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Emamectin benzoate

Human Health and Ecological Risk Assessment

FINAL REPORT

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ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
AEL	adverse-effect level
a.e.	acid equivalent
a.i.	active ingredient
ALS	acetolactate synthase
APHIS	Animal and Plant Health Inspection Service
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
bw	body weight
calc	calculated value
CBI	confidential business information
CEQ	Council on Environmental Quality
ChE	cholinesterase
CI	confidence interval
cm	centimeter
CNS	central nervous system
DAA	days after application
DAT	days after treatment
DER	data evaluation record
d.f.	degrees of freedom
EAB	emerald ash borer
EC_x	concentration causing X% inhibition of a process
EC_{25}	concentration causing 25% inhibition of a process
EC_{50}	concentration causing 50% inhibition of a process
EEC	expected environmental concentration
EFED	Environmental Fate and Effects Division (U.S. EPA/OPP)
ExToxNet	Extension Toxicology Network
F	female
FH	Forest Health
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FOIA	Freedom of Information Act
FQPA	Food Quality Protection Act
g	gram
GABA	gamma-aminobutyric acid
GLP	Good Laboratory Practices
ha	hectare
HED	Health Effects Division (U.S. EPA/OPP)
HQ	hazard quotient
IARC	International Agency for Research on Cancer
IRED	Interim Reregistration Eligibility Decision
IRIS	Integrated Risk Information System
k_a	absorption coefficient
k_e	elimination coefficient
kg	kilogram
$K_{o/c}$	organic carbon partition coefficient
$K_{o/w}$	octanol-water partition coefficient
K_p	skin permeability coefficient
L	liter
lb	pound

LC_{50}	lethal concentration, 50% kill
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LOC	level of concern
m	meter
M	male
mg	milligram
mg/kg/day	milligrams of agent per kilogram of body weight per day
mL	milliliter
mM	millimolar
mPa	millipascal, (0.001 Pa)
MOS	margin of safety
MRID	Master Record Identification Number
MSDS	material safety data sheet
MSMA	monosodium methanearsonate
MW	molecular weight
NAWQA	USGS National Water Quality Assessment
NCI	National Cancer Institute
NCOD	National Drinking Water Contaminant Occurrence Database
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOEL	no-observed-effect level
NOS	not otherwise specified
NRC	National Research Council
NTP	National Toxicology Program
OM	organic matter
OPP	Office of Pesticide Programs
OPPTS	Office of Pesticide Planning and Toxic Substances
OSHA	Occupational Safety and Health Administration
Pa	Pascal
PBPK	physiologically-based pharmacokinetic
PHED	Pesticide Handlers Exposure Database
ppm	parts per million
RBC	red blood cells
RED	re-registration eligibility decision
REI	restricted reentry interval
RfD	reference dose
SERA	Syracuse Environmental Research Associates
SLN	Special Local Needs
TEP	typical end-use product
T.G.I.A.	Technical grade active ingredient
TIPA	Triisopropanolamine
TRED	Tolerance Reassessment Eligibility Decision
UF	uncertainty factor
U.S.	United States
USDA	U.S. Department of Agriculture
U.S. EPA	U.S. Environmental Protection Agency
USGS	U.S. Geological Survey
WHO	World Health Organization

COMMON UNIT CONVERSIONS AND ABBREVIATIONS

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

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

CONVERSION OF SCIENTIFIC NOTATION

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

EXECUTIVE SUMMARY

General Considerations

Emamectin benzoate is used for control of the emerald ash borer (*Agrilus planipennis* Fairmaire, commonly abbreviated as EAB), an insect pest of ash trees (*Fraxinus spp.*). This document provides human health and ecological risk assessments to support an assessment of the environmental consequences of using this pesticide in Forest Service programs. Emamectin benzoate is an insecticide that acts by adversely affecting the nervous system. This insecticide is registered for national use on a variety of agricultural commodities. The anticipated uses of emamectin benzoate in Forest Service programs is limited to one formulation of emamectin benzoate, Tree-äge, and one application method, tree injection. Relatively little information is available on the transport of emamectin benzoate in trees following tree injection and uncertainties with the movement of emamectin benzoate in ash trees following tree injection is a dominant factor in the current Forest Service risk assessment in terms of adequately assessing exposures to humans and other nontarget species.

Human Health

In terms of potential human health effects, the most plausible exposure scenarios are those for workers applying emamectin benzoate in a manner that is consistent with labeled directions including the proper use of chemical resistant gloves. If workers handle emamectin benzoate with care and effectively use chemical resistant gloves, no substantial or significant risks to workers are anticipated. If workers fail to effectively use chemical resistant gloves or if workers do not effectively and rapidly respond to accidental exposures, adverse effects in workers, possibly including degenerative changes in nerve tissue, could occur.

Substantial exposures to members of the general public do not appear to be plausible although quantitative estimates of expected exposures and hence quantitative estimates of risks cannot be developed at this time. Based on accidental exposure scenarios associated with the spill of emamectin benzoate into a pond, the central estimates of hazard quotients are below the level of concern (HQ=1). The upper bound estimates of the hazard quotients range from 0.6 to 3. The inability to estimate exposures to members of the general public associated with the normal and expected use of emamectin benzoate – i.e., injection into ash trees – is a serious limitation in this risk assessment. Nonetheless, the upper bound HQ for all of the accidental exposure scenarios is only 3. Thus, in the normal use of emamectin benzoate, about one-third of the emamectin benzoate that is injected into an ash tree would need to be transported to surface water in order for the HQs associated with non-accidental exposures to reach a level of concern. It does not seem reasonable to assert that this level of exposure would or could occur.

Ecological Effects

As with the human health risk assessment, the ecological risk assessment for emamectin benzoate is dominated by uncertainties in the exposure assessment. Because of limited information on the transport of emamectin benzoate in trees following tree injection and the lack of information on the transport of emamectin benzoate in ash trees, reliable estimates of exposures in nontarget species associated with the injection of emamectin

benzoate into ash trees cannot be made. The inability to estimate expected exposures of nontarget species limits confidence in the risk characterization for nontarget species.

Uncertainties in the exposure assessments associated with the potential contamination of surface water in the normal use of emamectin benzoate for the injection of ash trees is addressed with an accidental spill scenario. Based on the accidental spill scenario, no risks are apparent for mammals, birds, fish, aquatic plants, or tolerant species of aquatic invertebrates. The lack of risk in the accidental spill scenarios for these groups of organisms suggests that the contamination of surface water associated with the normal use of emamectin benzoate to inject ash trees is not likely to adversely impact these organisms. Risks to sensitive species of aquatic invertebrates, however, are apparent in the accidental spill scenario with an upper bound HQ of 120. Thus, in the event of an accidental spill of a significant amount of emamectin benzoate into a pond, adverse effects including mortality could be anticipated. The high hazard quotients for sensitive species of aquatic invertebrates associated with the accidental spill scenario also prevent a clear risk characterization for this group of organisms in the normal use of emamectin benzoate. At least in situations in which high doses of emamectin benzoate are used or a relatively large number of trees are treated near surface water, risks to sensitive species of aquatic invertebrates can neither be discounted nor characterized clearly.

While uncertainties associated with contaminated surface water can be addressed reasonably well, other exposure pathways are problematic. The most likely exposures for mammals or birds involve the consumption of bark, stem tissue, or seeds of ash trees as well as the consumption of herbivorous insects that may feed on ash leaves. Only the pathway involving the consumption of herbivorous insects is developed quantitatively. Under worst-case exposure assumptions, risks to mammals are marginal (an upper bound HQ of 1.1) and risks to birds are negligible (an upper bound HQ of 0.03). For herbivorous insects, however, the risk characterization is well-defined. Both tolerant and sensitive species or populations of herbivorous insects are likely to be adversely affected if they feed on ash trees injected with effective doses of emamectin benzoate.

While the risk characterization for emamectin benzoate is dominated by uncertainties in the exposure assessments, it is worth noting that the most relevant toxicity studies on aquatic organisms and birds are limited to relatively standard bioassays on relatively few species of organisms compared to other more fully studied pesticides. In addition, no data are available on reptiles, amphibians, or soil invertebrates.

1. INTRODUCTION

1.1. Chemical Specific Information

Emamectin benzoate is used in Forest Service programs to control the emerald ash borer (*Agrilus planipennis* Fairmaire, commonly abbreviated as EAB), an insect pest of ash trees (*Fraxinus spp.*) (Herms et al. 2009). This document provides human health and ecological risk assessments to support an assessment of the environmental consequences of using this pesticide in Forest Service programs.

U.S. EPA/OPP has designated emamectin benzoate a Reduced Risk pesticide (http://www.epa.gov/pesticides/health/reducing.htm; Fishel 2009). In addition, the EPA conducted human health risk assessments on emamectin benzoate (EPA/OPP 1991a; 2008a) which are used to set pesticide tolerances for its agricultural uses as well as its injection into ornamental (non-fruit bearing) trees. The EPA also conducted ecological risk assessments relating to the use of emamectin benzoate on tree nuts, including pistachios (U.S. EPA/OPP 2008b); however, these use patterns do not involve tree injection.

Syngenta, the registrant for emamectin benzoate, has submitted rationales for classifying emamectin benzoate as a reduced risk pesticide to the U.S. EPA (Bray et al. 1999; Grosso 1995). Syngenta has also conducted reviews on the potential human health effects (Gerson 1993f; Neal 1995; Tisdel 2006f), ecological effects (O'Grodnick 1995d; Overmyer and Cox 2009; Overymyer 2009), and environmental fate (O'Grodnick 1995c) of emamectin benzoate.

Emamectin benzoate is not included in the U.S. EPA IRIS database (http://www.epa.gov/iriswebp/iris/subst/index.html), WHO INCHEM series (http://www.inchem.org/), the EXtension TOXicology NETwork series (http://extoxnet.orst.edu/), or the USDA/ARS Pesticide Properties Database (http://www.ars.usda.gov/Services/docs.htm?docid=14199). USGS (2003a) provides information on the agricultural use of emamectin benzoate; however, monitoring data are not included in the USGS (2003b) National Water Quality Assessment Program. The published literature on emamectin benzoate was identified using TOXLINE (http://toxnet.nlm.nih.gov/) and AGRICOLA (http://agricola.nal.usda.gov/), and ECOTOX (U.S. EPA/ORD 2010). Additional information on emamectin benzoate was identified through standard Internet search engines and databases (e.g., HSDB 2010; PAN 2010). As summarized in Section 5 (References), the open literature on emamectin benzoate is relatively modest but does contain information relevant to the current Forest Service risk assessment.

Emamectin benzoate has both forestry and agricultural uses. Although efficacy studies on agricultural uses (e.g., Cook et al. 2004; Fanigliulo and Sacchetti 2008; Fife et al. 1998) are peripheral to this Forest Service risk assessment, efficacy studies on forestry applications are considered (e.g., Grosman and Upton 2006; Grosman et al. 2009; Grosman et al. 2010) along with information on the development of resistance in insects

(Ahmad et al. 2002; Waldstein and Reissig 2000). Although studies regarding toxicity to target insects (e.g., Adamczyk et al. 1999; Argentine et al. 2002; Ioriatti et al. 2009; Mascarenhas et al. 1998) are noted in the risk assessment, greater emphasis is placed on toxicity studies concerning nontarget insects (Boyd and Boethel 1998; Chukwudebe et al. 1997; Hewa-Kapuge et al. 2003). Several other published studies involve relatively standard bioassays on nontarget species or studies on environmental fate, some of which appear to be publications of registrant-submitted studies (e.g., Chukwudebe et al. 1998; O'Grodnick et al. 1998; Mushtaq et al. 1996; O'Grodnick et al. 1998; Wrzesinski et al. 1998).

As discussed in Section 3.1 (Hazard Identification for the Human Health Risk Assessment), published studies are available on the pharmacokinetics (Mushtaq et al. 1996) and neurotoxicity (Wise et al. 1997) of emamectin benzoate, and there is one case report of a human poisoning (Yen and Lin 2004). Much of the information most relevant to the human health risk assessment comes from registrant-submitted studies.

In the preparation of this risk assessment, a Freedom of Information Act (FOIA) request, HQ-FOI-00787-10, was submitted to the U.S. EPA for a complete bibliography of all of the studies submitted in support of the registration of emamectin benzoate. As listed in Appendix 1, 402 submissions were identified in the FOIA to the U.S. EPA. In Appendix 1, these submissions are organized by *Guideline Number*. Here, the term *Guideline Number* refers to the type of study required by the U.S. EPA for pesticide registration. The study guidelines relevant to emamectin benzoate are summarized in Table 1.

As indicated in Table 1, the studies submitted to the U.S. EPA in support of the registration of emamectin benzoate include toxicity studies in mammals and ecological receptors, which are highly relevant to the current Forest Service risk assessment. These studies are typically classified as *Confidential Business Information* (CBI) and are not usually released or available to individuals outside of the U.S. EPA Office of Pesticides (U.S. EPA/OPP). In the preparation of this risk assessment, cleared reviews of registrant-submitted studies were obtained from the U.S. EPA/OPP through a FOIA request.

Emamectin benzoate is also used to treat sea lice in farmed Atlantic salmon (Armstrong et al. 2000; Ramstad et al. 2002). While this use is not directly germane to the current Forest Service risk assessment, several studies relating to this use are covered because the information is more generally relevant to the potential effects of emamectin benzoate on salmonids as well as some species of nontarget invertebrates.

1.2. General Information

This document has four chapters, including the introduction, program description, risk assessment for human health effects, and risk assessment for ecological effects or effects on wildlife species. Each of the two risk assessment chapters has four major sections, including an identification of the hazards, 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 and it addresses some specialized technical areas. Nevertheless an effort was made to ensure that the document can be understood by individuals who do not have specialized training in the chemical and biological sciences. Certain technical concepts, methods, and terms common to all parts of the risk assessment are described in plain language in a separate document (SERA 2007a). 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. 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 a review of the risk analyses.

As noted in Section 1.1, much of the most relevant information on the toxicity and environmental fate of emamectin benzoate is taken from studies submitted by the registrant to the U.S. EPA/OPP in support of its registration. The Forest Service is aware of and is sensitive to concerns about risk assessments based chiefly on registrant-submitted studies. 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 concern is largely unfounded. Although any study (published or unpublished) can be falsified, concerns with the design, conduct, and reporting of studies submitted to the U.S. EPA for pesticide registration are minor. Studies submitted for pesticide registration are designed in accordance with guidelines regarding the manner in which the studies are conducted and reported. These guidelines are developed by the U.S. EPA and not by the registrants. Full copies of the guidelines for these studies are available at http://www.epa.gov/opptsfrs/home/guidelin.htm. All studies are conducted under Good Laboratory Practices (GLPs). GLPs are elaborate sets of procedures that involve documentation and independent quality control and quality assurance, which substantially exceed the levels typically seen in open literature publications. Furthermore, the EPA reviews each of the submitted studies for adherence to the relevant study guidelines. These reviews most often take the form of Data Evaluation Records (DERs). While the nature and complexity of DERs will vary with the nature and complexity of the differing studies, each DER involves an independent assessment of the study to ensure that the EPA Guidelines are followed. In addition, each DER undergoes internal review within the EPA (and sometimes several layers of internal review).

As with all Forest Service risk assessments, the risk estimates in this document are almost never presented as a single number. 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 and are included in the body of the document.

Some of the calculations, however, are cumbersome. For those calculations, an EXCEL workbook (sets of EXCEL worksheets) is included as an attachment to this risk assessment. The worksheets provide the detail for the estimates cited in the body of the document. Documentation for the use of this workbook is presented in SERA (2009a).

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

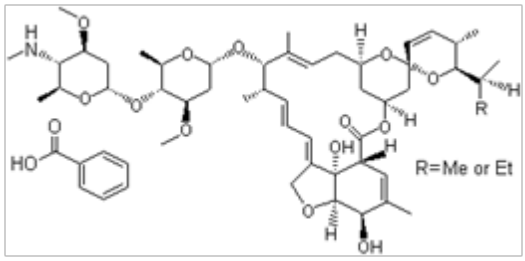
2. PROGRAMS DESCRIPTION

2.1. Overview

Emamectin benzoate is an insecticide which acts by causing insect paralysis. This insecticide is registered for national use on a variety of agricultural commodities. Only one forestry use, the control of the emerald ash borer, is currently registered, and this registration is limited to one formulation, Tree-äge. Tree-äge is applied only by tree injection. As indicated in Figure 2, Tree-äge is currently registered in only 24 states. Geographically, the uses of emamectin benzoate in forestry and agriculture do not overlap. Relatively little information is available on the transport of emamectin benzoate in trees following tree injection, and uncertainties with the movement of emamectin benzoate in ash trees following tree injection is a dominant factor in the current Forest Service risk assessment in terms of adequately assessing exposures to humans and other nontarget species.

2.2. Chemical Description and Commercial Formulations

Emamectin benzoate is a mixture of the benzoic acid salt of two structurally complex heterocyclic compounds.



Emamectin benzoate, which is classified as a second generation avermectin insecticide, is a derivative of abamectin. It differs from abamectin by the amino substituent in the terminal disaccharide unit (i.e., the amino group at the upper left of the above structure). As summarized in Appendix 1, details of the product chemistry (Guideline 61-1) and manufacturing process (Guideline 61-2) have been submitted to the U.S. EPA/OPP. This information is considered proprietary and is not available to the general public and this information has not been available in the conduct of the current Forest Service risk assessment.

Table 2 provides an overview of the chemical and physical properties of emamectin benzoate. Some of the chemical nomenclature for emamectin benzoate is complex (e.g., Lasota and Dybas 1991). This Forest Service risk assessment adopts the relatively simple nomenclature used by U.S. EPA/OPP (2008a)—i.e., a 9:1 mixture of the benzoic acid salts of 4'-epi-methylamino-4'-deoxyavermectin B1a and 4'-epi-methylamino-4'-deoxyavermectin B1b. As illustrated in Figure 1 as well as the above structure, the difference between the avermectin B1a and avermectin B1b is that the B1a compound has an ethyl group in the moiety labeled R and the B1b compound has a methyl group.

Emamectin benzoate was developed as a pesticide by Merck and Company and was first marketed in 1997 in Israel and Japan (Tomlin 2004). According to the U.S. EPA/OPP record of pesticide labels (http://www.epa.gov/pesticides/ pestlabels/index.htm), emamectin benzoate was first registered in the United States in 1999.

Table 3 summarizes the currently registered formulations. The only formulation with a forestry application appears to be Tree-äge, a 4% (w/w) formulation of emamectin benzoate. A general label for Tree-äge is available from Arborjet (http://www.arborjet.com/products/injectables.htm). Tree-äge, however, is not currently registered in all states. Based on information from the Arborjet web site (http://www.arborjet.com/products/labels-and-msds/), the states with registrations for Tree-äge, current as of 6/4/2010, are illustrated in Figure 2. The states in which Tree-äge is registered encompasses a large proportion of Forest Service Region 9 (the Eastern Region), the northeast section of Region 8 (the Southern Region), as well as some states included in Forest Service Region 1 (Northern Region), Region 2 (Rocky Mountain Region), and Region 4 (Intermountain Region).

