4.3.3.4

See Section 4.3 for discussion.

Table 33: Summary of Overwintering Studies in Bees

Concentration (ppb)	Vehicle	Days	Number of Failed Colonies (R)	Number of Tested Colonies (N)	% Response	Reference
0	Sucrose	32	0	8	0	Faucon et al. 2005
0.5	Sucrose	32	0	8	0	Faucon et al. 2005
5	Sucrose	32	0	8	0	Faucon et al. 2005
0	Paddies[1]	84	0	10	0	Dively et al. 2015, 2009 Exp.[3]
5	Paddies[1]	84	2	10	20	Dively et al. 2015, 2009 Exp. [3]
20	Paddies[1]	84	3	10	30	Dively et al. 2015, 2009 Exp. [3]
100	Paddies[1]	84	6	10	60	Dively et al. 2015, 2009 Exp. [3]
0	Paddies[1]	84	3	7	43	Dively et al. 2015, 2010 Exp.[3]
5	Paddies[1]	84	4	7	57	Dively et al. 2015, 2010 Exp. [3]
20	Paddies[1]	84	4	7	57	Dively et al. 2015, 2010 Exp. [3]
100	Paddies[1]	84	4	7	57	Dively et al. 2015, 2010 Exp. [3]
0	Paddies[1]	84	3	17	18	Dively et al. 2015, pooled Exp.[3]
5	Paddies[1]	84	6	17	35	Dively et al. 2015, pooled Exp. [3]
20	Paddies[1]	84	7	17	41	Dively et al. 2015, pooled Exp. [3]
100	Paddies[1]	84	10	17	59	Dively et al. 2015, pooled Exp. [3]
0	HFCS[2]	91	1	6	17	Lu et al. 2014
135	HFCS[2]	91	4	6	67	Lu et al. 2014
0	Sucrose	91	1	4	25	Lu et al. 2012
20	Sucrose	91	4	4	100	Lu et al. 2012
40	Sucrose	91	3	4	75	Lu et al. 2012
200	Sucrose	91	4	4	100	Lu et al. 2012
400	Sucrose	91	4	4	100	Lu et al. 2012

[1] Honey and Megabee powder.
[2] High fructose corn syrup [n=3] or sucrose [n=3] combined. No differences between vehicles.
[3] No dose-response relationship in 2010 study possibly due to abnormally high temperatures (and overfeeding). The 2010 study is not illustrated in Figure 8. Pooled results for 2009 and 2010 evidence a statistically significant (p=0.0136) dose-response relationship using the Cochran-Armitage Test (U.S. EPA 2015).

See Figure 8 for illustration.
See Section 4.3.2.4.1 for discussion.

Table 34: Dose-based HQs for Honeybee Colonies

Dose Based Analysis

Application Method	Central Estimate of HQ	Lower Bound of HQ	Upper Bound of HQ
Maple Tree Injection	**27,166**	**8,754**	**180,390**
Other Tree Injection	Indeterminate	Indeterminate	Indeterminate
Soil Injection	**203**	**58**	**575**
Bark Application	**20**	**6**	**57**
Foliar Application [1]	**105,150**	**57,187**	**192,444**

[1] Applies to nectar bearing flowers following a direct foliar application. Longer-term exposures after spray may be lower and similar to HQs associated with soil injection. See Section 4.4.2.4.1.4 for discussion.

Data from Worksheets G10 in Attachments 1, 2, 3, and 4.
See Section 4.4.2.4.1 for discussion.

Table 35: Concentration-based HQs for Honeybee Colonies

Concentrations in Nectar (mg/L)

Application Method	Central Estimate	Lower Bound	Upper Bound
Maple Tree Injection	1.5501	0.8389	5.7742
Soil Injection	0.0116	0.0056	0.0184
Bark Application	0.0012	0.0006	0.0018

Concentration Based HQs

Target Tree	Central Estimate of HQ	Lower Bound of HQ	Upper Bound of HQ
Maple Tree Injection	**310**	**168**	**1155**
Soil Injection	**2.3**	**1.1**	**3.7**
Bark Application	**0.2**	**0.1**	**0.4**

Note: Concentration based HQs calculated using a NOAEC of 5 ppb.

Concentration data from Worksheets G03 in Attachments 1, 2, and 3.
See Section 4.4.2.4.1 for discussion.

Table 36: HQs for Phytophagous Insects

Tree and Soil Injection

Target Tree	Central Estimate of HQ	Lower Bound of HQ	Upper Bound of HQ
Maple	79,130	16,174	468,696
Ash	4,804	261	12,243
Hemlock	565	78	1,913

Data from Worksheets G08b in Attachments 1 and 2.