The other two formulations of emamectin benzoate, Denim and Proclaim, appear to have only agricultural uses; accordingly, these formulations are not addressed in detail in the current Forest Service risk assessment.

All formulations appear to consist of emamectin benzoate in petroleum distillates. As summarized in Table 1 and detailed in Appendix 1, information on the other ingredients in emamectin benzoate formulations have been disclosed to the U.S. EPA—i.e., Guidelines 61-1, 61-2, 61-3, 830.1550, 830.1600, 830.1620, 830.1650, and 830.1670.

The identity of the other ingredients (formerly referred to as *inerts*) in the emamectin benzoate formulations are considered proprietary information; therefore, the manufacturer does not identify the other ingredients on the general or supplemental product labels or material safety data sheets. The potential significance of the other ingredients in emamectin benzoate formulations can be inferred based on differences in the toxicity of the formulations and technical grade emamectin benzoate, as discussed further in Section 3.1.14. The potential impact of impurities in technical grade emamectin benzoate is discussed in Section 3.1.15.

In a recent human health risk assessment, the U.S. EPA/OPP discusses a material referenced as *Emamectin Benzoate Technical II* (U.S. EPA/OPP 2008a, p. 39). The EPA raises concern for this material because of submitted acute toxicity data indicating that this material is more toxic than other samples of emamectin benzoate. The language in the EPA summary quoted below is not clear:

> *A recent submission of acute toxicity six-pack tests performed on a new technical product (Emamectin Benzoate Technical II, EPA Reg. No. 100-1207), resulted in new toxicity category assignments. Specifically, the toxicity category for inhalation changed from Category IV to Category II. Relevant to the REI* (Restricted Reentry Interval), *the eye irritation study changed from Category I to Category III. HED has concern for the possibility that a change in manufacturers and technical registrations can result in a different acute toxicity outcome, while the technical compound*

> *itself has not changed. Detailed confirmational information needs to be submitted describing the reasons (e.g., differences in labs or test methodology) that could account for the difference in acute toxicity study results prior to consideration for appropriateness of REI reduction.*
>
> U.S. EPA/OPP 2008a, p. 39

Although the quotation refers to the new material as *Emamectin Benzoate Technical II*, it seems to suggest that Technical II is actually a new formulation —i.e., *the technical compound itself has not changed*. It is also worth noting that the EPA registration number cited above appears to be incorrect. Based on information from the EPA label system (http://oaspub.epa.gov/pestlabl), EPA registration number 100-1207 is assigned to technical grade atrazine.

2.3. Application Methods

The only labeled application method for Tree-äge is tree injection. Tree injections are made with special equipment such as the Arborjet Tree Injection Delivery Systems (http://www.arborjet.com/products/devices.htm), which consist of an injection device, sometimes referred as a Tree IV or QUIK-jet injector in which the pesticide formulation is injected into the tree under pressure. As discussed further in Section 2.4, the pesticide is injected into a number of locations in the tree, depending on its size. For each injection, a hole is drilled through the bark and into the xylem to a xylem depth of about 5/8". Once the hole is drilled, plugs that hold injection lines are fixed into the holes. Injector needles are then placed into the plugs and the delivery device is used to infuse the insecticide into the tree.

Tree-äge applications are typically made only once per year. Treatments are made about 2-3 weeks prior to when emerald ash borer infestations are anticipated. In most states where Tree-äge is registered, the applications are made from early May to mid-June (Herms et al. 2009). The aim of tree injection is to generate emamectin benzoate concentrations lethal to emerald ash borer larvae in the cambium and phloem of the host tree where the larvae burrow and consume the cambium and phloem.

Relatively little information is available on the transport of emamectin benzoate in trees following tree injection. As discussed further in the exposure assessments for human health effects (Section 3.2) as well as ecological effects (Section 4.2), the lack of information on the movement of emamectin benzoate in ash trees following injection imposes limitations on the exposure assessments. Consequently, the limited information that is available is considered in some detail.

The Forest Service risk assessments conducted on imidacloprid (SERA 2005) and dinotefuran (SERA 2009b) involve applications by tree injection. Since there is only limited information about the kinetics involved in the transport of dinotefuran in trees treated by injection, as is the case with emamectin benzoate, imidacloprid data were used by analogy to crudely characterize the transport of dinotefuran in trees treated by injection. This approach is justified by the similarities of the chemical and physical

properties of dinotefuran and imidacloprid, based on a classification scheme developed by Bromilow et al. (1990).

The classification scheme developed by Bromilow et al. (1990) relates translocation characteristics in xylem (i.e., upward transport to leaves) and phloem (i.e., downward transport from leaves) to the pK_a and K_{ow} values for pesticides. As illustrated in Figure 3, the pK_a and K_{ow} values for dinotefuran and imidacloprid are reasonably similar, suggesting that both pesticides will be xylem mobile—i.e., they will be transported from the injection site to the leaves. As summarized in Table 2 and illustrated in Figure 3, however, the K_{ow} for emamectin benzoate is much greater than that for either dinotefuran or imidacloprid. According to the classification system developed by Bromilow et al. (1990), emamectin benzoate would not be very mobile in xylem or phloem.

The comparisons of emamectin benzoate to imidacloprid and dinotefuran are not intended to suggest that Tree-äge or other formulations of emamectin benzoate are ineffective as insecticides when applied by tree injection. Nonetheless, given the dissimilarity in physical and chemical properties of emamectin benzoate relative to imidacloprid and dinotefuran, information regarding the transport of imidacloprid in trees following tree injection cannot be used as a surrogate to estimate the transport of emamectin benzoate in trees following tree injection.

Speculatively, the efficacy of emamectin benzoate as an injectable insecticide appears to depend mostly on the other ingredients in the formulations. This speculation, however, is supported by the studies of Takai et al. (2001, 2003, and 2004), which provide the only direct information on the movement of emamectin benzoate in trees following tree injection, which is central to many aspects of the exposure assessments in the current Forest Service risk assessment. Accordingly, these studies are examined in some detail.

The Takai et al. (2001, 2003, and 2004) studies involve a formulation of emamectin benzoate developed to protect Japanese pine trees from pine wilt disease caused by the pine wood nematode, *Bursaphelenchus xylophilus*. The formulation, referred to in the publications as the Shot Wan Liquid Formulation (SWLF), consisted of emamectin benzoate, a commercial solubilizer (Sorpol SM-I00PM), a solvent (diethylene glycol monobutyl ether), and water (Takai et al. 2003). While various concentrations of emamectin benzoate were tested, the final formulation used in tree injection studies contained emamectin benzoate at a concentration of 40 g/L (≈4%). As indicated in Table 3 of the current Forest Service risk assessment, Tree-äge also contains emamectin benzoate at a concentration of 4%, although the other ingredients in Tree-äge appear to be different from those used in the studies by Takai et al. (2001, 2003, and 2004). Following tree injection at nominal doses of 10 g a.i./m^3 of tree mass, concentrations of emamectin benzoate in twigs from the pine trees reached levels of about 0.08-2.09 µg/g dry weight by 3 months after injection, and no substantial decreases in concentration were observed for a 27-month post-injection period (Takai et al. 2004, Figure 4, p. 46)—i.e., the concentrations at 27 months were 0.04-1.91 µg/g. In addition, no emamectin benzoate was detected in the tree roots or in soil surrounding the treated trees.

Furthermore, the concentrations in leaves falling from the treated trees ranged from 0.011 to 0.025 µg/g (Takai et al. 2004, p. 47).

In terms of transport within the tree, the difference between the nominal dose and monitored concentrations of emamectin benzoate in pine trees seems noteworthy. The nominal dose of 10 g a.i./m^3 of tree is equivalent to 0.01 mg/cm^3 [10 g = 10,000 mg; 1 m^3 = 1,000,000 cm^3]. Takai et al. (2004) do not report the density of the pine trees used in the study. Based on data from RPBC (2003), the density of pine is highly variable depending of the age and state of the tree, ranging from about 325 to about 525 kg/m^3, based on oven dry weights. The pine trees used in the study by Takai et al. (2004) were 6 years old. Data on the density of 6-year-old pine trees have not been located. Extrapolating the density values given in RPBC (2003) for 10-year-old pine, an upper bound density of 350 kg/ m^3, equivalent to 0.35 g/cm^3, is used as an approximation of the density of the pine in the study by Takai et al. (2004). Using this density and assuming uniform distribution within the tree, a dose of 0.01 mg/cm^3 would be expected to result in residues of about 0.029 mg/g dry weight [0.01 mg/cm^3 ÷ 0.35 g/cm^3] or about 29 µg/g dry weight.

Takai et al. (2004, Figure 5, p. 46) provide concentrations of emamectin benzoate in sapwood at distances of 2-8 meters above the injection point. At 5 months after injection, the average concentrations of emamectin benzoate in sapwood were 1.78, 1.88, 0.60 and 0.15 µg/g at 2, 4, 6, and 8 meters above the injection point. No data are provided on the concentration of emamectin benzoate at the injection point. These concentrations are below the estimated nominal concentration of about 29 µg/g by factors of about 15 to 193 [29 µg/g ÷ 0.15 µg/g to 1.88 µg/g ≈ 15.43 to 193.33].

In considering the difference between the nominal and measured concentrations, the distinction between sapwood and heartwood is important. Takai et al. (2004) report concentrations of emamectin benzoate only in sapwood – i.e., the viable tissue in the tree into which emamectin benzoate is injected and transported. Concentrations in the heartwood – i.e., the inner section of the tree trunk that does not contain viable tissue – would be expected to be negligible because it is not likely that significant amounts of emamectin benzoate would diffuse into the heartwood. Nonetheless, the nominal dose of 10 g a.i./m^3 of tree reported by Takai et al. (2004) appears to be similar to estimates which assume uniform distribution throughout the total tree volume – i.e., including both heartwood and sapwood. Given that no emamectin benzoate was monitored in soil or in tree roots by Takai et al. (2004), the discrepancy between the monitored concentrations in sapwood and the nominal dose to the tree based on the volume of both sapwood and heartwood suggest that most the emamectin benzoate may have remained close to the injection point.

The relevance of the studies by Takai et al. (2001, 2003, and 2004) to the current Forest Service risk assessment may be questionable. These investigators used a different formulation from that considered in the current Forest Service risk assessment and involve species of pine rather than ash. On the other hand, they are the only available studies concerned with the movement of emamectin benzoate in trees following tree

injection. As discussed further in Section 3.2.3.4, the failure of Takai et al. (2004) to note any substantial loss of emamectin benzoate from pine following tree injection influences the interpretation of potential exposures to emamectin benzoate in surface water. While formal exposure assessments are not developed for the consumption of contaminated vegetation (Section 3.2.3.6), some atypical oral exposures are considered, and the very low concentrations of emamectin benzoate in leaves noted by Takai et al. (2004) has an impact on the interpretation of these exposure scenarios (Section 3.4.3.2).

2.4. Mixing and Application Rates

The term application rate is only marginally relevant for tree injections with Tree-äge. A more meaningful term for application is *dose per tree*. As discussed above, the Tree-äge formulation is injected into the tree. As specified on the Special Local Need (SLN) labels for Tree-äge, the number of injections and the volume of the injections vary according to the size of the tree and the level of treatment (i.e., low, medium, or high) deemed appropriate for a specific area. As summarized in Table 3, the specific doses may range from about 630 to 46,000 mg a.i./tree, and the formulation is diluted with about 1-3 parts water.

A more detailed summary of application rates is given in Table 4 and illustrated in Figure 4. Table 4 is adopted from an application rate table in the product label for Tree-äge from the Arborjet website (http://www.arborjet.com/products/injectables.htm). The application rate table on the product label specifies different application rates based on the diameter of the tree at breast height (DBH) in units of inches. The values on the product label are given as ranges. For example, the first range given is a DBH of 4 to 6 inches. As a simplification and for the sake of plotting doses, the first column in Table 4 of the current Forest Service risk assessment gives the midpoint of the range of DBH values from the product label. The product label specifies four categories of doses: low, medium, medium high, and high. For simplification, Table 4 and Figure 4 include only the low, medium, and high doses. The product label specifies the doses only in units of mL of formulation per tree. Table 4 also includes the doses in units of mg a.i./tree. The conversion of mL per tree to mg a.i./tree is based on the density of Tree-äge (i.e., 1.04 g/mL as specified on the MSDS for Tree-äge) and the content of emamectin benzoate in Tree-äge (i.e., 4% w/w).

As illustrated in Figure 4, the doses are roughly but not consistently linear. The doses specified on the product label for trees with a DBH of 16-18 inches (plotted as 17 inches in Figure 3) appear to be somewhat a variance with the generally linear relationship between DBH and dose. It is not clear if this deviation is intentional or an error in the product label. The Special Local Needs labels for Tree-äge for Indiana, Missouri, and Wisconsin contain the same discontinuity for trees with a DBH of 16-18 inches.

This type of dosing, as opposed to broadcast application, somewhat complicates the exposure assessment. Typically, risk assessments conducted for the USDA Forest Service express application rates in units of lbs a.i./acre. These application rates are then used in the risk assessment to estimate exposure levels for workers (Section 3.2.2), members of the general public (Section 3.2.3), as well as various groups of non-target species (Section 4.2). An application rate expressed in units of lbs a.i./acre is a

particularly significant and, in some respects, a controlling parameter as input for environmental fate models to estimate pesticide concentrations in ambient water (Section 3.2.3.4). As discussed above, Tree-äge is applied only by tree injection, an application which is not amenable to simple assessments of application rates expressed in units of lbs a.i./acre. Thus, the exposure assessments for tree injections of emamectin benzoate (Section 3.2 for humans and Section 4.2 for other nontarget species) differ substantially from exposure assessments for broadcast applications of pesticides.

2.5. Use Statistics

Most Forest Service risk assessments attempt to characterize the use of a pesticide in Forest Service programs relative to the use of the herbicide or other pesticide in agricultural applications. The information on Forest Service use is typically taken from Forest Service pesticide use reports (http://www.fs.fed.us/foresthealth/pesticide/reports.shtml), and information on agricultural use is typically taken from use statistics compiled by the U.S. Geologic Survey (http://ca.water.usgs.gov/pnsp/ pesticide_use_maps/) and/or detailed pesticide use statistics compiled by the state of California (http://www.calepa.ca.gov/).
The Forest Service use statistics available to the public only cover the years up to 2004. As of 2004, emamectin benzoate uses are not reported by the Forest Service. As illustrated in Figure 2, Special Local Needs labels are available for Tree-äge in several states in Forest Service Region 9 and in the northern most states (i.e., Kentucky and Virginia) of Forest Service Region 8. Thus, it is seems reasonable to suggest that the use of emamectin benzoate in Forest Service programs will be limited to the states for which Special Local Needs labels have been issued. If the infestation range of the emerald ash borer expands, it also seems reasonable to suggest that the States in which emamectin benzoate has Special Local Needs labels will also expand.

The USGS (2003a) does provide information on the agricultural uses of emamectin benzoate. As illustrated in Figure 5, about 1950 lbs a.i. of emamectin benzoate was used in agricultural applications in 2002. Comparing Figure 2 with Figure 5, it is apparent that the agricultural uses of emamectin benzoate do not overlap with the area in which emamectin benzoate is used for the control of the emerald ash borer. Most of the agricultural uses of emamectin benzoate occur in Texas, California, and the western section of Tennessee. More specific use patterns are available for California (CDPR 2008). In 2007, the most recent year for which statistics are available, approximately 1862 pounds of emamectin benzoate were used in California (CDPR 2008, pp. 155-156). All of these uses appear to be agricultural, and no forestry uses are reported, which is consistent with the product labels for the agricultural formulations of emamectin benzoate (Table 3). Note that the amount used in California in 2007 is greater than the national use of emamectin benzoate in 2002 reported by the USGS (2003a). Thus, it appears that the total amount of emamectin benzoate used nationally in agriculture increased substantially between 2002 and 2007.

Because the regions in which emamectin benzoate is used for forestry do not overlap with the regions in which emamectin benzoate is used in agriculture, forestry uses of emamectin benzoate could potentially be a principal source of emamectin benzoate in environmental media (i.e., soil and water). The potential significance of the localized use

of emamectin benzoate in forestry applications is considered further in Section 3 (Human Health) and Section 4 (Ecological Effects) of the current Forest Service risk assessment.

2.6. Special Note on Data Limitations and the Treatment of Pine

This risk assessment specifically addresses the treatment of ash trees for the control of the emerald ash borer, which is the only currently registered forestry use of emamectin benzoate. Nonetheless, several studies have been conducted on the injection of emamectin benzoate into pine trees to control various pest insects, including the southern pine engraver beetle and various species of pine bark beetles (Grosman and Upton 2006; Grosman et al. 2009, 2010). Emamectin benzoate appears to be highly effective in these applications and the Forest Service has indicated that emamectin benzoate will be considered for the prevention of the damage to pine trees caused by certain species of beetles if these uses are approved by the U.S. EPA.

It is not clear whether Tree-äge or an alternate formulation of emamectin benzoate would be used in the injection of pine trees. For example, the recent efficacy study by Grosman et al. (2010) uses an unspecified experimental formulation of emamectin benzoate diluted with methanol. In addition, the dosing for pine trees could be different from that of ash trees. For example, in the recent study by Grosman et al. (2010), pine trees were injected at a rate of 200 mg a.i./inch DBH for trees less than 25 cm (≈9.8 inches) DBH and 400 mg a.i./inch DBH for trees greater than 25 cm DBH. Taking 300 mg/inch DBH as a typical dose for a pine tree with a DBH of about 10 inches, the dose per tree would be about 3000 mg a.i. As summarized in Table 4, the dose for a 26 cm (≈10.2 inch tree) ash is 5616 mg a.i. for the medium dose level and 16,848 mg a.i. at the high dose level.

The potential use of emamectin benzoate for pine tree injection is not explicitly covered in the current Forest Service risk assessment because it is not a currently registered use of the product and because of the uncertainties regarding the formulation and doses to be injected into pine trees. Nonetheless, the information in this document could be used to evaluate the use of emamectin benzoate for tree injection of pine, and the EXCEL workbook that accompanies this risk assessment (Attachment 1) could be modified to support the evaluation, as explained below.

As discussed in Section 3.2.2.1, general exposures to workers are based on the estimated amount of emamectin benzoate handled by a worker during a single day. This amount is calculated in Attachment 1, Worksheet A01, based on the assumption that each injection consists of 0.0034 lb a.i. and that 80 (40 to 160) injections are made in a single day by a worker. In any site-specific application of Attachment 1, the amount of emamectin benzoate injected per injection site and the number of injection sites made by a worker during a single day can be changed. Such changes would be appropriate regardless of the species of tree to be treated.

As discussed in Section 3.2.2.2, the estimated exposures in all of the accidental scenarios for workers depend on the concentration of emamectin benzoate in the formulation or dilution of the formulation to be applied. As indicated in Worksheet A01, the emamectin benzoate concentrations in the field solution is taken as 21.6 (10.8 to 43.2) mg/L. These values are based on the emamectin benzoate concentration in Tree-äge and the mixing

directions provided on the product label. If Tree-äge is not the formulation used for the injection of pine trees, the density of the formulation (in units of g/mL) in Cell C12 and the percent a.i. (w/w) of the formulation Cell C13 of Worksheet A01 would need to be modified. Note that these cells are used only to calculate the concentration of emamectin benzoate in the formulation in Cell C14 in units of mg/mL.

The other parameter that influences the emamectin benzoate concentration in the field solution—i.e., the concentrations used in the accidental exposure scenarios for workers—is the extent to which the formulation is diluted. As specified in Worksheet A01 of Attachment 1, the current Forest Service risk assessment uses dilution factors of 0.5 (0.25 to 1), which are based on the mixing directions on the Tree-äge label. These dilution factors might be different for an emamectin benzoate formulation developed for pine trees. In addition, it is likely that only a single dilution factor would be used in any project or program-specific application—i.e., the same proportion would be entered in Cells C16, C17, and C18. This change applies to the injection of any species of tree.

As discussed in Section 3.2.3, exposure scenarios used to derive HQs for members of the general public are limited to accidental spills of emamectin benzoate into a small pond. As detailed in Section 3.2.3.4, the exposure scenario developed in the current Forest Service risk assessment assumes that the amount of emamectin benzoate used to inject one large ash tree is spilled into a 20 million liter pond. This scenario is intended to parallel and encompass the exposure scenario developed by the EPA (U.S. EPA/OPP 2009a) and is not specific to the treatment of ash trees. Thus, unless there is a compelling reason to do otherwise, there may be no reason to modify the pond scenario when considering injections into pine trees. Nonetheless, if modifications appear to be appropriate, simply modify Worksheet A01 in the cells that specify the amount of emamectin benzoate that is spilled (Cells C24 to C26) as well as the volume of the pond in liters (Cell C27). These modifications will be reflected in accidental spill scenarios for the human health risk assessment (Worksheets D05, D08a, D08b, and D11) as well as the corresponding worksheets for the ecological risk assessment (F05a-e, F08, and G03).

As discussed in Section 4.2.3.2.1, the ecological risk assessment considers exposures to herbivorous insects consuming the leaves of treated ash trees under the assumption of both uniform distribution (Worksheet G07a) and restricted distribution to leaves (Worksheet G07b). There are serious reservations with these exposure scenarios because of the limited information available on the distribution of emamectin benzoate in trees following injection. As detailed in Section 4.2.3.2.1, the estimated concentrations in leaves of 3 (0.4 to 19) mg/kg based on the assumption of uniform distribution as well as the 10-fold lower concentrations based on the assumption of restricted distribution to leaves are all substantially higher than the concentrations of 0.011 to 0.025 mg/kg monitored in leaves of Japanese pine by Takai et al. (2004). Based on discussions with Forest Service personnel, studies on the distribution of emamectin benzoate should be available in the near future, and these studies are likely to include time-course data on emamectin benzoate concentrations in leaves. While somewhat speculative, it is likely that these studies will demonstrate lower and perhaps much lower emamectin benzoate concentrations in leaves than the values used in the current Forest Service risk

assessment. In any project-specific application involving the injection of hardwood or softwood trees, the results of studies on the distribution of emamectin benzoate in trees could be used in a modification to Worksheet G07a by changing the values in Cells C12 to C14. If these data are available, Worksheet G07b based on the assumption of restricted distribution to leaves will probably not be needed or appropriate and Worksheet G07b should probably be deleted.

The ecological risk assessment also considers the consumption of contaminated insects—i.e., insects that fed on a treated tree—by both a small mammal (Worksheet G14a) and a small bird (Worksheet G14b). As discussed in Section 4.2.2.3, these exposure scenarios are based on the toxicity of emamectin benzoate to insects rather than the concentrations of emamectin benzoate in leaves. Consequently, it should not be necessary to modify these exposure scenarios or the corresponding worksheets when considering the injection of pine trees with emamectin benzoate.

Lastly and as discussed in Section 4.2.2.3, the current Forest Service risk assessment does not develop exposure scenarios for mammals and birds that might consume the bark, stem tissue, or seeds of ash trees. These scenarios are not developed because no information is available on the movement and kinetics of emamectin benzoate in ash trees. If studies are developed that provide sufficient information on the distribution of emamectin benzoate in pine, consideration could be given to elaborating the exposures assessments for mammals and birds. This recommendation would also apply to the treatment of ash trees.

3. HUMAN HEALTH

3.1. HAZARD IDENTIFICATION

3.1.1. Overview

Most of the information used in the hazard identification in terms of potential human health effects comes from reviews of studies submitted to U.S. EPA/OPP in support of the registration of emamectin benzoate. Relatively little information is available in the open literature on the mammalian toxicology of emamectin benzoate. Emamectin benzoate is a semi-synthetic avermectin insecticide that interferes with the normal function of nerve cells. While emamectin benzoate is more toxic to invertebrates than to mammals, the underlying mechanism of action, binding to GABA receptors, is common to both groups of organism. Neurotoxicity is clearly the primary and critical effect—i.e., the effect occurring at the lowest dose—for emamectin benzoate.

Emamectin benzoate will cause signs of pathological changes in tissues of the nervous system, including neurodegenerative changes in the brain, spinal cord, peripheral nerves, and sensory nerves (i.e., the optic nerve). Gross toxicological signs of neurotoxicity (such as tremors and impaired or uncoordinated movements) tend to occur earlier and at lower doses than pathological changes in nervous system tissue. Other effects associated with exposures to emamectin benzoate include changes in body weight (in some cases weight gain and in other cases weight loss), reproductive effects, and possibly changes in immune function. While the data on emamectin benzoate are not as extensive as the data on many other insecticides, it appears that most if not all of the non-neurotoxic effects caused by emamectin benzoate are secondary to neurotoxicity.

Emamectin benzoate is a relatively large molecule (actually a mixture of four closely related molecules) which is not completely absorbed on oral administration, is poorly absorbed by the dermal administration, and rapidly eliminated in the feces with whole-body half-lives of about 1.5 days. Thus, emamectin benzoate will not substantially accumulate over periods of long-term dosing. While emamectin benzoate is not extensively metabolized in mammals, the limited information on the metabolites of emamectin benzoate suggests that metabolism does not result in the detoxification of emamectin benzoate. One plant metabolite of emamectin benzoate is somewhat more toxic than emamectin benzoate itself. As discussed further in the dose-response assessment, the U.S. EPA/OPP used a relatively short-term (14 day) toxicity study on the plant metabolite of emamectin benzoate as the basis for both the acute and chronic RfDs.

3.1.2. Mechanism of Action

Emamectin benzoate is a neurotoxin that interferes with the normal function of gamma-aminobutyric acid (GABA). GABA is one of several amino acids that act as neurotransmitters in both vertebrates and invertebrates. Specifically, GABA is the primary transmitter for fast inhibitory synaptic transmission (Olsen 2002). Emamectin benzoate, as well as other avermectins, binds to GABA receptors resulting in an increase in the permeability of the chloride ion in nerve and muscle membranes by opening chloride channels. There is no specific antidote for the action of emamectin benzoate on GABA receptors (Yen and Lin 2004).

As discussed further in Section 4.1.2.4, emamectin benzoate is over 600 times more toxic to bees than to the most sensitive mammalian species. The greater toxicity of emamectin benzoate to invertebrates, relative to mammals, is due apparently to the lesser affinity of emamectin benzoate to GABA receptors in mammals, relative to invertebrates, as well as the impermeability of emamectin benzoate in the mammalian blood-brain barrier. As noted in Section 2.2, emamectin benzoate differs from abamectin by an amino substituent on the terminal disaccharide. The major impact of this difference appears to be an increased toxicity of emamectin benzoate to many species of lepidopterans (Lasota and Dybas 1991). The data on lepidopterans are discussed further in Section 4.1.2.4.

Using the classification system developed by the Insecticide Resistance Action Committee (www.irac-online.org), emamectin benzoate is classified as a chloride channel activator, IRAC Group 6 (IRAC 2009). Other pesticides in this group include abamectin and milbemectin. In this respect, emamectin benzoate differs from both dinotefuran (SERA 2009a) and imidacloprid (SERA 2004), both of which are nicotinic acetylcholine receptor agonists which are also used in Forest Service programs to control insect pests.

The specific studies on the neurotoxicity of emamectin benzoate are discussed in Section 3.1.6. At the cellular level, emamectin benzoate causes degeneration of nerve axons in both the central nervous system and the peripheral nervous system. In some instances, nerve tissue degeneration leads to muscular degeneration. As detailed in Appendix 2, these effects have been noted in both acute and longer-term toxicity studies in mammals. Emamectin benzoate may also be specifically toxic to ocular nerves, causing degenerative changes in both optic nerve and retinal tissue. At the level of the whole animal, signs of neurotoxicity include dilation of the pupils (mydriasis), salivation, tremors, incoordination or ataxia, limb stiffness, weakness, and general decreases in activity. Nonspecific signs of toxicity, which are probably secondary to neurotoxicity, include decreased food consumption and decreased body weight gain.

3.1.3. Pharmacokinetics and Metabolism

Pharmacokinetics concerns the behavior of chemicals in the body, including their absorption, distribution, alteration (metabolism), and elimination as well as the rates at which these processes occur. The focus of this section of the risk assessment is the available information on the pharmacokinetic processes for emamectin benzoate, including a general discussion about metabolism (Section 3.1.3.1), with a focus on the kinetics of absorption (Section 3.1.3.2) and excretion (Section 3.1.3.3). Absorption kinetics, particularly the kinetics of dermal absorption, is important to this risk assessment because some of the included exposure assessments (Section 3.2) involve dermal exposure. Rates of excretion are generally used in Forest Service risk assessment to evaluate the likely body burdens associated with repeated exposure.

3.1.3.1. General Considerations

As summarized in the U.S. EPA/OPP (2008a) human health risk assessment on emamectin benzoate, a standard metabolism study in rats was submitted in support of the registration of emamectin benzoate (MRID 42851523). This registrant-submitted study appears to be published in the open literature (Mushtaq et al. 1996b). Because the open

literature study presents a much more detailed description of the metabolism study, the following discussion is taken largely from Mushtaq et al. (1996b). In this study, ^{14}C-labelled emamectin benzoate was administered both intravenously and orally at 0.5 mg/kg bw to groups of male and female rats. Additional groups of male and female rats were given a single high dose (20 mg/kg bw) by oral administration. Emamectin benzoate was rapidly cleared from plasma with half-lives ranging from about 15 to 28 hours after oral or intravenous dosing. Emamectin benzoate residues were widely distributed in the body with the highest concentrations in the lungs. Following high dose oral exposures, relatively high concentrations of emamectin benzoate residues were also noted in the gastrointestinal tract, suggesting limited oral absorption. Based on differences in the time-course of residues after intravenous and oral dosing, about 40-60% of the orally administered emamectin benzoate was absorbed. Although the nervous system is clearly the target of emamectin benzoate toxicity, residues in the brain and spinal cord were very low, relative to most other tissues. As discussed further in Section 3.1.3.3, emamectin benzoate and one N-demethylated metabolite were excreted almost exclusively in the feces, and very little parent or metabolite was found in the urine.

The only other metabolism study on emamectin benzoate is a relatively standard dietary study in lactating goats (Syintsskos and Mushtaq 1995; Mushtaq et al. 1997). Metabolism studies in lactating goats are designed to assess the potential for the contamination of milk in ruminants consuming food treated with pesticides. In this study, goats were administered ^{14}C-labeled and ^{3}H-labeled emamectin benzoate in the diet at a concentration of 10 ppm. The number of tissues assayed in this study was more limited than in the rat study and did not include lung tissue. Of the tissues assayed, the highest concentrations were found in the liver (≈1000 ppb) and kidney (≈500 ppb). As in the metabolism study in rats, emamectin benzoate was excreted almost completely in the in the feces with very low concentrations of emamectin benzoate found in the urine. Concentrations of emamectin benzoate in milk (12-56 ppb) were only modestly higher than concentrations found in the plasma (8-38 ppb).

3.1.3.2. Absorption

As noted above, the oral bioavailability of emamectin benzoate is about 40-60%, relative to intravenous administration (Mushtaq et al. 1996b). In the current Forest Service risk assessment as well as the U.S. EPA/OPP (2008a) risk assessment, all toxicity values are based on nominal oral doses under the assumption that bioavailability in humans will be comparable to that in other mammalian species. Thus, the oral bioavailability of emamectin benzoate does not have a direct impact the current risk assessment.

For dermal exposure scenarios, dermal absorption is estimated and compared to an estimated acceptable level of exposure based on oral toxicity studies in mammals. Thus, it is necessary to assess the consequences of dermal exposure relative to oral exposure and the extent to which emamectin benzoate is likely to be absorbed from the surface of the skin.

3.1.3.2.1. First-order Dermal Absorption

Wrzesinski et al. (1997) is the only available dermal absorption study of emamectin benzoate. This open literature study appears to be identical to the dermal absorption

study submitted to the U.S. EPA/OPP (2008a)—i.e., MRID 43850113. In this study, the excretion of radiolabelled emamectin benzoate by monkeys was assayed after both intravenous and dermal exposures. In the dermal phase of the study, the labeled emamectin benzoate was applied in a proprietary emulsifiable concentrate identical to that used in an agricultural formulation. While Wrzesinski et al. (1997) do not specify the formulation, this study was conducted at a Merck laboratory, and it seems likely that the dermal study used the concentrate from either Denim or Proclaim. Based on a comparison of the excretion rates in the intravenous and dermal phases of the study, the dermal absorption of emamectin benzoate was estimated at 1.6%. While not explicitly given as a dermal absorption rate constant, it is clear from the discussion as well as the data on excretion (Figures 2 and 3 in Wrzesinski et al. 1997) that the 1.6% represents the proportion that would be absorbed by a worker in a single day—i.e., a dermal absorption rate constant of 0.016 day^{-1}. The U.S. EPA/OPP (2008a) does not discuss this dermal absorption study in detail, and a DER for this study is not available in the cleared reviews. U.S. EPA/OPP (2008a), however, reports and uses a somewhat higher dermal absorption rate constant of 0.018 day^{-1}, corresponding to 0.00075 $hour^{-1}$.

In the absence of experimental data, Forest Service risk assessments generally adopt estimates of dermal absorption rate constants based on quantitative structure activity relationships (QSAR), as documented in SERA (2007a). Using these methods with a molecular weight of 886.1 g/mole for the B_{1a} component of emamectin benzoate and a K_{ow} (100,000), the estimated first-order dermal absorption rate constants are approximately 0.0000045 (0.000000057– 0.00036) $hour^{-1}$. The calculation of these rate constants is detailed in Worksheet B06 in the EXCEL workbooks that accompany this risk assessment. These estimated rates constants correspond to 0.00011 (0.0000014–0.0087) day^{-1}. It is worth noting that the central estimate of 0.00011 day^{-1} is lower than the experimental value of 0.018 day^{-1} used by U.S. EPA/OPP (2008a) by a factor of about 164 [$0.018\ day^{-1} \div 1.1x10^{-4}\ day^{-1} \approx 163.64$].

It is obvious that the algorithm typically used in Forest Service risk assessment is not appropriate for emamectin benzoate. This is probably due to the higher molecular weight of emamectin benzoate. The algorithm used in Forest Service risk assessments to estimate the first-order dermal absorption rate constant is based on an analysis of compounds with K_{ow} values ranging up to about 3,000,000 and molecular weights up to 400 g/mole. While the K_{ow} for emamectin benzoate is well below the upper bound of 3,000,000 used to develop the first-order algorithm, the molecular weight used for emamectin benzoate (886.1 g/mole) is more than 2 times greater than the upper bound molecular weight of 400 g/mole used to develop the first-order algorithm. In terms of using sufficiently protective estimates, the molecular weight is important because the estimated absorption rate decreases as the molecular weight increases.

To explore the potential impact of the molecular weight on the estimate of the first-order dermal absorption rate constant, the first-order algorithm was reapplied using the K_{ow} for emamectin benzoate with the upper bound molecular weight used to develop the algorithm (i.e., MW=400). This analysis is detailed in Worksheet B06-Alt in the EXCEL workbook that accompanies this risk assessment. Based on this reanalysis, the estimated

first-order dermal absorption rate constant is 0.0026 (0.00078-0.0083) $hour^{-1}$, which corresponds to 0.061 (0.019 – 0.20) day^{-1}. It is worth noting that these estimates are greater than the experimental first-order dermal absorption rate constant of 0.016 day^{-1} reported by Wrzesinski et al. (1997).

The most reasonable interpretation of this analysis is that the algorithm generally used in Forest Service risk assessments to estimate first-order dermal absorption is not applicable to emamectin benzoate because of its molecular weight which substantially exceeds that of the compounds used to the develop the first-order algorithm.

For the current Forest Service risk assessment, the central estimate of the first-order dermal absorption rate constant is taken as 0.018 day^{-1}, which is the same value used by U.S. EPA/OPP (2008a). In the EXCEL workbook, this rate constant is converted to 0.00075 $hour^{-1}$ [0.018 day^{-1} ÷ 24 h/day]. Wrzesinski et al. (1997) do not provide a standard deviation or other estimates of variability. Thus, in the EXCEL workbook that accompanies this risk assessment, the lower and upper bounds of the dermal absorption rate constant are identical to the central estimate. Uncertainties associated with this approach are discussed in the risk characterization (Section 3.4).

3.1.3.2.2. Zero-order Dermal Absorption

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

As also discussed in SERA(2007a), Forest Service risk assessments generally use a QSAR algorithm developed by the EPA (U.S. EPA1992, 2007), when experimental data are not available to estimate a dermal permeability coefficient (i.e., typically referred to as a K_p and expressed in units of cm/hour). Using the same inputs as for the first-order model (i.e., MW=886.1 g/mole and K_{ow} = 100,000), the QSAR algorithm developed by the EPA results in an estimated dermal permeability coefficient of 0.000023 (0.0000045-0.00011) cm/hour. These calculations are detailed in Worksheet B05 of the EXCEL workbook that accompanies this risk assessment. The EPA human health risk assessment on emamectin benzoate (U.S. EPA/OPP 2008a) does not use exposure scenarios involving zero-order absorption, and the EPA has not proposed a dermal permeability coefficient for emamectin benzoate.