Bark Application

Target Tree	Central Estimate of HQ	Lower Bound of HQ	Upper Bound of HQ
Fruit/Large Insects	1,583	334	5,739
Broadleaf/Small Insects	10,174	1,565	51,652
Short Grass	19,217	3,130	91,826
Long Grass	8,139	1,252	42,087

Data from Worksheets G08b in Attachment 3.

See Section 4.4.2.4.2 for discussion.

Table 37: HQs for Sensitive Species of Aquatic Invertebrates

Application Method/ Scenario	Central	Lower	Upper
Tree Injection			
Accidental	**2,492**	**498**	**4,985**
Acute	N/A	N/A	N/A
Chronic	N/A	N/A	N/A
Soil Injection			
Accidental	**559**	**22**	**4,472**
Acute	**16**	1E-03	**209**
Chronic	**140**	8E-03	**800**
Bark Application			
Accidental	**559**	**22**	**4,472**
Acute	**2.0**	2E-04	**12**
Chronic	**12**	3E-04	**135**
Directed Foliar			
Accidental	**280**	**28**	**1,281**
Acute	**20**	2E-03	**117**
Chronic	**115**	3E-03	**1,350**

Data from Worksheets G03 in Attachments 2, 3, and 4.
See Section 4.4.3.4. for discussion.

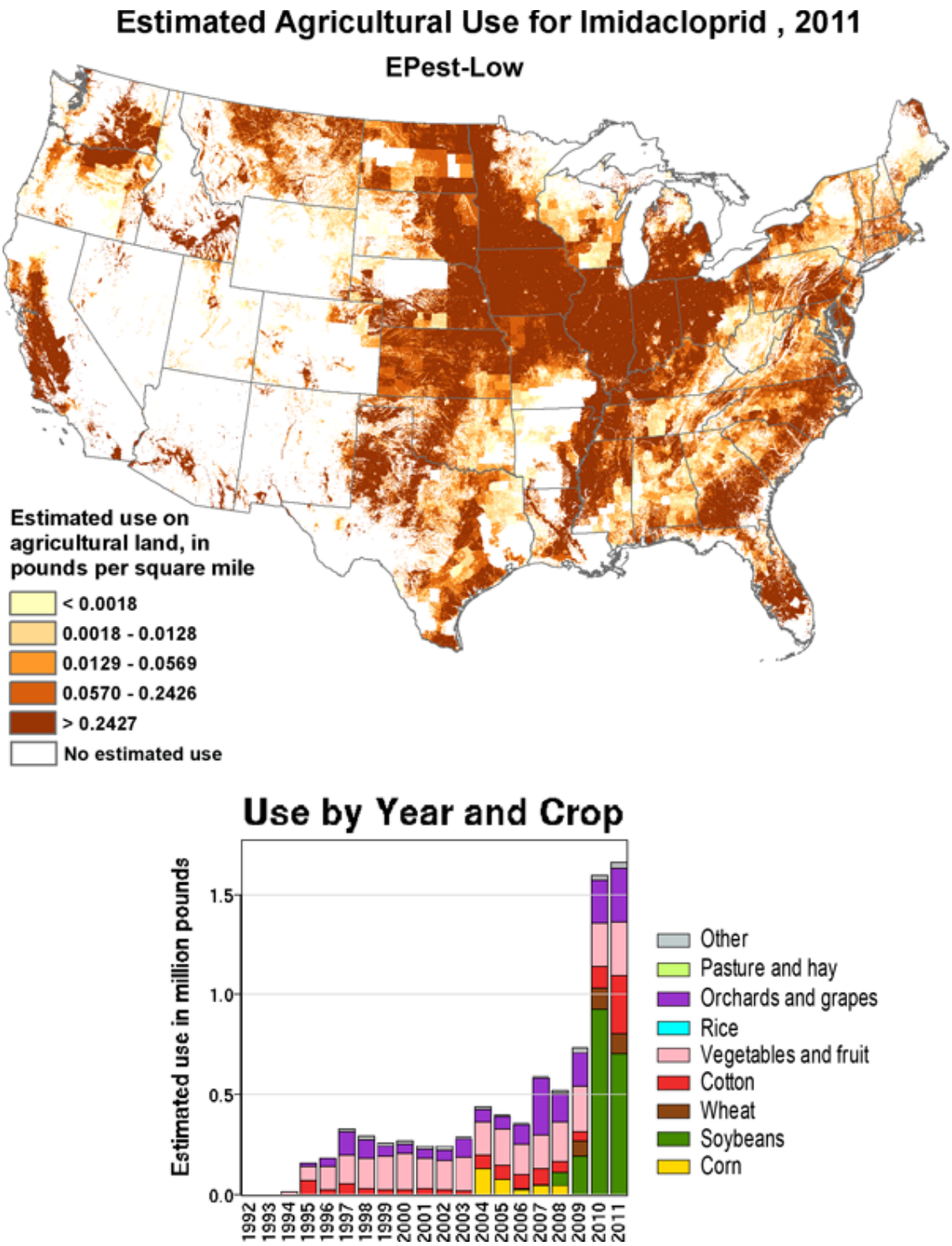
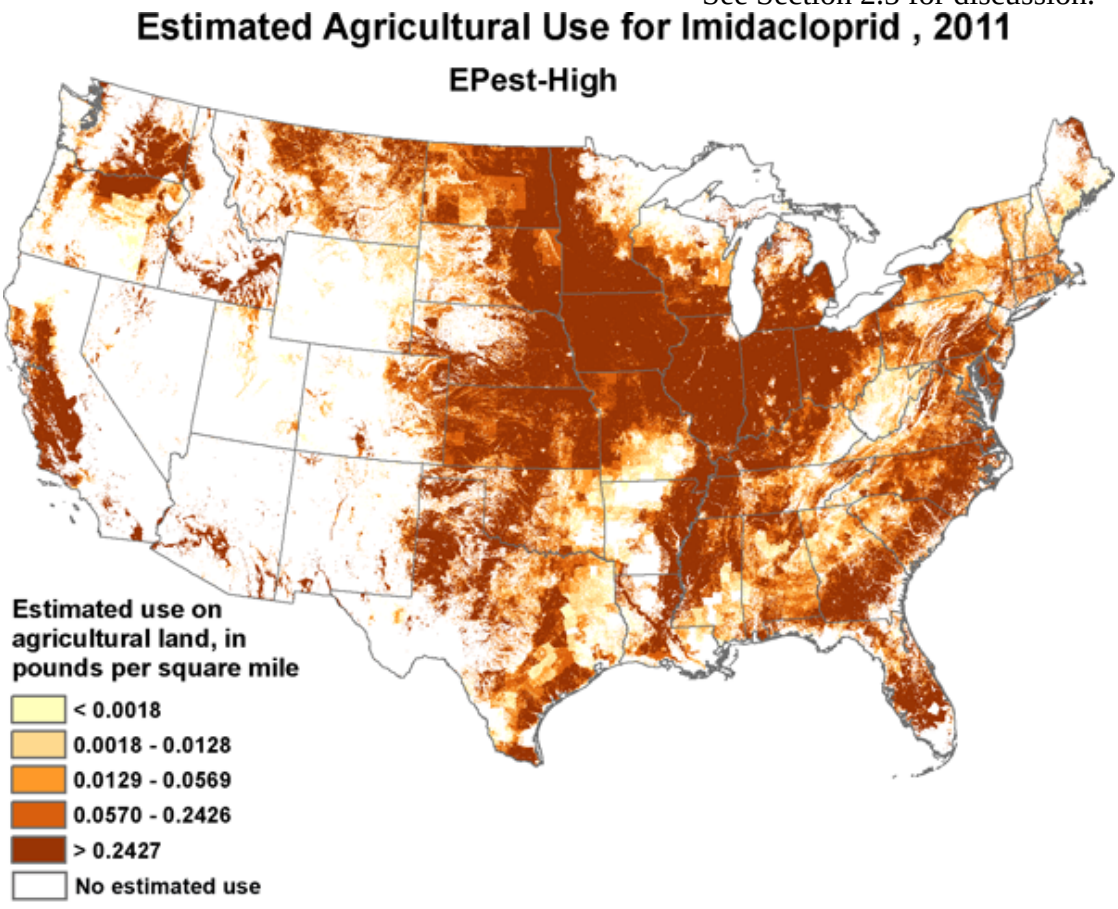