The algorithm for estimating the dermal permeability coefficient developed by U.S. EPA is somewhat more robust than the first-order algorithm in that the algorithm for dermal permeability coefficients is based on compounds that span a wider range of molecular weights (from 30 to 700 g/mole) and K_{ow} values (from 0.006 to 3,160,000). While the range for the K_{ow} values encompasses the K_{ow} for emamectin benzoate (100,000), the molecular weight used in the algorithm for emamectin benzoate (886.1 g/mole) is somewhat greater than the upper bound of the molecular weights used to develop the

algorithm for dermal permeability coefficients. As with the algorithm for estimating the first-order dermal absorption rate constant, the high molecular weight of emamectin benzoate is a concern because the estimate of K_p decreases as the molecular weight increases.

As an exploratory measure to assess the impact of molecular weight on the estimates of the K_p, the algorithm from U.S. EPA (1992, 2007) was used with the K_{ow} for emamectin benzoate but with a molecular weight of 700 g/mole, which is the upper bound of the range of molecular weights on which the U.S. EPA algorithm is based. As detailed in Worksheet B05-Alt, the resulting estimate of the K_p is 0.00032 (0.000092-0.0011) cm/hr. Compared with the estimates based on a molecular weight of 886.1 g/mole, the estimates based on a molecular weight of 700 g/mole are higher by a factor of about 14, based on the central estimates [0.00032 cm/hr ÷ 0.000023 cm/hr ≈ 13.91] and a factor of 10, based on the upper bounds [0.0011 cm/hr ÷ 0.00011 cm/hr].

Given the underestimate of the first-order dermal absorption rate constant based on the standard algorithm for estimating these coefficients (Section 3.1.3.2.1), the current Forest Service risk assessment uses the higher K_p values of 0.00032 (0.000092-0.0011) cm/hr, based on the upper bound molecular weight of 700 g/mole.

3.1.3.3. Excretion

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

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

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

As noted in Section 3.1.3.1, the plasma half-lives in rats range from about 15 to 28 hours after oral or intravenous dosing (Mushtaq et al. 1996b). For estimates of body burden, whole body excretion half-lives are more relevant than plasma half-lives. Mushtaq et al. (1996b) do not provide an estimate of whole-body half-lives in rats but note that more than 90% of the administered dose was eliminated within 5 days of dosing (Mushtaq et al. 1996b, Figure 2). Under the assumption of first-order excretion, the first-order excretion rate (k_e) can be estimated from the proportion (P_t) excreted by time t—i.e., $k_e = -\ln(1-P_t)/t$. Taking 90% as the proportion excreted by Day 5, the excretion rate is estimated at about 0.46 day^{-1} [$-(\ln(1-0.9)/5 \text{ days} \approx 0.4605$], which corresponds to a whole-body half-life of about 1.5 days [$\ln(2)/k_e = \ln(2)/0.46\ day^{-1} \approx 1.5068$ days]. Wrzesinski et al. (1997) do not provide a formal kinetic analysis of the half-life of emamectin benzoate in monkeys, as discussed in Section 3.1.3.2,. Nonetheless, as in the rat study, most of the emamectin benzoate was eliminated in the feces after intravenous

dosing. Based on the a graphical summary of the excretion data (Figure 2 in Wrzesinski et al. 1997), about 50% of the emamectin benzoate was eliminated by about 2.5 days after dosing with an apparent lag time of about 1 day. The lag time of 1 day is probably associated with fecal transit time. There appear to be no data on whole-gut transit time in monkeys, but transit times for dogs and humans are about 0.5 and 1.6 days, respectively (Davies and Morris 1993, Table IV, p. 1095). Thus, the data regarding the excretion of emamectin benzoate in monkeys appear to be reasonably consistent with the data in rats—i.e., a half-time of about 1.5 days.

Taking 1.5 days as a reasonable approximation of the whole body half-life of emamectin benzoate, the whole body excretion rate constant is about 0.46 day^{-1} [$\ln(2)/1.5$ days $\approx$ 0.462 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 2.7 [$1 \div (1-e^{-0.46/day \times 1\ day} \approx 2.7121$]. Thus, consistent with the interpretation of the kinetics of emamectin benzoate offered by U.S. EPA/OPP (2008a, p. 25), the bioaccumulation potential of emamectin benzoate in mammals appears to be very low.

For emamectin benzoate, the low bioaccumulation potential in mammals is particularly important because U.S. EPA/OPP (2008a) bases both the acute and longer-term RfDs for emamectin benzoate on relatively short-term (i.e., 14 day) toxicity studies. The specific study used for the RfD is discussed Section 3.1.6 (Effects on Nervous System), and the derivations of the acute and chronic RfDs are detailed in the dose-response assessment (Section 3.3).

3.1.4. Acute Oral Toxicity

Studies on the acute oral toxicity of emamectin benzoate are summarized in Appendix 2, Table 1. As is true for other types of mammalian toxicity studies, the only information on the acute oral toxicity of emamectin benzoate comes from studies conducted as part of the registration process. Most of the acute oral toxicity studies summarized in Appendix 2 are taken from the EPA risk assessments (U.S. EPA/OPP 2008a, 2009). A DER is available on only one study, MRID 42743619 (Manson 1992e).

As summarized in Appendix 2 (Table 1), the reported acute oral LD_{50} values in rats range from >25 mg/kg bw (Manson 1992e) to 88 mg/kg bw (males in MRID 42743612). The study by Manson (1992e) is not a standard acute oral toxicity study because, although it involves a single oral gavage dose, as in standard acute oral toxicity studies, it is intended as an acute neurotoxicity study. In this study, no adverse effects were noted at 5 mg/kg bw, tremors were noted at 10 mg/kg bw, and neuronal lesions were noted 25 mg/kg bw.

U.S. EPA's Office of Pesticide Programs (U.S. EPA/OPP) classifies potential acute hazards, based on several standard tests, ranging from the most hazardous (Category I) to the least hazardous (Category IV). In the human health risk assessment (U.S. EPA/OPP 2008a), the EPA selected the LD_{50} of 53 mg/kg bw reported in both MRID 42851519 and MRID 47002104 to classify emamectin benzoate as Category II for acute oral toxicity. Based on the summary of these studies provided in U.S. EPA/OPP (2008a, p. 43), these two studies are distinct, with MRID 42851519 assaying emamectin benzoate technical and MRID 47002104 assaying emamectin benzoate technical II. As discussed in Section

2.2, emamectin benzoate technical II appears to be a distinct formulation of emamectin benzoate.

As also summarized in Appendix 2 (Table 1), mice appear to be more sensitive than rats to emamectin benzoate. The reported acute oral LD_{50} of emamectin benzoate is 22 mg/kg bw for males and 31 mg/kg bw for females (MRID 42743612). The greater sensitivity of mice, relative to rats, is also apparent in longer-term toxicity studies, as discussed in the following subsection. In mice, like in rats, the effects of emamectin benzoate are associated with neurotoxicity —i.e., incoordination and tremors.

3.1.5. Subchronic or Chronic Systemic Toxic Effects

As discussed in SERA (2007a, Section 3.1.5), *subchronic* and *chronic* are somewhat general terms that refer to studies involving repeated dosing. The distinction between subchronic and chronic studies, as these terms are commonly used in risk assessment, is somewhat vague and inconsistent. For rodents (i.e., mice and rats), chronic studies generally involve exposures over the lifetime, or at least a substantial proportion of the lifetime. Typical chronic studies with rodents involve 18-month exposure durations for mice and 2-years exposure durations for rats. Since the lifespan of dogs is much longer than that of rodents, lifetime exposure studies are generally not conducted with dogs. Instead, *chronic studies* with dogs generally involve repeated dosing for only about 1 year. By convention, the term *subchronic* typically refers to 90-day (about 13 weeks) studies with mammals. Shorter-term studies involving repeated dosing are sometimes conducted as range-finding studies to establish dose levels for longer-term studies.

The repeated dose studies for emamectin benzoate are summarized in Appendix 2. Table 4 of Appendix 2 summarizes the subchronic and range finding studies, and Table 5 of Appendix 2 summarizes the chronic toxicity studies. As discussed in Section 3.2 (Mechanism of Action), emamectin benzoate is a neurotoxin, and most of the effects noted in repeated dose studies involve neurotoxicity, as discussed below.

Subchronic and chronic toxicity studies were conducted in rats, mice, and dogs to support of the registration of emamectin benzoate. The open literature for emamectin benzoate does not include mammalian toxicity studies. Data Evaluation Records (DERs) are available for most of the repeated dose studies, which are identified by standard author/year citations in Appendix 2. DERs are not available for two studies (MRIDs 43868104 and 43868105), and summaries of these studies are taken from the most recent EPA human health risk assessment on emamectin benzoate (U.S. EPA/OPP 2008a).

Very few non-specific toxic effects—i.e., effects other than neurotoxicity—are reported in repeated dose studies. Some studies report decreases in body weight (e.g., Gillet 1992a; Lankas 1992c, MRID 43868104, MRID 43868105). Decreased body weight is also noted in several developmental studies on emamectin benzoate, as discussed further in Section 3.1.9. For many pesticides, decreases in body weight may be sensitive endpoints for toxicity and may form the basis for the dose-response assessment. This is not the case for emamectin benzoate. Decreased body weight associated with exposure to emamectin benzoate appears to be a secondary effect to neurotoxicity. In other words,

decreased body weight in severely poisoned animals is often evidence of decreased food consumption.

One subchronic study in mice reports an increase in body weight gain in males dosed at 0.6 or 1.2 mg/kg bw/day for 14 days (Lankas 1992a). Mice in the control group evidenced a body weight gain of 19% over the 2-week exposure period; whereas, body weight gains in the 0.6 and 1.2 mg/kg bw/day groups were 25 and 37%, respectively. No increase in body weight gain was noted in male mice in the 2 mg/kg bw/day dose group, and 2 mg/kg bw/day was the NOAEL for signs of neurotoxicity. Nonetheless, the increases in body weight gain at the two lower doses were considered treatment-related, based on the review of this study in the DER. The information contained in the DER for the study by Lankas (1992a) is not sufficient to offer any further interpretation of the body weight gain in the 0.6 and 1.2 mg/kg bw/day dose groups. Increased body weight gain is an unusual effect for a neurotoxin. Given the lack of any increased body weight gain or neurotoxicity in the 2 mg/kg bw/day dose groups, it is seems possible that the increased body weights observed at the lower doses may have been incidental to exposure.

Muscular atrophy or degeneration is reported in a subchronic study in dogs (Mason 1992a), two subchronic studies in rats (Lankas 1992d; Gerson 1992c), and the chronic study in dogs (Gillet 1992a). The muscular atrophy is probably secondary to nerve damage, as discussed further in Section 3.1.6.

There is little indication that emamectin benzoate specifically impacts organs other than nerve tissue. Mason (1992a) conducted a subchronic toxicity study in dogs in which exposure to emamectin benzoate caused thymus atrophy. As discussed further in Section 3.1.7, damage to the thymus raises concern for potential effects on immune function. This effect, however, is not reported for other species. Moreover, in the chronic toxicity study in dogs, Gillet (1992a) investigated the effects of emamectin benzoate exposure on thymus tissue, and found no effects.

3.1.6. Effects on Nervous System

Neurotoxicity is clearly the primary effect of emamectin benzoate in mammals. As discussed in Section 3.1.2 (Mechanism of Action), emamectin benzoate interferes with the normal function of gamma-aminobutyric acid, an important neurotransmitter in mammals. Neurotoxicity is evident in acute, subchronic, and chronic exposures.

In an acute neurotoxicity study in rats (Manson 1992e), single doses of 25 mg/kg bw were associated with degenerative nerve tissue damage in the brain and spinal cord. A dose of 10 mg/kg bw did not cause frank pathological changes in nervous system tissue but gross signs of neurotoxicity—i.e., tremors—were evident. Similarly, the acute neurotoxicity study in rats by Mason (1992d) reports neuropathological changes in the brain, spinal cord, and sciatic nerve at doses of 27.4-82.2 mg/kg bw. The histopathological changes were characterized as focal vacuolation of the white matter or nerve fiber, swollen axon, or dead nerve cells—i.e., nerve cell debris. The pathological damage was noted as early as 2 days after dosing. Gross signs of neurotoxicity, such as tremors, however, were apparent within hours after dosing. Thus, while damage to the

nervous system was confirmed by neuropathology, gross signs of neurotoxicity appear to be more sensitive indicators of toxicity than are pathological changes in nervous system tissue.

Signs of neurotoxicity are also apparent in dogs, rats, and mice exposed to emamectin benzoate in subchronic studies (Appendix 2, Table 4) and chronic toxicity studies (Appendix 2, Table 5). As in the acute neurotoxicity studies, the predominant signs of neurotoxicity from repeated exposures include tremors and abnormal movements, characterized as ataxia or incoordination. Also as in the acute toxicity studies, the neuropathological lesions are most frequently associated with degenerative changes in the brain, spinal cord, and peripheral nerves.

Unlike in the acute neurotoxicity studies, however, damage to the optic nerve is reported in subchronic toxicity studies in dogs (Mason 1992a) and rats (Lankas 1992d) as well as in the chronic toxicity study in dogs (Gillet 1992a). In the subchronic study in dogs (Mason 1992a), damage to the optic nerve was observed only at 1 mg/kg bw/day but not at lower doses (i.e., 0.25 and 0.5 mg/kg bw/day). In the chronic toxicity study in dogs, damage to the optic nerve was observed at 0.75 and 1 mg/kg bw/day but not at 0.5 mg/kg bw/day. In the subchronic study in rats, damage to the optic nerve was observed at doses as low as 2.5 mg/kg bw/day but not at 0.5 mg/kg bw/day (Lankas 1992d). In the 1-year chronic study in rats (Gerson 1992b), no damage to the optic nerve was noted at doses of up to 2.5 mg/kg bw/day. U.S. EPA/OPP (2008a) summarizes the results of a 2-year chronic study in rats (i.e., MRID 43868104) in which there were no effects on the optic nerve.

Damage to the optic nerve is not reported in the subchronic toxicity studies in mice (Gerson 1992a; Gerson 1992e; Lankas 1992a). At least in the study by Gerson (1992a), the DER indicates that a pathological examination of the optic nerve was conducted. U.S. EPA/OPP (2008a) summarizes the results of a 78-week study in which no damage to the optic nerve was observed in mice after exposure to daily doses of up to 7.5 mg/kg bw/day (MRID 43868105).

One potentially confusing but very important aspect of the repeated dosing studies on emamectin benzoate involves MRID 42851503. In the EPA human health risk assessment (U.S. EPA/OPP 2008a), MRID 42851503 is summarized in Table A.2 (p. 45) which incorrectly identifies the test material as MK-244—i.e., emamectin benzoate. According to MRID 42851503, the study was conducted by Gerson (1992g), and the DER for this study clearly indicates that the test material is 4"-epi-(N-formyl-N-methyl)-amino-4"-deoxyavermectin B1, also referenced as L-660,599, which is a plant metabolite of emamectin benzoate. This study is also discussed on p. 14 of U.S. EPA/OPP (2008a), and this discussion correctly indicates that the test compound is a metabolite of emamectin benzoate. Gerson (1992g) is summarized in Appendix 2, Table 6 and is discussed further in Section 3.1.15 (Impurities and Metabolites). The proper designation of the test material used in this study is important because the study by Gerson (1992g) is the basis for the acute and chronic RfDs proposed by U.S. EPA/OPP (2008a). These RfDs are discussed further in Section 3.3 (Dose-Response Assessment).

3.1.7. Effects on Immune System

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

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

The only indication of effects on lymphoid tissue comes from the subchronic toxicity study in dogs (Mason 1992a). In the high dose group (1 mg/kg bw/day), thymus atrophy was noted in one of four male and two of four female dogs. The thymus was examined in the control group and this effect was not noted in control animals. Based on information from the DER for this study, it appears that the thymus of dogs in the lower dose groups was not examined. Thymus atrophy was accompanied by decreases in the number of erythropoietic cells in bone marrow. Dogs in the high dose groups displayed severe signs of neurotoxicity, and the effects on the thymus were considered secondary to neurotoxicity. No effects on the thymus were observed in dogs in the chronic study conducted by Gillet (1992a) in which the 1 mg/kg bw/day dose was discontinued after 3 weeks because of severe toxicity. In the lower dose groups (0.25, 0.5, and 0.75 mg/kg bw/day), no effects on thymus or other lymphoid tissue were noted over the 53-week exposure period.

In the chronic mouse study (MRID 43868105), an increase in the severity of infections was noted in high dose males (5 mg/kg bw/day) and high dose females (7.5 mg/kg bw/day). A DER for this study was not available in the cleared reviews. The EPA human health risk assessment (U.S. EPA/OPP 2008a) discusses the increased incidence of infections as well as the thymus effects from the subchronic study in dogs (Mason 1992a). It seems reasonable to assert that U.S. EPA/OPP (2008a) would discuss damage to lymphoid tissue of mice had the effect been reported in the chronic exposure study. In the chronic mouse study, high dose animals exhibited severe signs of neurotoxicity as well as increased mortality. In the absence of pathological changes in lymphoid tissue, it is conceivable that the increased infections in the high dose mice were associated with the generally poor health of the animals rather than a specific effect on immune function.

3.1.8. Effects on Endocrine System

Assessment of the direct effects of chemicals on endocrine function are most often based on mechanistic studies on estrogen, androgen, or thyroid hormone systems (i.e., assessments on hormone synthesis, hormone receptor binding, or post-receptor processing). The U.S. EPA/OPP has developed a battery of screening assays for endocrine disruption (i.e., http://www.epa.gov/ocspp/pubs/frs/publications/Test_Guidelines/series890.htm). Abamectin, but not emamectin benzoate, was selected as one of the pesticides for which the EPA is requiring screening assays (U.S. EPA/OPP 2009b). Results of the screening assays were not located in a search of the EPA website.

Inferences concerning the potential for endocrine disruption can sometimes be made from responses seen in standard toxicity tests—i.e., changes in the structure of major endocrine glands (i.e., the adrenal, hypothalamus, pancreas, parathyroid, pituitary, thyroid, ovary, and testis) or changes in growth rates. As with effects on the nervous system and immune function, however, effects on organs associated with endocrine function may be secondary to other toxic effects. Thus, in the absence of information on specific endocrine mechanisms, pathological changes in endocrine tissues do not necessarily indicate a direct effect on endocrine function. U.S. EPA/OPP (2008a, p. 22) specifically addresses endocrine function but does not identify any data on emamectin benzoate that suggests that this compound or its metabolites are endocrine disruptors. Furthermore, there is no information in the open literature or available toxicity data (Appendix 2) to suggest that emamectin benzoate affects endocrine function.

In terms of functional effects that have important public health implications, effects on endocrine function would be expressed as diminished reproductive performance or abnormal development. This issue is addressed below.