Figure 1: Lower Bound Estimated Agricultural Use of Imidacloprid for 2011

Source USGS (2014)

See Section 2.5 for discussion.

Source: USGS(2013)
See Section 2.5 for discussion.



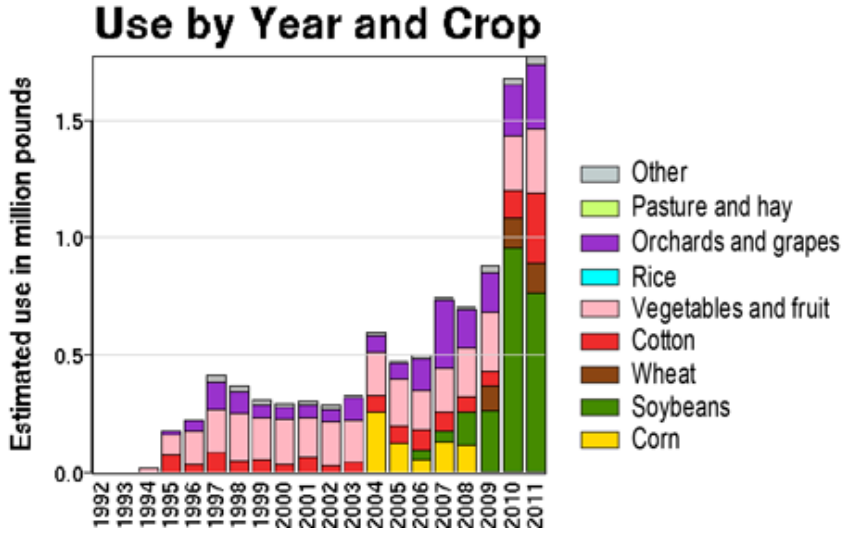
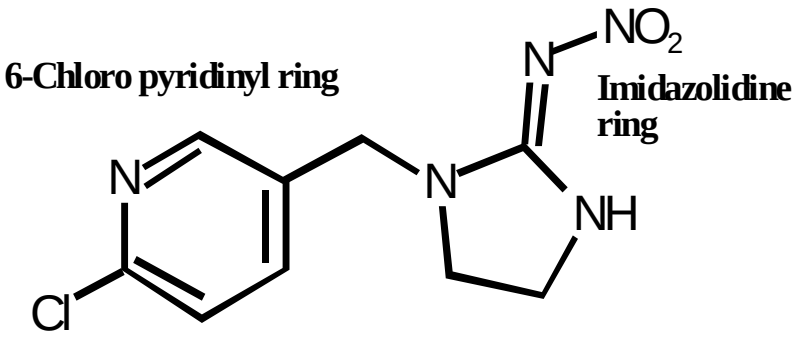


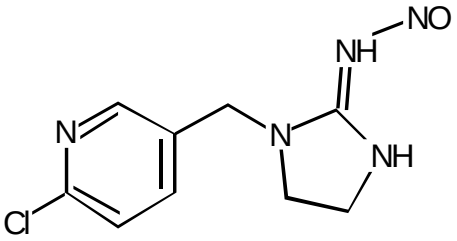
Figure 2: Upper Bound Estimated Agricultural Use of Imidacloprid for 2011

Source USGS (2014)
See Section 2.5 for discussion.

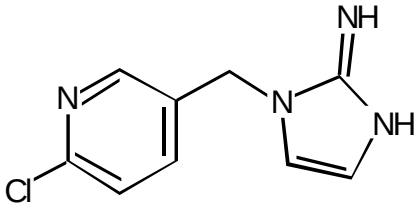
IMIDACHLOPRID



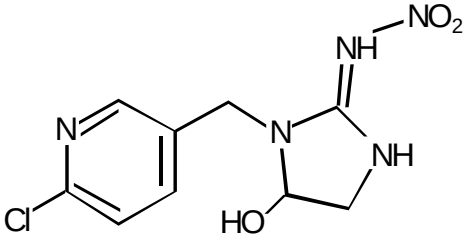
Urea metabolite



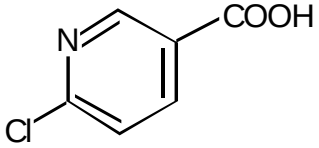
Olefin metabolite



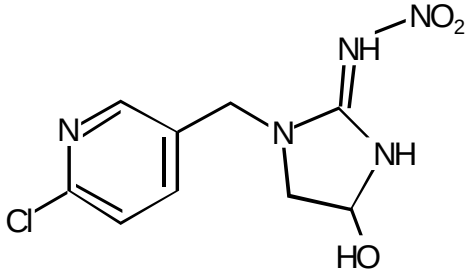
5-Hydroxyimidacloprid



6-Chloronicotinic acid



4-Hydroxyimidacloprid



6-Hydroxynicotinic acid

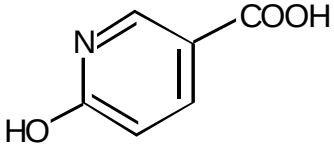


Figure 3: Structure of Imidacloprid and Related Compounds

Modified from U.S. EPA/OPP/HED 2007a, Attachment 2, p. 82 and Nauen et al. 1999, Fig. 1
See Section 3.1.3.1 for discussion.