3.1.9. Reproductive and Developmental Effects

3.1.9.1. Developmental Studies

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

As detailed in Appendix 2, three developmental studies were submitted to the U.S. EPA in support of the registration of emamectin benzoate: one study in rabbits (Manson 1992b) and two studies in rats (Manson 1992c; Wise 1993a). The developmental study in rats by Wise (1993a) also appears to be published in the open literature as Wise et al. (1997). The earlier studies by Mason (1992b,c) in rats and rabbits are standard developmental studies in which the maternal NOAELs (3 mg/kg bw/day in rabbits and 2 mg/kg bw in rats) were lower than developmental NOAELs (6 mg/kg bw/day in rabbits

and 8 mg/kg bw/day in rats). In other words, in these studies, the dams displayed signs of toxicity at doses that did not cause developmental effects.

The developmental study by Wise and coworkers (Wise 1993a; Wise et al. 1997) is a developmental neurotoxicity study. Developmental neurotoxicity studies are similar in general design to standard developmental studies but also include post-natal observations for behavioral changes and overt signs of neurotoxicity. In this study, a dose of 0.6 mg/kg bw/day caused no signs of neurotoxicity in dams; however, behavioral changes (decreased open field activity and tremors) were observed in offspring.

There is no indication in the developmental studies that exposure to emamectin benzoate causes birth defects.

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. The EPA requires only one acceptable multi-generation reproduction study for pesticide registration.

A single two-generation reproduction study in rats (Lankas 1992c) was submitted to and accepted by the U.S. EPA/OPP. A DER is available for this study. As summarized in U.S. EPA/OPP (2008a), the NOAEL for both systemic toxicity and reproductive effects was 0.6 mg/kg bw/day. The next highest dose, 1.8 mg/kg bw/day, caused neural degeneration (brain and spinal cord) and decreased body weight gain, indicating systemic toxicity. Furthermore, reproductive toxicity was evident from a decrease in fecundity and fertility. As in the subchronic and chronic toxicity studies, signs of overt toxicity at 1.8 mg/kg bw/day included tremors and hind limb extension in offspring. The DER for this study provides some elaboration indicating that Lankas (1992c) conducted two studies, one gavage and the other dietary. In both studies, the DER reports a NOAEL of 0.7 mg/kg bw/day. In the gavage study, the LOAEL is given as 5 mg/kg bw/day based on decreased body weight gain and food consumption. In the dietary study, the LOAEL is reported as 4.6 mg/kg bw/day (corresponding to a dietary concentration of 50 ppm) based on clinical and histopathological signs of neurotoxicity as well as decreased body weight in pups.

3.1.10. Carcinogenicity and Mutagenicity

In terms of a quantitative significance to the human health risk assessment, carcinogenicity is an issue only if the data are adequate to support the derivation of a cancer potency factor. A cancer potency factor is typically derived based on a dose-

related increase in malignant tumors from a chronic toxicity study that encompasses a significant portion of the test animals' lifespan.

U.S. EPA/OPP (2008a) classifies emamectin benzoate as … *"Not likely to be carcinogenic to Humans" based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies*. As summarized in Appendix 2 (Table 5), the two rodent toxicity studies refer to the 78-week study in mice (MRID 43868105) and the 105-week study in rats (MRID 43868104). Neither of the two studies reports an increased incidence of malignant tumors. Furthermore, as summarized in U.S. EPA/OPP (2008a, Table A.2, p. 45), emamectin benzoate displayed no mutagenic activity in several standard bioassays of gene mutation and chromosomal damage.

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

The U.S. EPA/OPP requires standard studies with pesticide formulations for skin and eye irritation as well as skin sensitization (http://www.epa.gov/opptsfrs/publications/OPPTS_Harmonized). These studies are summarized in Appendix 2, Table2. Most of the study summaries are taken from the EPA human health risk assessment for emamectin benzoate (U.S. EPA/OPP 2008a). DERs for these studies are not available in the cleared reviews.

U.S. EPA/OPP (2008a, p. 43) summarizes eye and skin irritation and skin sensitization studies for materials referred to as *emamectin benzoate technical* and *emamectin benzoate technical II*. As discussed in Section 2.2, it appears these tests were conducted on two different formulations of emamectin benzoate rather than on technical grade emamectin benzoate. Nonetheless, it is impossible to confirm this supposition without more detailed summaries of the studies. Based on the summary in U.S. EPA/OPP (2008a), the emamectin benzoate formulations do not appear to be skin sensitizers or skin irritants.

One cleared review (Bagdon 1992, MRID 42743611) reports slight to severe skin irritation. This study was conducted in rats using a material designated only as *MK-0243 0.16 EC Formulation*. Apparently, the *0.16 EC* refers to the Denim formulation which contains emamectin benzoate at a concentration of 0.16 lb a.i./gallon (Table 3). The study by Bagdon (1992) assayed skin irritation using the 0.16 EC formulation as well as the carrier alone—i.e., the other ingredients in the formulation with no emamectin benzoate. Both agents caused slight to severe skin irritation. Thus, it appears that the skin irritancy of the formulation could be attributed to the other ingredients in the formulation rather than emamectin benzoate. This study is not discussed in U.S. EPA/OPP (2008a).

For emamectin benzoate technical, U.S. EPA/OPP (2008a) indicates severe ocular irritation and classifies emamectin benzoate as a Category I eye irritant, the most severe classification for eye irritants. For emamectin benzoate technical II, U.S. EPA/OPP (2008a) also indicates severe eye irritation but classifies emamectin benzoate technical II as Category III, the second lowest category of eye irritation.

3.1.12. Systemic Toxic Effects from Dermal Exposure

The only data available on the dermal toxicity of emamectin benzoate are dermal LD_{50} values of >2,000 mg/kg bw in rats reported in U.S. EPA/OPP (2008a, p. 43) for both emamectin benzoate technical (MRID 43850111) and emamectin benzoate technical II (MRID 47002106). As discussed in Section 2.2 as well as the previous subsection, these two materials appear to be different formulations of emamectin benzoate. Based on these acute dermal LD_{50} values, U.S. EPA/OPP (2008a, p. 43) classifies emamectin benzoate as Category III for dermal toxicity, the second to the least hazardous category. As discussed in Section 3.1.3.2, emamectin benzoate appears to be poorly absorbed as a result of dermal exposure, which justifies its low dermal toxicity ranking.

3.1.13. Inhalation Exposure

3.1.13.1. General Considerations

As with dermal toxicity, the only data on the inhalation toxicity of emamectin benzoate come from summaries in the EPA human health risk assessment (U.S. EPA/OPP 2008a, p. 43). LC_{50} values of 0.1 mg/L are reported for inhalation exposure to both emamectin benzoate technical (MRID 43868101) and emamectin benzoate technical II (MRID 47002107). The two LC_{50} values are identical; yet, U.S. EPA/OPP (2008a) classifies emamectin benzoate technical as Category IV, the least toxicity category, and emamectin benzoate technical II as Category II, the second highest toxicity category.

The summary of the inhalation studies in U.S. EPA/OPP (2008a) is somewhat confusing. The U.S. EPA has a standard classification system for grading inhalation toxicity (SERA 2007, Table 3-2). All compounds with inhalation LC_{50} values of 0.2 mg/L or less are typically classified as Category I, the highest hazard category for inhalation. Nevertheless, as noted above, U.S. EPA/OPP (2008a) classifies emamectin benzoate technical as Category IV and emamectin benzoate technical II as Category II based on reported LC_{50} values of 0.1 mg/L. In addition, the hazard and dose-response characterization in U.S. EPA/OPP (2008a, p. 13) indicates that emamectin benzoate has low acute toxicity by the inhalation route.

The uncertainties regarding the inhalation toxicity of emamectin benzoate summarized in U.S. EPA/OPP (2008a) do not have a substantial impact on the current Forest Service risk assessment. Given that emamectin benzoate is applied only by tree injection in Forest Service programs, the potential for significant inhalation exposure seems remote.

3.1.13.2. Combustion of Ash Wood

The wood from treated ash trees may be used for firewood, which could raise concern for indoor inhalation exposures to emamectin benzoate. In addition, inhalation exposures to emamectin benzoate could be a potential concern in the case of a fire in stands of ash trees treated with emamectin benzoate.

No information is available on the combustion products of emamectin benzoate. In addition, no information is available on concentrations of emamectin benzoate or the combustion products of emamectin benzoate in indoor air (e.g., during the use of treated ash wood in fireplaces) or outdoor air (e.g., during a fire in treated stands of ash).

The combustion of wood, either in a fireplace or during an outdoor fire, will generate smoke that contains numerous toxic chemicals, many of which are carcinogenic. The specific composition of wood smoke will, of course, vary depending on the combustion conditions as well as the type of wood that is burned (e.g., Fine et al. 2002; Naeher et al. 2007).

In terms of the hazard identification for emamectin benzoate, the key issue is whether or not it is likely that residues of emamectin benzoate in wood might add substantially to the risks of any inhalation exposure. As illustrated in Figure 7 and discussed further in Section 3.2.3.6, the concentration of emamectin benzoate in treated ash trees will range from about 0.4 to 20 mg a.i./kg wood. The major toxic component of burning wood is carbon monoxide, and the amount of carbon monoxide generated by burning wood is about 130,000 mg/kg wood (McDonald et al. 2000). Thus, in terms of relative potential exposure, the potential for exposure to emamectin benzoate is less than the potential exposure to carbon monoxide by factors ranging from about 6500 to 325,000 [130,000 mg CO/kg wood ÷ 0.4 to 20 mg a.i./kg wood]. Given the greater proportion of carbon monoxide to emamectin benzoate in combustion products of treated ash trees, it seems unlikely that emamectin benzoate residues will substantially increase the hazards associated with indoor or outdoor inhalation exposure.

3.1.14. Adjuvants and Other Ingredients

Adjuvants are not used with emamectin benzoate in tree injections. As discussed in Section 2.4, the Tree-äge formulation is diluted with water and injected directly into trees.

As summarized in Table 3, the Tree-äge formulation contains tetrahydrofurfuryl alcohol and petroleum distillates. 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). The composition of the petroleum distillates in Tree-äge (e.g., aromatic or aliphatic) is proprietary. As reviewed by ATSDR (1995, 1999), petroleum distillates are a very complex class of diverse aromatic and aliphatic hydrocarbons. Nonetheless, the primary toxicological effect of petroleum distillates involves nonspecific effects (general CNS depression) on the central nervous system. Yen and Lin (2004) indicate that a Taiwanese formulation of Proclaim contains 2, 6-bis (1, 1-dimethylethyl)-4-methyl-phenol and 1-hexanol . It is not clear that these inerts are in Tree-äge.

In addition to effects on the central nervous system, many solvents cause skin damage. As noted in Section 3.1.13, the dermal irritation study by Bagdon (1992, MRID 42743611) suggests that the solvents in one formulation of emamectin benzoate may be the primary cause of dermal irritation.

While the toxicity of the other ingredients in Tree-äge cannot be dismissed, the highly specific and highly potent neurotoxic effects of emamectin benzoate suggest that emamectin benzoate is the toxic agent of primary concern.

3.1.15. Impurities and Metabolites

3.1.15.1. Impurities

As noted in Section 2.2, emamectin is a derivative of abamectin. Abamectin, in turn, is isolated from the fermentation byproducts of a soil bacterium, *Streptomyces avermitilis* (ExToxNet 1994). Thus, it is reasonable to presume that emamectin and hence emamectin benzoate contains some impurities. As summarized in Appendix 1, specific information on the impurities in technical grade emamectin benzoate was submitted to the U.S. EPA—i.e., MRID 43393010. This information, however, is considered proprietary and could not be reviewed in the conduct of the current Forest Service risk assessment. The U.S. EPA/OPP, however, has reviewed the information on impurities. The EPA human health risk assessment (U.S. EPA/OPP 2008a, p. 11) notes that there are no known impurities of concern in technical grade emamectin benzoate.

3.1.15.2. Metabolites

As illustrated in Figure 1, emamectin is a relatively complex molecule and could be subject to a number of metabolic processes. As summarized in Appendix 2 (Table 6), several metabolites of emamectin were identified and assayed in 14- to15-day toxicity studies in mice by Gerson (1992d,g,h,i,j). In addition, Lankas (1992b) conducted concurrent single dose toxicity studies in dogs using emamectin benzoate as well as four metabolites of emamectin.

Because of the structural complexity of emamectin, the nomenclature for its metabolites is also complex. The current Forest Service risk assessment adopts the abbreviated nomenclature used by U.S. EPA/OPP (2008a) in which the metabolites are identified by an alphanumeric code (e.g., L-660,599 for the 4"-epi-(N-formyl-N-methyl)-amino-4"-deoxyavermectin B1 metabolite of emamectin). U.S. EPA/OPP (2008a) provides the structure of several metabolites of emamectin, which are illustrated in Figure 6 of the current Forest Service risk assessment.

Some metabolites of emamectin appear to be clearly less toxic than emamectin. For example, in the repeated dose studies in mice, the 8,9-Z isomer (a photodegradation metabolite of emamectin benzoate illustrated in Figure 6) is clearly less toxic than emamectin benzoate and other metabolites with a NOAEL of 0.3 mg/kg bw/day. The most toxic metabolite of emamectin benzoate appears to be a plant metabolite, referenced as L-660,599, which has a NOAEL of 0.075 mg/kg bw/day in mice with a corresponding LOAEL of 0.1 mg/kg bw/day based on neurotoxicity as well as mortality (Gerson 1992g). As discussed in Section 3.1.5, the NOAEL for emamectin benzoate is 0.1 mg/kg bw/day with a corresponding LOAEL of 0.3 mg/kg bw/day based on severe signs of neurotoxicity but no mortality (Gerson 1992e). As illustrated in Figure 6, the L-660,599 metabolite is an N-formyl-N-methyl derivative of the B1a component of emamectin. As discussed further in Section 3.3 (Dose-Response Assessment), the toxicity study on the L-660,599 metabolite is the basis for the RfDs on emamectin benzoate derived in U.S. EPA/OPP (2008a).

As discussed in Section 3.1.3.1, a single mammalian metabolite has been identified. This metabolite is characterized in Mushtaq et al. (1996b) as an N-demethylation byproduct of

emamectin. Based on this description, the mammalian metabolite appears to correspond to L'649 in Figure 6. This metabolite was not assayed in the repeated dosing studies in mice—i.e., the series of studies conducted by Gerson in 1992; however, L'649 was included in the single dose studies in dogs by Lankas (1992b). As summarized in Appendix 2, Table 6, Lankas (1992b) dosed groups of four dogs each with emamectin benzoate as well as four emamectin metabolites (including L'649) at a single dose of 1.5 mg/kg bw. Emamectin benzoate caused slight neuronal degeneration as well as tremors in two of four dogs. L'649 also caused slight neuronal degeneration and tremors in two of four dogs. In addition, however, L'649 caused dilation of the pupils in three of four dogs. By the end of the 14-day observation period, one of four dogs displayed signs of neurotoxicity—i.e., the dog was drooling and recumbent prior to sacrifice. While the study by Lankas (1992b) cannot be used to quantify the toxicity of the L'649 metabolite relative to emamectin, it seems apparent that the limited metabolism of emamectin benzoate in mammals does not involve significant detoxification, and the L'649 metabolite appears to be as, if not more, toxic than emamectin benzoate itself.

3.1.16. Toxicological Interactions

Since there is no information in the available literature regarding the toxicological interaction of emamectin benzoate with other agents, the assessment of the potential toxicological interactions of emamectin benzoate with other compounds is largely speculative. As discussed in Section 3.1.2, the mechanism of action of emamectin benzoate is similar to that of abamectin and milbemectin. Based on the concept of simple similar action (e.g., ATSDR 2004; Finney 1971), compounds with similar modes of action are likely to display additive joint action—i.e., the interaction will be additive rather than antagonistic or synergistic.

Many toxicological interactions are based on the effect of one compound on the metabolism of another compound (e.g., U.S. EPA 2000). Emamectin benzoate is not extensively metabolized by mammals (Section 3.1.2.1); however, limited comparative studies on emamectin benzoate and the mammalian metabolite of emamectin benzoate (i.e., L'649) suggest that the mammalian metabolite may be somewhat more toxic than emamectin benzoate (Section 3.1.15). Based on unpublished studies summarized in Mushtaq et al. (1996b, p. 3342), emamectin benzoate appears to be metabolized in the liver, as would be expected for compounds which are excreted largely in the feces. Thus, it is possible that some compounds which stimulate nonspecific liver enzymes involved in the metabolism of xenobiotics might enhance the toxicity of emamectin benzoate. There is no experimental evidence, however, to support this conjecture.

3.2. EXPOSURE ASSESSMENT

3.2.1. Overview

An overview of the exposure assessments used in the human health risk assessment is given in EXCEL workbook that accompanies this risk assessment: Worksheet E01 for workers and Worksheet E03 for members of the general public.

The most plausible exposures are those associated with workers during the mixing, loading, and tree injection processes. No worker exposure studies are available for tree injections of emamectin benzoate or other pesticides. Nonetheless, using exposure assumptions for surrogate application methods, the central estimates of absorbed doses for workers are virtually identical—i.e., about 0.000006 mg/kg bw/day—using either the deposition based approach of U.S. EPA/OPP or the standard biomonitoring based approach typically used in Forest Service risk assessments. The range of exposures estimated using the Forest Service method are somewhat broader than the range of exposures using the EPA method; however, as discussed further in Section 3.4.2, the differences between the two methods do not materially affect the risk characterization. The most significant factor in the worker exposure assessment involves the use of gloves. Tree-äge is a restricted use pesticide that requires workers to wear chemical resistant gloves. If gloves are not used, worker exposure rates will be much higher. Moreover, as also discussed in Section 3.4.2, the failure to use chemically resistant gloves properly could result in unacceptable risks to workers.

This risk assessment covers only the injection of Tree-äge into ash trees. Consequently, it seems unlikely that members of the general public are at risk of significant exposures. No studies, however, are available on the distribution and kinetics of emamectin benzoate in ash trees following tree injection. Consequently, exposures to members of the general public are difficult to quantify. In previous Forest Service risk assessments that cover tree injections with imidacloprid and dinotefuran, no exposure scenarios for members of the general public were developed. Based on an approach developed by the U.S. EPA/OPP in an ecological risk assessment, the current Forest Service risk assessment does develop scenarios covering accidental spills of emamectin benzoate into a pond. The upper bound exposure estimates for these accidental exposures range from about 0.0001 to 0.0007 mg/kg bw/day.

3.2.2. Workers

Exposure assessments for workers are summarized in Worksheet E01 of each of the EXCEL workbooks that accompany this risk assessment. Two types of exposure assessments are considered: general exposures and accidental/incidental exposures. The term *general exposure* is used to designate exposures involving 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. The development of general exposure estimates as well as accidental exposure estimates is the standard approach used in most Forest Service risk assessments.

For emamectin benzoate, however, two types of general exposures are considered: expected applications in which personal protective equipment is properly used and applications in which personal protective equipment is not used or is ineffective. This distinction is not made in most Forest Service risk assessments; however, with respect to emamectin benzoate, the improper use of or the failure to use personal protective equipment has a substantial impact on both the estimated levels of exposure as well as the subsequent risk characterization (Section 3.4.2).

3.2.2.1. General Exposures

3.2.2.1.1. Studies on Tree-äge

Joseph (2008) conducted an occupational exposure assessment of the application of a 4% formulation of emamectin benzoate by tree injection. A cleared review is not available for this study which was submitted to the U.S. EPA (i.e., MRID 47419601) in support of the registration of emamectin benzoate. During the preparation of the current Forest Service risk assessment, a Freedom of Information Act (FOIA) request for a copy or summary of this study was submitted to the U.S. EPA/OPP (HQ-FOI-01225-10 submitted on May 10, 2010). In addition, the occupational exposure assessment (Joseph 2008) was requested (March 27, 2010) from the registrant (Durkin 2010). In response to the FOIA request, the U.S. EPA/OPP (2010a) indicated that a cleared review of this study was not available, and a full copy of Joseph (2008) was not provided. This is not an unusual situation. Studies submitted to the U.S. EPA/OPP in support of pesticide registration are typically regarded as proprietary (i.e., Confidential Business Information or CBI) and are not available to groups outside of the U.S. EPA/OPP, unless the studies are released by the registrant. The Forest Service has no regulatory authority to require the release of information submitted to the U.S. EPA/OPP in support of pesticide registration. In response to the FOIA, a copy of the U.S. EPA/OPP (2008d) occupational exposure assessment was provided; however, it does not reference or review the study by Joseph (2008).

As indicated in Section 5, Joseph (2008) is only 18 pages long. It seems reasonable to speculate that this short submission is unlikely to involve a specific study on Tree-äge. It is more likely that Joseph (2008) is an occupational exposure assessment based on the Pesticide Handler Exposure Database (PHED) or a similar compilation.

3.2.2.1.2. Deposition Based Exposure Assessments

As part of a human health risk assessment for emamectin benzoate applied by tree injection, the EPA conducted an occupational exposure assessment involving tree injection of Tree-äge (U.S. EPA/OPP 2008a,d). This occupational exposure assessment is based on the Pesticide Handler Exposure Database (PHED), Version 1.1. As discussed in SERA (2007a, Section 3.2.2), 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.

In its worker exposure assessment (U.S. EPA/OPP 2008a,d), 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) . The conversion of mL formulation to lb a.i., which is not detailed in U.S. EPA/OPP (2008a), is correct. The MSDS for Tree-äge gives a formulation density of 1.08 g/mL for the 4% (0.04) formulation. Thus, 36 mL of the formulation is equivalent to about 1.55 grams a.i. [36 mL formulation x 1.08 g/mL x 0.04 $_{\text{a.i./formulation}}$ = 1.5552 g a.i.]. Using an estimate of 453.6 g/lb, this amount is equivalent to about 0.0034 lb a.i.[1.5552 g a.i. ÷ 453.6 g/lb = 0.003429 lb a.i.].

In exposure assessments based on PHED, the amount of the pesticide handled per day is multiplied by dermal and inhalation exposure rates in units of mg a.i./lb a.i handled. U.S. EPA/OPP (2008, Table 9.1, p. 36) uses an inhalation exposure rate of 0.0012 mg a.i./lb a.i. and two dermal exposure rates, a baseline rate of 2.9 mg a.i./lb a.i. and a rate with gloves of 0.0024 mg a.i./lb a.i. As summarized in Table 5 of the current Forest Service risk assessment, PHED does not contain exposure rates for tree injections. As indicated in bold typeface in Table 5, the exposure rates selected by the EPA (U.S. EPA/OPP 2008) are based on PHED Scenario 3—i.e., all liquids, open mixing and loading. The dermal baseline rate of 2.9 mg a.i./lb a.i. is based on a single layer of standard clothing but without the use of gloves. As summarized in U.S. EPA/OPP (2008, Table 9.1), the resulting estimates of absorbed doses are 0.00041 mg a.i./kg bw/day for dermal absorption without gloves, 0.0000032 mg a.i./kg bw/day with gloves, and 0.0000093 mg a.i./kg bw/day for inhalation exposure. The total absorbed doses are estimated as 0.00041 mg a.i./kg bw/day without the use of gloves and 0.000013 mg a.i./kg bw/day with the use of gloves.

Details of the dose estimates provided in U.S. EPA/OPP (2008a) are reproduced in the EXCEL workbook that accompanies this risk assessment: Worksheet C02a (the scenario including the use of gloves) and Worksheet C02a-Sup (the scenario without the use of gloves). In these worksheets, the number of injections is taken as a range—i.e., 80 (40 to 160) injections per day. Thus, the EPA calculated doses (U.S. EPA/OPP 2008) are reproduced as the upper bound estimates.

These worksheets differ in structure from the calculations provided in U.S. EPA/OPP (2008a) only in terms of the conversion of dose as mg/day to mg/kg bw/day. For example, the EPA calculates the dermal dose without gloves as 0.00041 mg/kg bw/day (U.S. EPA/OPP 2008a,d). The estimated absorbed dermal dose is given in Worksheet C01b-Sup (no gloves) as 0.0283968 mg/kg. Dividing by the body weight used in U.S. EPA/OPP (2008a)—i.e., 70 kg—and rounding to two significant digits, 0.0283968 mg/day is equivalent to 0.00041 mg/kg bw [0.0283968 mg/day ÷ 70 kg = 0.000405668 mg/kg bw/day].

U.S. EPA/OPP (2008a) does not specifically discuss the efficiency of gloves. Nonetheless, the impact of wearing gloves can be calculated by dividing the dermal dose with gloves by the dermal dose without gloves—i.e., 0.0000032 mg/kg bw/day ÷ 0.00041

mg/kg bw/day ≈ 0.0078. Thus, the EPA exposure assessment (U.S. EPA/OPP 2008a) estimates that gloves reduce exposure by about 99.22% [1-0.0078 x 100].

As discussed further in Section 3.4.2, the protection factor for gloves is extremely important in the risk characterization for workers. Thus, it is important to understand that the protection factor for gloves is not arbitrary. PHED is based on numerous worker exposure studies with many different pesticides. For Scenario 3—i.e., the exposure rates used in U.S. EPA/OPP (2008a)—the dermal exposure estimates are based on 72-122 replicates for sites other than hands and 53 replicates for hands. Both sets of replicates are graded as AB (relatively high quality), and the overall confidence in the data is ranked as high (Keigwin 1998, p. 19).

3.2.2.1.3. Absorption Based Exposure Assessment

As described in SERA (2007a), worker exposure rates in Forest Service risk assessments are expressed in units of mg of absorbed dose per kilogram of body weight per pound of chemical handled. These exposure rates are based on biomonitoring estimates of several different pesticides using various application methods. Default exposure rates are estimated for three different types of applications: directed foliar (backpack), boom spray (hydraulic ground spray), and aerial. These exposure rates, taken from Table 3-3 in SERA 2007a, are summarized in Table 6 of the current Forest Service risk assessment.

As with the PHED exposure rates summarized in Table 5 and discussed in the previous subsection, the standard exposure rates used in Forest Service risk assessments do not include rates for tree injection. In a recent Forest Service risk assessment on dinotefuran (SERA 2009b), the exposure assessment for workers is based on directed foliar/backpack applications. This approach is taken because tree injection appears to be more closely related to directed foliar applications, in terms of the nature of the worker exposure. Furthermore, it is a general practice in Forest Service risk assessments to use the most conservative assumption in the absence of data. As summarized in Table 6, the worker exposure rates for directed foliar application exceed the worker exposure rates for other application methods by more than a factor of 10.

As with the corresponding estimates based on PHED (Section 3.2.2.1.2), worker exposures based on the exposure rates for directed foliar applications are estimated for applications of Tree-äge in Worksheet C01a (including the use of gloves) and Worksheet C01-Sup (excluding the use of gloves). In the worker exposure assessment considering the use of gloves (Worksheet C01a), the protection factor for gloves is taken as 0.9922, equivalent to the factor used in U.S. EPA/OPP (2008a). Some of the studies used in developing the absorbed dose rate did involve the use of standard work gloves. Nonetheless, the product labels for Tree-äge indicate that only chemical resistant gloves should be used—i.e., *chemical resistant gloves (Category C) such as barrier laminate, butyl rubber >14 mils, nitrile rubber >14 mils, or neoprene rubber >14 mils*. Consequently, the use of the protection factor for gloves is appropriate.

3.2.2.1.4. Comparison of Methods

Worksheet E01 of the EXCEL workbook that accompanies this risk assessment provides an overview of the estimated absorbed doses for workers.

Based on the proper use of chemically resistant gloves, the central estimates of the absorbed dose are virtually identical using both the standard Forest Service method—i.e., 6.36×10^{-6} mg/kg bw/day as detailed in Worksheet C01a—and the PHED method—i.e., 6.24×10^{-6} mg/kg bw/day as detailed in Worksheet C01b. As noted by Ross et al. (2008), central estimates of worker exposures based on biomonitoring (i.e., the approach used in Forest Service risk assessments) and deposition (i.e., the approach used in PHED) are generally similar. Nonetheless, the very close correspondence of the exposure estimates based on Forest Service and PHED exposure rates is most certainly coincidental.

There is, however, substantial variability in the exposure rates. The exposure rates based on the standard Forest Service methods range from 3.18×10^{-7} to 4.24×10^{-5} mg/kg bw/day. The lower bound of this range is about a factor of 10 below the lower bound based on PHED—i.e., 3.12×10^{-6} mg/kg bw/day. Similarly, the upper bound of the range based on standard Forest Service methods (i.e., 4.24×10^{-5} mg/kg bw/day) is about a factor of 3 higher than the upper bound of the range based on PHED methods (1.25×10^{-5} mg/kg bw/day) [4.24×10^{-5} mg/kg bw/day $\div$ 1.25×10^{-5} mg/kg bw/day ≈ 3.4].

The greater variability in the exposure rates based on standard Forest Service methods, relative to PHED methods, is common. It is worth noting that the variability in the exposure estimates from PHED is based on the variability of the expected amounts of Tree-äge that workers will apply (Worksheet C01b). The variability in the exposure estimates using the standard Forest Service methods is based on the variability in worker exposure rates, as detailed in Table 6, as well as variability in the amount of Tree-äge that a worker will handle.

The worker exposure rates based on the failure to use gloves are substantially higher than rates based on the proper use of chemically resistant gloves. This difference is due to the very high dermal protection factor for gloves used in the exposure assessments. As discussed in Section 3.2.2.1.2, U.S. EPA/OPP (2008a) estimates that gloves reduce exposure by a factor of about 99.22%. In other words, the proper use of chemically resistant gloves reduces exposure by a factor of about 130 [$1 \div (1 - 0.9922) \approx 128.21$]. As also discussed in Section 3.2.2.1.2, the protection factor is not arbitrary and is based on a relatively large number of studies that the U.S. EPA/OPP judges to be of high quality. The importance of the use of chemically resistant gloves is emphasized further in the risk characterization (Section 3.4.2).

A comparison of exposure assessments without the use of contaminated gloves (Worksheet E01) indicates that the central estimates of exposure vary considerably according to the method of estimating dermal exposure. For instance, the central estimate based on the Forest Service method is 8.14×10^{-4} mg/kg bw/day, which exceeds the PHED estimate of 2.07×10^{-4} mg/kg bw/day by a factor of 4. This difference is due to the underlying assumption in the Forest Service method that the dermal route is the predominant exposure pathway in pesticide applications (e.g. Ecobichon 1998; van Hemmen 1992). Thus, for a fixed dermal protection factor, the Forest Service method has a greater impact on exposure estimates, compared with the PHED method. As an

aside, Forest Service risk assessments typically do not use protection factors based solely on estimates from PHED.

Despite the similarities between the worker exposure estimates based on PHED (Section 3.2.2.1.2) and standard Forest Service methods (Section 3.2.2.1.3) which may be viewed as mutually supportive, it must be emphasized that no worker studies involving tree injection are available. The lack of a worker exposure study on tree injection adds uncertainty to the risk assessment for workers.

3.2.2.2. Accidental Exposures

For Tree-äge applications, accidental exposures are most likely to occur during the dilution of formulations or the loading of the injector devices. Unlike certain pesticide formulations that are available in self-contained injectable capsules, Tree-äge is available in a 1 liter solution (e.g., http://www.arborjet.com/products/injectables.htm). As discussed in Section 2.4, the Tree-äge formulation may be injected without dilution or may be mixed with 1-3 parts water. If the formulation is mixed prior to application, accidental dermal or ocular exposures might occur. Accidental exposures involving 'blow-back' on the applicator during the injection process are less likely to occur (except in the case of equipment failure) because high pressure application systems are equipped with plugs to prevent back-flow (Cregg 2010).

Accidental exposures to the eye are most likely to involve splashing a pesticide solution into the eyes or contaminating the surface of the skin. There are no quantitative methods by which to estimate exposure associated with splashing a pesticide solution in the eyes; consequently, this type of accidental exposure is addressed qualitatively in the risk characterization (Section 3.4.2).

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

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

Exposure scenarios involving direct contact with chemical solutions of emamectin benzoate are characterized either by immersion of the hands in a field solution for 1 hour or wearing pesticide contaminated gloves for 1 hour. The assumption that the hands or any other part of a worker will be immersed in a chemical solution for any given period of time may not be reasonable. Nonetheless, it is credible 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 a chemical solution. In both cases, the concentration of the chemical solution in contact with the skin and the resulting dermal absorption rate are basically constant, meaning that zero-order absorption is a reasonable assumption.

For both scenarios (hand immersion and contaminated gloves), 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 emamectin benzoate are provided in Section 3.1.3.2.2. As discussed in Section 3.1.3.2.2, the estimated Kp values for emamectin benzoate are based on the conservative use of a molecular weight of 700 g/mole. This molecular weight is the upper bound of the molecular weights used to develop the algorithm on which the K_p is estimated but is less than the molecular weights of any of the components of emamectin benzoate. Consequently, there is minimal confidence in the exposure assessments for zero-order exposure scenarios.

The amount of the pesticide absorbed per unit time depends directly on the chemical concentration of the solution. As detailed in Worksheet A01, the range of concentrations of emamectin benzoate in a field solution is taken as 21.6 (10.8 to 43.2) mg a.i./L. The upper bound of this range is the concentration of emamectin benzoate in undiluted Tree-äge. The central estimate of the concentration is based on a 1:1 dilution of Tree-äge and the lower bound is based on a 3:1 dilution of Tree-äge.

Exposure scenarios involving chemical spills onto the skin are characterized by a spill on to the lower legs as well as a spill on to the hands. In these scenarios, it is assumed that a chemical solution is spilled on to a given surface area of skin and that a certain amount of the chemical adheres to the skin. The absorbed dose is then calculated as the product of the amount of the chemical on the surface of the skin (i.e., the amount of liquid per unit surface area multiplied by the surface area of the skin over which the spill occurs and the concentration of the chemical in the liquid), the first-order absorption rate, and the duration of exposure. As discussed in Section 3.1.3.2.1, the first-order absorption rate (k_a) for emamectin benzoate is based on the experimental dermal absorption rate from the study in monkeys (Wrzesinski et al. 1997). Accordingly, confidence in the exposure estimates based on first-order dermal absorption rates is much higher than the confidence in the zero-order dermal absorption rates.

3.2.3. General Public

3.2.3.1. General Considerations

3.2.3.1.1. Likelihood and Magnitude of Exposure

The current Forest Service risk assessment covers only the injection of ash trees with Tree-äge. Tree-äge is a restricted use pesticide. In other words, it can only be applied by certified pesticide applicators. While tree injection is a relatively labor-intensive and expensive application method, one of the reasons that tree injection is used is that the

pesticide is applied in a very controlled manner. Consequently, the likelihood of significant exposures to members of the general public is minimal.

3.2.3.1.2. Summary of Assessments

The Forest Service has developed a relatively uniform set of exposure assessments for various application methods including broadcast foliar, broadcast soil, bark applications, and soil injections. Table 7 provides an overview of these exposure scenarios.

Tree injection is given in the last column of Table 7, representing the exposure scenarios used in the current Forest Service risk assessment for emamectin benzoate. Pesticide application by tree injection is covered in two previously conducted Forest Service risk assessments: imidacloprid (SERA 2005) and dinotefuran (SERA 2006b). In both of these risk assessments, no exposure scenarios were made for members of the general public because, as noted above, the likelihood of significant exposures to members of the general public appears to be minimal. In addition, as discussed further in the following subsections, the available information on imidacloprid, dinotefuran, and emamectin benzoate are not amenable to quantitatively estimating exposures for most of the scenarios used in standard Forest Service risk assessments involving broadcast applications.

For emamectin benzoate, four exposure scenarios for members of the general public are developed. The accidental spill of emamectin benzoate into a small pond is central to each of these exposure scenarios: the consumption of water by a small child, the consumption of contaminated fish by the general public and subsistence populations, and swimming in water after an accidental spill. Furthermore, each of these exposure scenarios is based on highly conservative estimates of emamectin benzoate in surface water developed by the EPA (U.S. EPA/OPP 2009a). The specifics of these exposure scenarios are discussed in the following subsections and the basic approach used by U.S. EPA/OPP (2009a) is detailed further in Section 3.2.3.4.1.

This development of elaborate exposure assessments for members of the general public following tree injection is based on discussions with Forest Service personnel concerning a general practice in all Forest Service risk assessments—i.e., Forest Service risk assessments will be at least as conservative as risk assessments proposed by the U.S. EPA.

Notwithstanding their elaborate nature, the exposure scenarios for emamectin benzoate represent a only small subset of the exposure scenarios typical for other application methods (Table 7). Accordingly, section designations are included below for exposure scenarios which are not considered for emamectin benzoate. This approach is taken as a matter of convenience for individuals who regularly use many different Forest Service risk assessments—i.e., the section designations in all Forest Service risk assessments remain as consistent as possible.

3.2.3.2. Direct Spray

The direct spray of a member of the general public during tree injections of emamectin benzoate is an implausible exposure scenario.

3.2.3.3. Dermal Exposure from Contaminated Vegetation

Dermal exposure from contaminated vegetation is considered in broadcast applications in which members of the general public could come in contract with contaminated grass or other surface vegetation. The current Forest Service risk assessment addresses only injections of ash trees. While some bizarre scenarios—e.g., dermal contact with an ash tree felled by lightning —might be conceivable, they are highly unlikely. In addition, no data are available on dislodgeable residues of emamectin benzoate on the leaves of ash trees. Thus, this exposure scenario is not developed for the current Forest Service risk assessment.