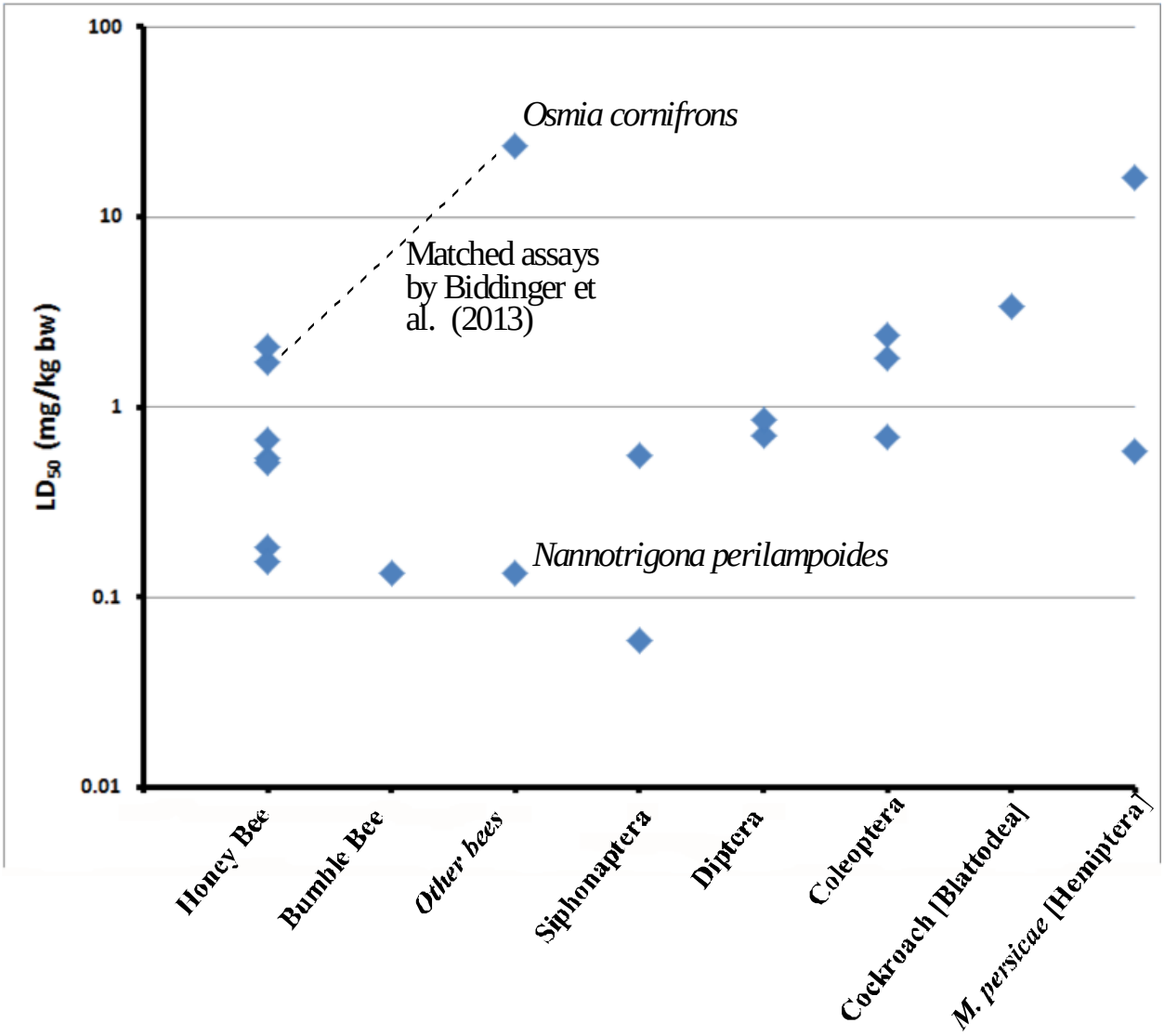


Figure 4: Topical LD_{50} Values in Terrestrial Invertebrates

See Table 16 for data.
See Section 4.1.2.4.2.1.1 for discussion.