3.2.3.4. Contaminated Water

Most Forest Service risk assessments consider both accidental spills of pesticides into surface water as well as expected concentrations of pesticides in surface water associated with leaching or runoff from contaminated soil.

If a tree located near surface water is injected with pesticide, it is conceivable that the surface water may be contaminated either through pesticide loss from the tree roots into the surrounding soil or, more likely, from the incidental loss of leaves from the treated tree into the surface water. It is not possible, however, to quantify the amount of pesticide that might reach the surface water. Accordingly, the Forest Service risk assessments of imidacloprid (SERA 2005) and dinotefuran (SERA 2006b) tree injection do not include exposure scenarios for surface water contamination. In addition, as discussed in those the Forest Service risk assessments, this approach is consistent with U.S. EPA risk assessments of these pesticides. The EPA human health risk assessment of emamectin benzoate (U.S. EPA/OPP 2008a) includes surface water exposure assessments for broadcast applications of Proclaim at an application rate of 0.045 lb a.i./acre but does not include surface water exposure assessments for tree injection.

On the other hand, a recent ecological risk assessment conducted by the Environmental Fate and Effects Division (EFED) of the U.S. EPA/OPP (U.S. EPA/OPP 2009a) proposes a surface water exposure assessment for tree injections using Tree-äge. Specifically, based on the labeled rates for tree injection with emamectin benzoate, U.S. EPA/OPP (2009) assumes that 600-42,600 mg a.i. may be applied per tree. These estimates appear to be reasonable, based on the product label. To estimate expected environmental concentrations (EECs), U.S. EPA/OPP (2009a, p. 13) takes the following approach:

> *The total mass of chemical applied to the tree was assumed to enter a 20,000,000 L water body directly; EEC = total mass of chemical/concentration of water.*

The resulting concentrations in surface water range from 0.03 to 2.1 µg/L [600 to 42,600 mg a.i. x 1000 µg/mg ÷ 20,000,000 L]. In the EPA human health risk assessment discussed above, the estimated broadcast application of emamectin benzoate at the maximum allowable rate would lead to peak EECs of 0.57 µg/L emamectin benzoate in surface water (U.S. EPA/OPP 2008a, Table 5.1.9, p. 27). Thus, the EFED assessment seems to suggest that expected concentrations of emamectin benzoate in surface water

following tree injection could be about 4-fold greater [2.1 µg/L ÷ 0.57 µg/L ≈ 3.68] than expected concentrations after broadcast applications.

Although on the face of it, the EFED analysis does not appear to be plausible or even sensible, it is important to understand the full context of the EFED analysis. The discussion in U.S. EPA/OPP (2009a) is not meant to suggest that up to 2.1 µg/L emamectin benzoate might occur in surface water as a result of tree injection. Instead, EPA/OPP uses concentrations of up to 2.1 µg/L as a *screening level* estimate of exposure to determine what if any potential risks may be associated with the application of emamectin benzoate by tree injection. Because this point is critical to the Forest Service risk assessment, the rationale provided by EFED is quoted in detail below:

> *After emamectin benzoate is injected into a tree, it is translocated throughout the tree by the sap. There is currently not an approved model or standard methodology that allows for an estimation of exposure to a pesticide resulting from tree injection. This assessment used screening level estimates of exposure to evaluate potential risks and the value of additional data to refine potential exposures and risks. Submission of a study that measures the fate, uptake and translocation (magnitude of residue study) of emamectin benzoate in trees after injection to allow for an estimation of exposure to terrestrial animals is of high value to this assessment.*
> …
>
> *In addition, if emamectin benzoate is translocated primarily to leaves, then the chemical could enter the soil and be available for runoff into aquatic environments when the leaves fall to the ground. The amount of chemical that could enter the soil and water is related to the number and type of trees that are treated in a given area and the amount of chemical in the leaves.*
>
> U.S. EPA/OPP 2009a, p. 5

The thrust of EPA/OPP's approach appears to be to develop an extreme worst-case assessment that would encourage the development of a study of the fate of emamectin benzoate in trees following tree injection. In response to the registrant's request for approval of tree injection as a labeled application method for emamectin benzoate, the EPA requested a study on the kinetics of emamectin benzoate in trees following tree injection. In response to this request, the registrant appears to have submitted a summary of a study on residues of emamectin benzoate in the pollen of cherry trees following tree injection (U.S. EPA/OPP 2010b). Further information on this study is not available.

Unless there is a compelling reason to take a less conservative approach, Forest Service risk assessments adopt methods that are at least as conservative as those used by U.S. EPA. The current Forest Service risk assessment adopts an approach which is essentially identical to one taken in U.S. EPA/OPP (2009a), which assumes that from 600 to 42,600 mg a.i. of emamectin benzoate contaminate a 20,000,000 liter pond. Forest Service risk

assessments generally use a central estimate as well as upper and lower bounds. For the surface water scenario, the central estimate is taken as 5000 mg a.i., the approximate geometric mean of the upper and lower bounds [$(600 \times 42{,}600)^{0.5} \approx 5055.7$].

The only substantive difference between the current Forest Service risk assessment and the analysis presented in U.S. EPA/OPP (2009a) is that these concentrations are based on the assumption of an accidental spill. This approach is taken because the studies by Takai et al. (2001, 2003, and 2004) discussed in Section 2.3 do not support the assumption that substantial amounts of emamectin benzoate will be transported to surface water following tree injections.

Most Forest Service risk assessments include accidental spill scenarios. These scenarios, however, are based on the assumption that up to 200 gallons of a field solution are spilled into a pond. The underlying scenario entails situations such as the emergency ejection of a full load of a field solution from an aircraft or some other type of vehicle accident. For emamectin benzoate, however, this type of scenario is implausible. As discussed in Section 2, the maximum dose per tree is about 46 grams, equivalent to about 0.1 lbs. Tree-äge contains about 0.36 lbs of emamectin or about 0.4 lb emamectin benzoate, enough to treat about four trees. Thus, 200 gallons of Tree-äge would be sufficient to treat about 800 trees. It does not seem reasonable to assume that 200 gallons of Tree-äge would be used (and thus available for a spill) during the course any single Forest Service operation.

It is more reasonable to assume that a worker drops Tree-äge, equal to a dose used on a single tree, into a pond. This accidental scenario results in surface water concentrations of emamectin benzoate identical to those estimated in U.S. EPA/OPP (2009a).

The accidental spill of emamectin benzoate into a small pond is central to four separate and distinct exposure scenarios, as summarized in Table 7: the consumption of water by a small child, the consumption of fish by the general public or subsistence populations, and swimming in contaminated water. The exposure assessment for the consumption of contaminated water following an accidental spill is detailed in Worksheet D05. This is a standard scenario used in most Forest Service risk assessment in which a child consumes contaminated pond water equal in amount to drinking water a child might assume over the course of an entire day. This exposure scenario is inherently conservative in that it is more likely that any water consumption by a child following an accidental spill would be incidental. In other words, following an accidental spill, steps would be taken to limit exposures to members of the general public. Other exposure scenarios associated with surface water are discussed in the appropriate subsections below.

As also indicated in Table 7, no non-accidental exposure scenarios involving surface water are developed for members of the general public. While it is conceivable that some amount of emamectin benzoate will be transported to surface water at some point following tree injection, the concentrations that might occur in surface water cannot be estimated with any confidence. Takai et al. (2004, p. 47) do provide crude estimates of concentrations in surface water following the injection of pine trees. Based on the

concentrations of emamectin benzoate in pine needles—i.e., 0.011-0.025 µg/g as discussed above—Takai et al. (2004) estimate concentrations of emamectin benzoate in surface water at 3.9-8.9 parts per trillion, equivalent to 0.0039-0.0089 µg/L. These concentrations, however, are based on annual rainfall rates in Japan. The use of annual rainfall rates could underestimate peak concentrations of emamectin benzoate in surface water. Given the lack of information on emamectin benzoate residue in the leaves of ash trees and other tenuous assumptions concerning the transport of leaves to surface water, it is not possible to estimate likely surface water concentrations of emamectin benzoate following its injection into ash trees.

As discussed further in Section 3.4.3, this limitation does not have a severe impact on the human health risk assessment because the apparent risks from accidental exposures suggest that non-accidental exposures associated with incidental surface water contamination are likely to be insubstantial.

3.2.3.5. Oral Exposure from Contaminated Fish

This risk assessment includes acute exposure scenarios involving the consumption of fish from water contaminated with emamectin benzoate as the result of an accidental spill (Worksheets D08a and D08b). The two worksheets account for different rates of wild-caught fish consumption in both general (Worksheet D08a) and subsistence populations (Worksheet D08b). Details of exposure scenarios involving the consumption of contaminated fish are provided in Section 3.2.3.5 of SERA (2007a). As discussed in Section 3.2.3.4, the concentration of emamectin benzoate in surface water associated with non-accidental events (i.e., the typical tree injection) cannot be estimated. Thus, non-accidental exposure scenarios for the consumption of contaminated fish are not developed.

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

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

Bioconcentration is measured as the ratio of the concentration in the organism to the concentration in the water. For example, if the concentration in the organism is 5 mg/kg and the concentration in the water is 1 mg/L, the BCF is 5 L/kg [5 mg/kg ÷ 1 mg/L].

There is only one available study regarding the bioconcentration of emamectin benzoate in fish (Chukwudebe et al. 1996a). In this study, the bioconcentration factor (BCF) for emamectin benzoate in fillet—i.e., the edible portion of fish—is 30 L/kg in bluegill sunfish.

3.2.3.6. Dermal Exposure from Swimming in Contaminated Water

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

water after an accidental spill. As discussed in Section 3.2.3.4, estimates of the concentration of emamectin benzoate in surface water associated with non-accidental events (i.e., the typical tree injection) cannot be made. Thus, non-accidental exposure scenarios for swimming are not developed.

Conceptually and computationally, this exposure scenario is virtually identical to the contaminated gloves scenario used for workers (Section 3.2.2.2)—i.e., a portion of the body is immersed in an aqueous solution of the compound at a fixed concentration for a fixed period of time. The major differences in the two scenarios involve the pesticide concentration in water and the exposed surface area of the body. For the worker wearing contaminated gloves, the assumption is made that both hands are exposed to the field solution—i.e., the concentration of the compound in the applied solution. For the swimmer, the assumption is made that the entire surface area of the body is exposed. Also, like the exposure scenario involving contaminated gloves, the swimming scenario is conservative in that it assumes zero-order absorption directly from the water to the systemic circulation. While the swimmer will not be immersed for 1 hour, the entire body surface is used both as a conservative approximation and to consider intermittent episodes during which the whole body might be immersed or at least wet. The concentration of the pesticide in water is identical to that used in the scenario for the consumption of contaminated water based on peak concentrations in surface water (Section 3.2.3.4).

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

3.2.3.6. Oral Exposure from Contaminated Vegetation

Oral exposure from the consumption of contaminated vegetation often leads to the highest estimates of exposure for members of the general public. Principally in the case of pesticides applied to fruit or berries by broadcast application. The current Forest Service risk assessment addresses only injections of ash trees. It is not plausible to assert that members of the general public will consume the leaves of ash trees. Thus, this exposure scenario is not developed formally for the current Forest Service risk assessment.

While no formal exposure assessment is developed for the consumption of contaminated vegetation, estimated concentrations of emamectin benzoate in the leaves of treated ash trees can be useful to make semi-quantitative elaborations about potential exposures associated with highly improbable events—e.g., contacting leaves on a felled branch from a treated ash tree due to high wind or a lightning strike. Moreover, estimated

concentrations of emamectin benzoate in the leaves of treated ash trees are useful for the ecological risk assessment (Section 4.2.2.3).

While the significance of being able to estimate emamectin benzoate concentrations in the leaves of ash trees treated by tree injection is evident, it must be emphasized that there are no data from which to make realistic estimates. In an ecological risk assessment (U.S. EPA/OPP 2009a, pp. 17-18), the EPA developed an approach to estimating concentrations of emamectin benzoate in the leaves of oak trees treated by tree injection. Based on relationships of tree mass and leaf mass to tree diameter as well as the dosing directions used for Tree-äge (Table 4), U.S. EPA/OPP (2009a) estimates concentrations of emamectin benzoate in oak trees under the assumption that emamectin benzoate is evenly distributed over the entire mass of the tree and under the assumption that emamectin benzoate is distributed only to the leaves in the tree. Based on the assumption of even distribution over the entire mass of the tree, U.S. EPA/OPP (2009a, Table 3.2, p. 17) estimates concentrations of emamectin benzoate in the oak tree at 2.8-9.8 mg a.i./kg tree. Based on the assumption that emamectin benzoate is distributed only to the leaves, U.S. EPA/OPP (2009a, Table 3.3, p. 18) estimates concentrations of emamectin benzoate in the leaves of an oak tree at 80-510 mg a.i./kg leaf. Because of the relationships of dosing to both tree and leaf mass, concentrations of emamectin benzoate are estimated to be higher in smaller trees than in larger trees.

Note that the concentrations estimated in U.S. EPA/OPP (2009a), based on the assumption of uniform distribution throughout the tree (i.e., 2.8-9.8 mg a.i./kg tree), are higher than the upper bound concentrations of emamectin benzoate monitored by Takai et al. (2004) in pine twigs after injections with emamectin benzoate (i.e., about 1.91-2.09 µg/g or mg/kg), as discussed in Section 3.2.3.4. As discussed in Section 2.3, it might be expected that the estimated concentrations based on the assumption of uniform distribution within the entire mass of the tree – i.e., sapwood and heart wood – might underestimate that concentration of emamectin benzoate in sapwood because emamectin benzoate would be expected to distribute predominantly to sapwood. While somewhat speculative, the apparent overestimate of emamectin benzoate in tree tissue based on the assumption of uniform distribution may reflect the limited movement of emamectin benzoate from the injection site. A more detailed study considering the mass balance of emamectin benzoate at various intervals after tree injection is needed in order to further refine the projected concentrations of emamectin benzoate in various tree tissues.

As noted in Section 3.2.3.4, the upper bound concentration of emamectin benzoate in the leaves of pine trees was 0.025 µg/g, below the highest concentration in twigs by a factor of over 80 [2.09 µg/g ÷ 0.025 µg/g ≈ 83.6]. Given the relatively low concentrations of emamectin benzoate in leaves from the study by Takai et al. (2004), the assumption that emamectin benzoate will distribute entirely to leaves does not seem plausible.

The current Forest Service risk assessment is concerned only with injections of Tree-äge into ash trees. Several algorithms are available for estimating the biomass of ash trees (e.g., Ter-Mikaelian and Korzukhin 1997). For the current Forest Service risk assessment, the algorithm for white ash (*Fraxinus americana*) from the study by

Brenneman et al. (1978) as adapted by Ter-Mikaelian and Korzukhin (1997) is used:

$$M = 0.1063\ DBH^{2.4798}$$

where M is the mass in kg (dry weight) and DBH is the diameter at breast high in cm. Of the algorithms reviewed by Ter-Mikaelian and Korzukhin (1997), the above algorithm is selected because it is based on the widest range of DBH—i.e., 5-50 cm—and the correlation coefficient for the algorithm evidences a satisfactory fit—i.e., $r^2 = 0.99$.

Worksheet B07 of the EXCEL workbook that accompanies this risk assessment, implements the above equation to estimate the weight of ash trees with diameters (DBH) of 5-71 inches. The corresponding doses for trees of differing sizes (Table 4) are divided by their estimated mass to determine emamectin benzoate concentrations in ash trees, assuming uniform distribution. The results of this analysis are illustrated in Figure 7 and indicate that emamectin benzoate concentrations in treated ash trees, based on the assumption of uniform distribution, could range from about 0.37 to 18.61 mg a.i./kg tree. For 12 and 36 inch oak trees, the EPA estimates concentrations of 9.8 and 2.8 mg a.i./kg, respectively (U.S. EPA/OPP EPA 2009a). For ash trees of the same size, the above estimates are similar—i.e., 14 and 2.9 mg a.i./kg, respectively. As indicated in U.S. EPA/OPP (2009a) and illustrated in Figure 7, the concentration of emamectin benzoate in ash trees tends to decrease with increasing tree size.

For injection treatments with emamectin benzoate, the relationship between tree size and its estimated concentrations in trees may be a significant factor. An equally significant factor, however, may be the concentration of emamectin benzoate in leaves, as opposed to whole trees. As discussed above, Takai et al. (2004) noted that the upper bound concentrations in leaves were below the upper bound concentrations in the leaves of pine by a factor of over 80. For exploring potential risks of humans or other nontarget species to exposure from the injection of ash trees, adjusting the concentrations downward by a factor of 80 may be questionable, given the lack of available data on residues in the leaves of ash trees. As a more protective approximation, the concentrations of emamectin benzoate are estimated as one-tenth that based on concentrations in the whole tree. As illustrated in Figure 7, the estimated concentrations of emamectin benzoate in whole trees range from about 0.4 to 18.6 mg/kg.

In terms of potential human exposure from a child mouthing ash leaves, the concentrations of emamectin benzoate are taken as about 0.04 to 2 mg/kg leaf (equivalent to 0.00004 to 0.002 mg/g). These concentrations are used to construct crude exposure scenarios for a small child (10 kg) coming into contact with a downed limb from a treated ash tree. While it is not reasonable to assume that a child would eat ash leaves, small children may engage in hand-to-mouth activities that adults would avoid. If a 10 kg child were to place one gram (0.001 kg) of ash leaves into his or her mouth, the total potential dose to the child would be in the range of 0.00004-0.0002 mg a.i./kg bw [0.00004-0.002 mg/g leaf x 1 g leaf ÷ 10 kg bw]. While these doses are not proposed as a formal exposure scenario, the estimates may be used to modestly elaborate the risk characterization (Section 3.4.3). Given the inability to provide reasonable estimates for

many of the exposure assessments typically included in a Forest Service risk assessment, this modest elaboration seems justified.

3.3. DOSE-RESPONSE ASSESSMENT

3.3.1. Overview

An overview of the acute and chronic RfDs for emamectin benzoate is provided in Table 8 of the current Forest Service risk assessment. All RfDs are adopted directly from the recent EPA human health risk assessment (U.S. EPA/OPP 2008a). The use of EPA RfDs is a common practice in Forest Service risk assessments. The EPA designates several toxicity values for different routes and durations of exposure—i.e., seven toxicity values for non-occupational exposure (U.S. EPA/OPP 2008a, Table 3.4.1, pp. 19-20) and four toxicity values for occupational exposure (U.S. EPA/OPP 2008a, Table 3.4.2, p. 21). Nonetheless, all of the toxicity values are based on the same NOAEL, 0.075 mg/kg bw/day for the 14-day neurotoxicity study by Gerson (1992g) on a plant metabolite of emamectin benzoate. All acute toxicity values use an uncertainty factor of 300 to derive an acute RfD of 0.00025 mg/kg bw/day. All of the longer-term toxicity values use an uncertainty factor of 1000 to derive a chronic RfD of 0.000075 mg/kg bw/day.