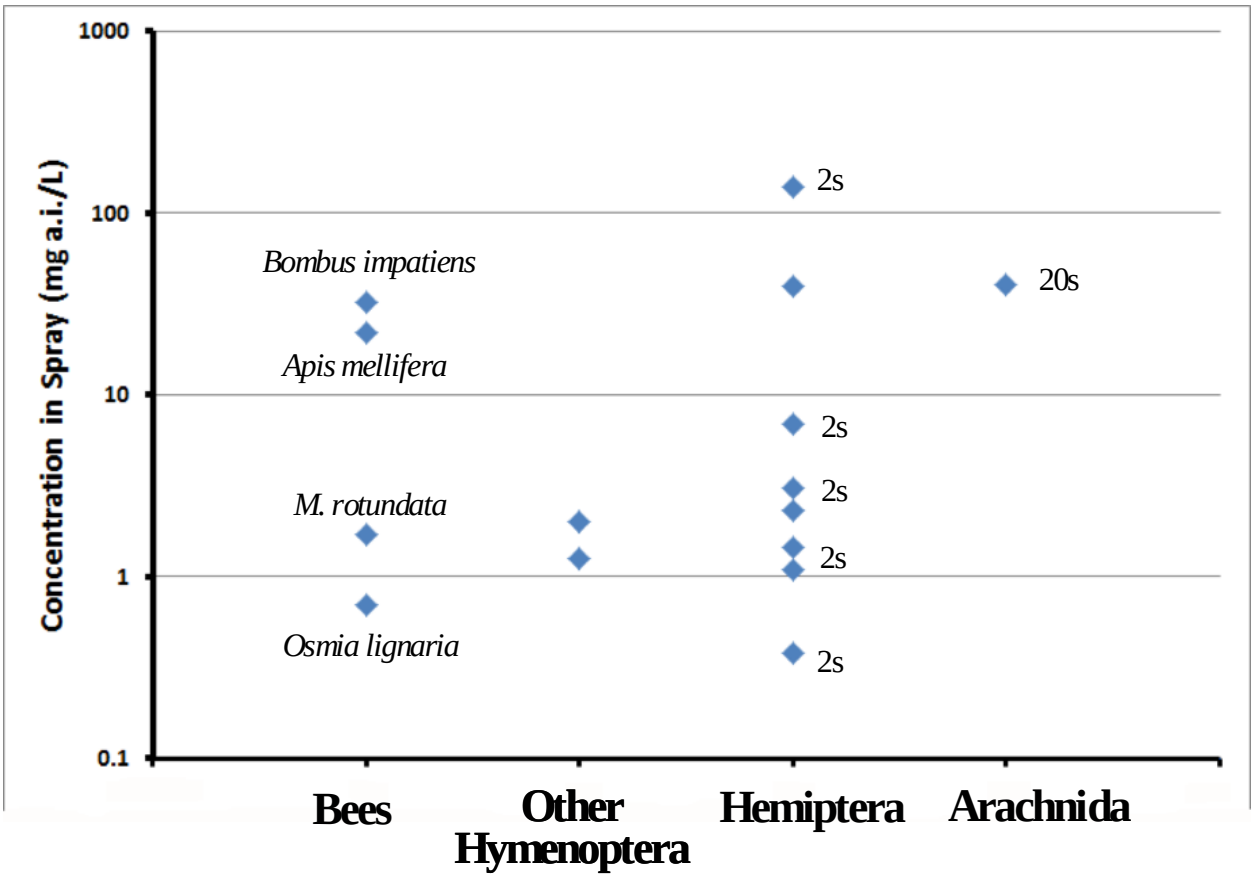


Figure 5: LC_{50} Values in Terrestrial Invertebrates for Spray/Immersion

Note: For immersion or dip assays, the duration of the immersion or dip in seconds is specified by a number followed by an "s" after the word "Dip". Points with an indication of duration involved direct spray rather than dip.

See Table 17 for data.
See Section 4.1.2.4.2.1.2 for discussion.

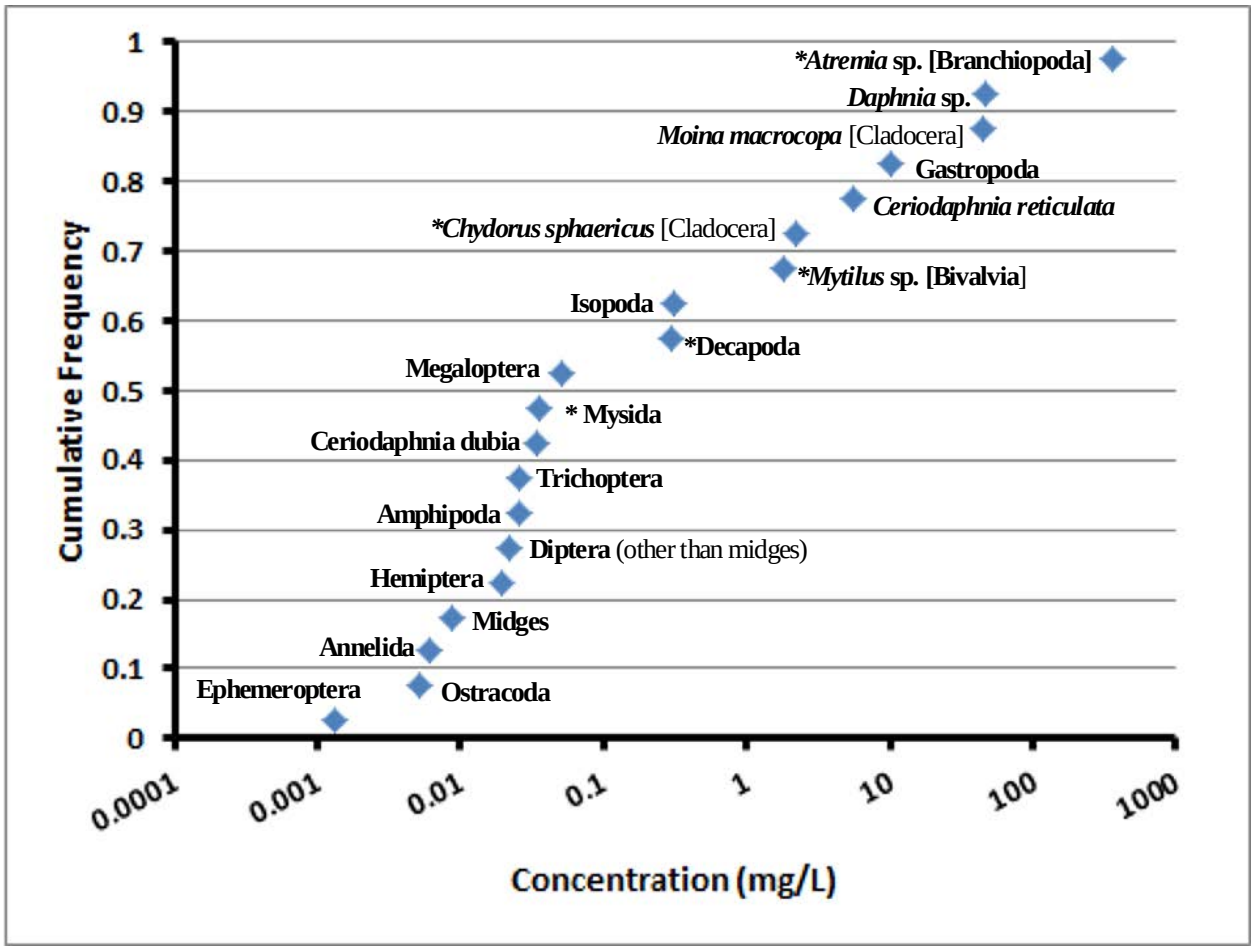


Figure 6: Overview of Acute Toxicity to Aquatic Invertebrates

Note: Organism names preceded by an asterisk (*) are marine organisms.

See Table 23 for data.
See Section 4.1.3.3.1 for discussion.

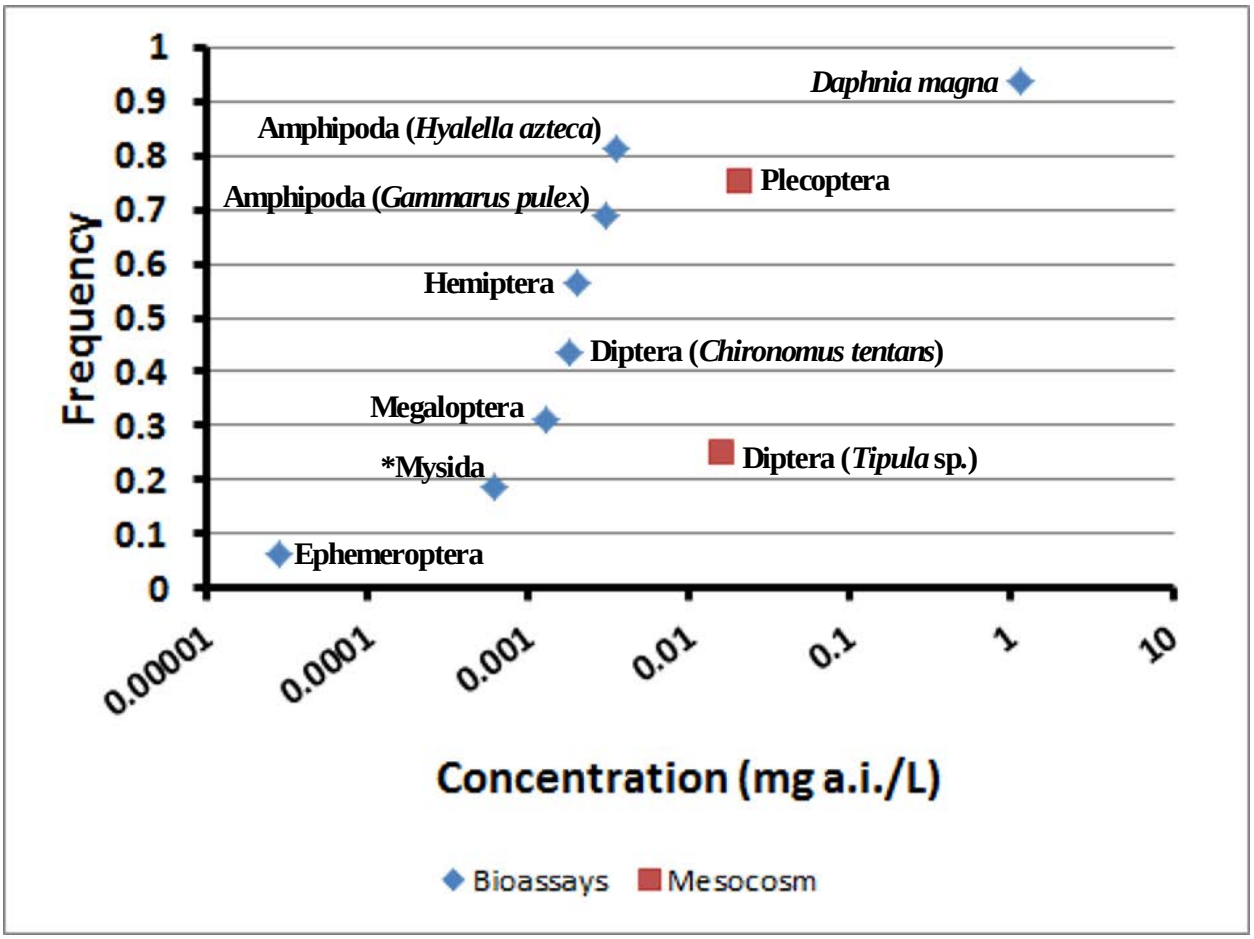


Figure 7: Overview of Chronic Toxicity to Aquatic Invertebrates

Note: Organism names preceded by an asterisk (*) are marine organisms. The x-axis gives concentrations associated with NOAEC or EC_{10} values.

See Table 25 for data.
See Section 4.1.3.3.2 for discussion.

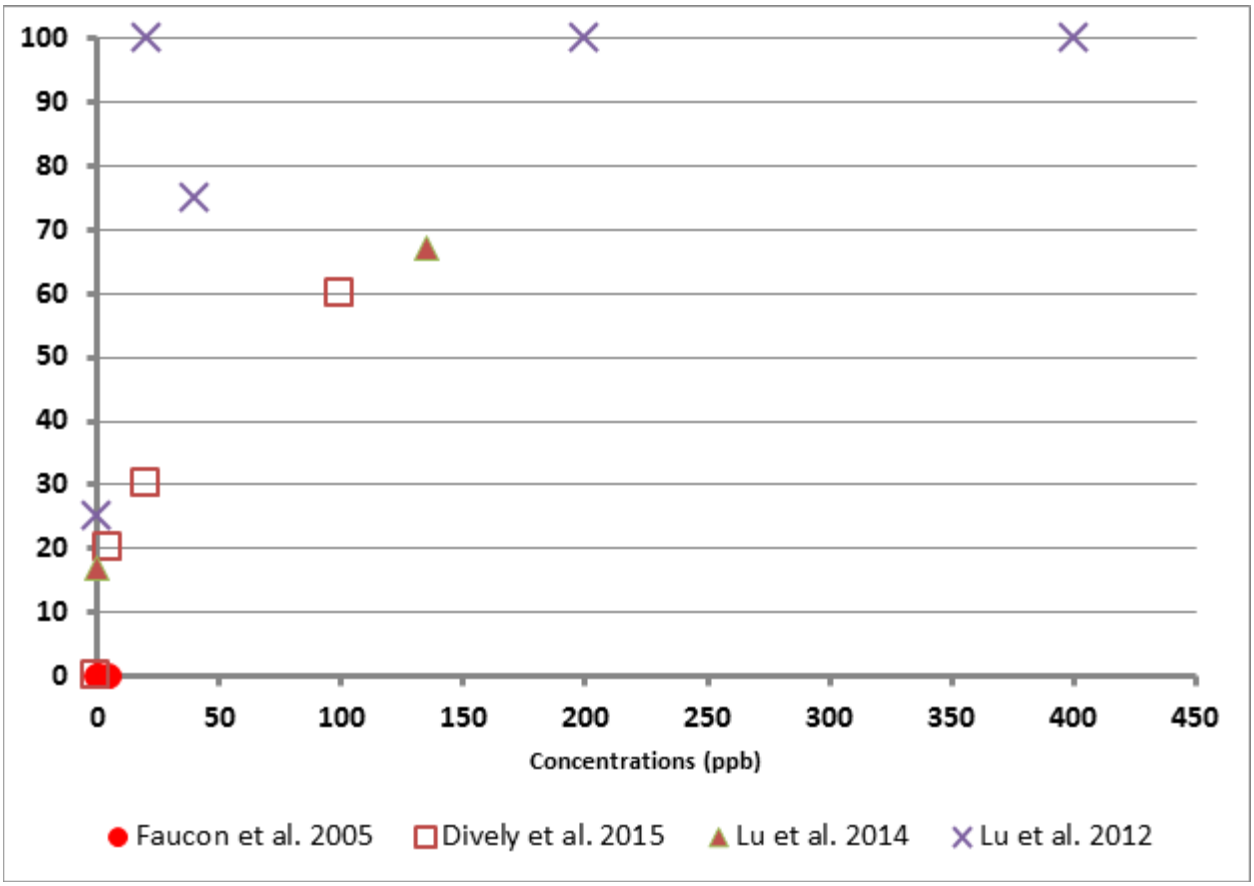


Figure 8: Overwintering Studies in Bees

See Table 33 for data.
See Section 4.3.2.4.1 for discussion.