3.3.2. Acute RfD

Acute RfDs are generally derived from developmental (i.e., teratology) studies in rats or rabbits. These studies involve relatively short-term periods of exposure, and the observed effects often associated with a single dose. As discussed in Section 3.1.9.1 and summarized in Appendix 2 (Table 3), the developmental toxicity study by Wise (Wise 1993a; Wise et al. 1997) yielded a NOAEL of 0.1 mg/kg bw/day with signs of neurotoxicity at a dose of 0.6 mg/kg bw/day.

While the NOAEL of 0.1 mg/kg bw/day typically would be used as the basis for the acute RfD, U.S. EPA/OPP (2008a) adopts a somewhat more conservative approach, using the NOAEL of 0.075 mg/kg bw/day from the 14-day neurotoxicity study by Gerson (1992g) in which the LOAEL is 0.1 mg/kg bw/day, based on gross signs of toxicity (neural degeneration and mortality) as well as decreases in food consumption and body weight. This approach is somewhat unusual in that the study by Gerson (1992g) involves a plant metabolite of emamectin benzoate—i.e., 4"-epi-(N-formyl-N-methyl)-amino-4"-deoxyavermectin B1, also designated as L-660,599.

The EPA human health risk assessment (U.S. EPA/OPP 2008a) considers broadcast applications of emamectin benzoate to nut-bearing trees as well as the injection of ornamental trees. Because the EPA risk assessment considers applications to trees that produce consumable items, basing the RfD for members of the general public on the more toxic plant metabolite of emamectin benzoate seems reasonable.

The acute RfD is derived by dividing the NOAEL of 0.075 mg/kg bw by an uncertainty factor of 300, a factor of 10 for animal-to-human extrapolation, a factor of 10 sensitive individuals in the human population, and a factor of 3 for concerns that infants and children may be particularly sensitive to emamectin benzoate. Thus, the RfD is 0.00025 mg/kg bw [0.075 mg/kg bw ÷ 300].

The concern for infants and children is based on the developmental study by Wise (Wise 1993a; Wise et al. 1997). In this study, no signs of maternal toxicity were noted at the

highest dose tested (lowered from 3.6 to 2.4 mg/kg bw/day); however, signs of neurotoxicity in offspring were noted at 0.6 mg/kg bw/day. Accordingly, the EPA judged that children may be more sensitive than adults. Under the Food Quality Protection Act (FQPA), the EPA is mandated to consider the potential sensitivity of children to pesticides and elected to use the factor of 3 to account for that potentially greater sensitivity to emamectin benzoate.

Within the context of the current Forest Service risk assessment, using the study Gerson (1992g) conducted on the more toxic plant metabolite of emamectin benzoate is questionable. As discussed in Section 2, the current Forest Service risk assessment is concerned only with the injection of ash trees. As noted in Section 3.2.3.6, there is no reasonable basis for asserting that humans will consume the leaves of ash trees. A case could clearly be made for using the somewhat higher NOAEL for emamectin benzoate—i.e., 0.1 mg/kg bw/day from the study by Wise (Wise 1993a; Wise et al. 1997). The difference in the resulting RfD, however, would be insubstantial. Because the FQPA uncertainty factor of 3 is based on the study by Wise, the RfD would use the uncertainty factor of 300 as used by U.S. EPA/OPP. Thus, the RfD based on the study by Wise would be 0.0003 mg/kg bw/day rather than 0.00025 mg/kg bw. This difference is insubstantial. As discussed further in Section 3.4.3, using the modestly higher acute RfD of 0.0003 mg/kg bw would not have a substantial impact on the risk characterization. Thus, the U.S. EPA/OPP (2008a) acute RfD of 0.00025 mg/kg bw/day is maintained in the current Forest Service risk assessment.

3.3.3. Chronic RfD

Chronic RfDs are typically based on chronic NOAELs involving lifespan or close to lifespan exposures in mice or rats. U.S. EPA/OPP (2008a) bases the chronic RfD on the same study used to derive the acute RfD. As discussed in the previous subsection, the NOAEL used to derive the RfD is 0.075 mg/kg bw/day is taken from the 14-day neurotoxicity study by Gerson (1992g) on the plant metabolite of emamectin benzoate.

The only difference between the acute and chronic RfD is the uncertainty factor. For the chronic RfD, U.S. EPA/OPP (2008a) uses an uncertainty factor of 1000 rather than 300. As with the acute RfD, the uncertainty factor consists of a factor of 10 for animal-to-human extrapolation and a factor of 10 for sensitive individuals in the human population. The third element of the uncertainty factor for the chronic RfD is taken as 10 rather than 3 based on concerns for greater sensitivity of children to emamectin benzoate, relative to adults. The increase in the uncertainty factor from 3 to 10 appears to be a judgmental adjustment made by U.S. EPA/OPP to account for longer-term exposures. Thus, the chronic RfD is 0.000075 mg/kg bw/day [0.075 mg/kg bw/day ÷ 1000], a factor of about 3 below the acute RfD [0.00025 mg/kg bw/day ÷ 0.000075 mg/kg bw/day ≈ 3.33].

The apparent rationale for using an acute neurotoxicity study rather than a more standard chronic toxicity is simple. As discussed in Section 3.1.5 and summarized in Appendix 2, Table 5, the NOAELs from chronic toxicity studies with emamectin benzoate are substantially higher than the NOAEL of 0.075 mg/kg bw/day for the plant metabolite—i.e., 0.25 mg/kg bw/day in the chronic dog study (Gillet 1992a), 2.5 mg/kg bw/day from the chronic mouse study (MRID 43868105), and 1 mg/kg bw/day from the chronic rat

studies (Gerson 1992b; MRID 43868104). It is also worth noting that the NOAEL from the 16-day neurotoxicity study in mice with emamectin benzoate—i.e., 0.1 mg/kg bw/day (Gerson 1992e)—is likewise below the chronic NOAELs for emamectin benzoate.

U.S. EPA/OPP (2008a) does not specifically discuss the issue of lower NOAELs in the subchronic neurotoxicity studies relative to the NOAELs in the chronic toxicity studies. This pattern, however, is not unique to emamectin benzoate. In some chronic toxicity studies, transient effects may be seen early in the study at a dose which is classified as a chronic NOAEL. As noted in 3.1.5, cleared reviews are available only for the chronic toxicity study in dogs (Gillet 1992a). For dogs, the chronic NOAEL of 0.25 mg/kg bw/day (Gillet 1992a) is identical to the NOAEL in the subchronic toxicity study in dogs (Mason 1992a). In the absence of DERs and/or access to the full chronic studies in mice and rats, no further discussion of relationship of the NOAELs from the subchronic neurotoxicity studies to the NOAELs in the chronic toxicity studies in mice and rats is warranted. In any event, the EPA's selection of the more sensitive subchronic toxicity studies in mice rather than the chronic toxicity studies in mice or rats as the basis for the chronic RfD appears to be justified by (U.S. EPA/OPP 2008a).

In the context of the current Forest Service risk assessment, concerns with the chronic RfD are essentially identical to concerns with the acute RfD. Injection of emamectin benzoate into ash trees should not put members of the general public at risk of exposure to plant metabolites of emamectin benzoate. As discussed in Section 3.2.3, the only plausible exposures that can be quantified in the current Forest Service risk assessment involve acute exposures associated with the accidental spill of emamectin benzoate into a small pond. Thus, the value of the chronic RfD has no direct impact on the risk characterization for members of the general public in the current Forest Service risk assessment.

3.3.4. Surrogate RfD for Occupational Exposures

Technically, the U.S. EPA/OPP does not use RfDs to characterize risks to workers. Instead, the EPA uses a margin of exposure (MOE) approach which involves dividing a selected animal NOAEL by the estimated worker exposure. If the ratio is greater than the EPA specified MOE for a particular chemical, risks to workers are not of concern. If the ratio of the animal NOAEL to the worker exposure is less than the MOE, risks to workers are a concern. As discussed in the documentation for preparing Forest Service risk assessments (SERA 2007), this approach is mathematically equivalent to using the animal NOAEL divided by the EPA specified MOE as a surrogate RfD.

As summarized in Table 8, the surrogate acute and chronic RfDs derived from the designated NOAELs and MOEs in U.S. EPA/OPP (2008a) are identical to the acute and chronic RfDs discussed in the previous subsections. The only difference involves the rationale for the MOEs/uncertainty factors. Two components of the MOEs are identical to those used for the uncertainty factors in the RfDs—i.e., a factor of 10 for animal-to-human extrapolation and a factor of 10 for sensitive individuals in the human population.

Quantitatively, the third component of the MOEs for occupational exposures is identical to the uncertainty factors —i.e., a factor of 3 for acute exposures and a factor of 10 for

chronic exposures. The rationale for these factors, however, is different from the FQPA considerations used in the RfDs. Rather than concern for the sensitivity of children, U.S. EPA/OPP (2008a) indicates that the third component is based on … *the steepness of the dose response curve,* [and] *severity of effects at the LOAEL (death and neuropathology)* (U.S. EPA/OPP 2008a, p. 17). For acute exposures, this is the basis for a factor of 3. For chronic effects, these considerations as well as the use of a subchronic study are the basis for using a factor of 10.

Nonetheless, the rationale for using severity of effects as a consideration in the uncertainty factors of 3 and 10 appears to relate only to the study by Gerson (1992g) on the plant metabolite. As noted in Section 3.3.2 and emphasized in the above quotation from U.S. EPA/OPP (2008a), the NOAEL in the Gerson (1992g) study is 0.075 mg/kg bw/day. At a dose of 0.1 mg/kg bw/day, adverse effects included frank signs of neurotoxicity as well as death, which is clearly a reasonable concern to U.S. EPA/OPP.

On the other hand, the Gerson (1992g) study on the plant metabolite of emamectin benzoate is not directly relevant to worker exposure scenarios involving only broadcast or tree injection applications of emamectin benzoate and not simultaneous consumption of the treated plants, which might expose the workers to substantial levels of the plant metabolite. Thus, a compelling argument can be made that the rationale for the MOE specified in U.S. EPA/OPP (2008a) is flawed.

Notwithstanding the above concerns, it is likely that the numerical values of the MOEs can be supported. Although the issue is addressed specifically in U.S. EPA/OPP (2008a), some pesticide applicators may be female; in which case, the requirements of the Food Quality Protection Act (FQPA) could and probably would be used to support the uncertainty factor of 3 for acute exposures and 10 for chronic exposures. If this approach were taken, the only numerical difference between the approach taken in U.S. EPA/OPP (2008a) and an approach based on the toxicity values for emamectin benzoate would concern the NOAEL—i.e., a NOAEL of 0.1 mg/kg bw/day for emamectin benzoate versus a NOAEL of 0.075 mg/kg bw/day for the plant metabolite. As discussed in Section 3.3.2, the differences between these two approaches are insubstantial. Thus, while this Forest Service risk assessment questions the rationale for the MOE recommended by U.S. EPA/OPP (2008a), it uses RfD equivalents for occupational exposure (Table 8) that are identical to those based on the EPA's MOE (U.S. EPA/OPP 2008a).

3.3.5. Dose-Severity Relationships

Forest Service risk assessments typically consider dose-severity relationships to elaborate concerns for modest excursions above the acute or chronic RfD. As discussed further in Section 3.4, considerations of dose-severity relationships are not especially useful in the risk assessment for workers. For members of the general public, however, some exposure scenarios lead to modest excursions (i.e.,HQ of 2-3) above the acute RfD.

As discussed in the previous subsections, the dose-severity relationships for the plant metabolite of emamectin benzoate appear to be very steep with a NOAEL of 0.075 mg/kg bw/day but a LOAEL of 0.1 mg/kg bw/day (Gerson 1992g). As noted above, the

LOAEL should probably be referred to as a frank effect level—gross signs of neurotoxicity as well as death in some animals. Albeit highly improbable, exposure of members of the general public to plant metabolites of emamectin benzoate would result in HQs of 2-3.

For emamectin benzoate, the dose-severity relationships do not appear to be as steep as those for the plant metabolite. Nonetheless, in the 16-day neurotoxicity in mice, the NOAEL for emamectin benzoate is 0.1 mg/kg bw/day with a corresponding LOAEL of 0.3 mg/kg bw/day (Gerson 1992e). While this LOAEL was not associated with mortality, a broad spectrum of neurotoxicity, including a moribund condition in some animals, was noted. Thus, the dose-severity relationships for emamectin benzoate itself appear to be reasonably steep, and modest excursions above the RfD are a concern.

3.4. RISK CHARACTERIZATION

3.4.1. Overview

Summaries of the risk characterizations are provided in Table 9 for workers and in Table 10 for members of the general public. As detailed in the exposure assessment (Section 3.2), the most plausible exposure scenarios are those for workers applying emamectin benzoate in a manner consistent with labeled directions, which include the proper use of chemical resistant gloves. For these exposure scenarios, there is no basis for asserting that workers will be at risk.

If workers do not effectively use chemical resistant gloves, hazard quotients (HQs) could substantially exceed the level of concern (HQ=1) with upper bound HQs ranging from about 2 to more than 70, depending on the duration of exposure and the method used to estimate worker exposure. In addition, accidental exposure scenarios involving spills of emamectin benzoate onto the lower legs or hands lead to upper bound HQs ranging from 12 to more than 2000. Despite the varying degrees of confidence in the exposure estimates for the scenarios involving the failure to use gloves as well as the accidental exposure scenarios, the qualitative risk characterization for workers is unambiguous. If workers handle emamectin benzoate with care and effectively use chemical resistant gloves, they are not at substantial or significant risk of adverse effects. If, however, they fail to use chemical resistant gloves effectively or do not effectively and rapidly respond to accidental exposures, they may be at risk of adverse effects, including degenerative changes in nerve tissue.

Members of the general public do not appear to be at risk of significant exposure to emamectin benzoate used in Forest Service programs, although risks from possible exposure cannot be estimated quantitatively at this time. Based on accidental exposure scenarios associated with the spill of emamectin benzoate into a pond, the central estimates of HQs are below the level of concern (HQ=1). The upper bound estimates of the HQs range from 0.6 to 3.

A serious limitation in this risk assessment is the inability to estimate exposures for members of the general public with respect to the normal and expected use of emamectin benzoate—i.e., injection of Tree-äge into ash trees. Nonetheless, the upper bound HQ for all of the accidental exposure scenarios involving members of the general public is only 3. Thus, under conditions of normal use, about one-third of the emamectin benzoate injected into an ash tree would have to be transported to surface water in order for the HQs associated with non-accidental exposures to reach a level of concern. It does not seem reasonable to assert that this level of exposure would or could occur.

3.4.2. Workers

3.4.2.1. Summary of Scenarios

From a practical perspective, most exposures to emamectin benzoate are likely to be occupational (i.e., to involve workers applying Tree-äge by injection into ash trees). Consequently, several elaborations to the exposure assessment and hence risk characterization for workers are made. Typical Forest Service risk assessments

characterize worker risks associated with general exposures—i.e., the types of exposure anticipated in the normal application of the pesticides—as well as a standard set of accidental exposures. For emamectin benzoate, a more elaborate risk characterization is made using both exposure assessments based on standard Forest Service methods (Section 3.2.2.1.3) as well as deposition-based exposure assessments typically used by U.S. EPA/OPP (Section 3.2.2.1.2). A further elaboration is made based on the use of chemical resistant gloves. This elaboration is made because the use of chemical resistant gloves has a major impact on the risk characterization. A final elaboration is made based on the duration of exposure. Tree injection is a labor intensive process, and the extent and frequency of this application method is not clear at this time. Thus, risks are characterized based on both acute exposures that may occur if tree injections are made infrequently as well as longer-term exposures that might apply to workers over the course of an application season.

Table 9, which provides an overview of the risk characterization for workers, is a duplicate of Worksheet E02 in the EXCEL workbook that accompanies this risk assessment. Table 9 is divided into three sections: accidental exposures, general exposures associated with the ineffective use of personal protective equipment, and general exposures associated with the effective use of personal protective equipment. Each section involving general exposures is further divided into longer-term exposures in which HQs are based on the chronic RfD, and shorter-term exposures are based on the acute RfD.

3.4.2.2. Proper Use of Protective Equipment

Work exposure to emamectin benzoate is most likely to involve general applications of Tree-äge with the effective use of personal protective equipment. As discussed in Section 3.2.2.1, Tree-äge is a restricted use pesticide and the product label for Tree-äge requires the use of chemical resistant gloves. Because Tree-äge is a restricted use pesticide, applications can only be made by or under the supervision of certified pesticide applicators. Consequently, it is reasonable to assume that applications will be made using all precautions mandated on the product label, including the use of chemical resistant gloves.

Under the assumption that chemical resistant gloves and other prudent application practices are followed, there is no basis for asserting that risks to workers are likely to occur. As indicated in Table 9, the HQs for longer-term applications of emamectin benzoate are 0.08 (0.004 to 0.6) based on standard Forest Service exposure methods and 0.08 (0.03 to 0.2) based on exposure methods used by U.S. EPA/OPP. The only major reservation with the benign risk characterization for workers is the lack of worker exposure studies involving tree injections of emamectin benzoate or other pesticides, which adds obvious uncertainty to the risk assessment.

As discussed in Section 3.2.2.1, two independent methods for estimating worker exposure yield extremely similar results. The upper bound of the HQs based on the absorbed dose rate method typically used in Forest Service risk assessments (HQ=0.6) is somewhat higher than the upper bound of the HQs based on EPA methods (HQ=0.2). The worker exposure rates based on the Forest Service method, however, are derived

from backpack applications. Backpack applications are associated with the highest rates of worker exposure rates based on biomonitoring (Table 6); accordingly, it is reasonable to assert that the use of exposure rates for backpack applications would overestimate, and probably grossly overestimate, worker exposures that might occur during tree injection. Both sets of worker exposure assessments are based on the assumption that chemical resistant gloves will be highly effective (i.e., 99.22%) in reducing worker exposures. As discussed in Section 3.2.2.1.2, this worker protection factor is based on a data set judged to be of high quality by the U.S. EPA/OPP (Keigwin 1998).

As also discussed in Section 3.2.2.1, the upper bound of the HQs for workers is based on the U.S. EPA/OPP estimate that workers might make up to 160 injections in a single day. Thus, in a typical 8-hour work day, a worker might make up to 20 injections per hour or one injection every 3 minutes. Given that workers need a certain amount of setup time as well as time to travel to the different trees that might be treated in the course of a single day, the estimate of 160 injections per day may overestimate plausible exposures. Given the highest HQ (i.e., 0.7 using the Forest Service exposure methods), a worker would have to make about 230 injections per day [$160 \div 0.7 \approx 228.6$] or about 1 injection every 2 minutes in order to reach the level of concern (HQ=1).

3.4.2.3. Ineffective Use of Protective Equipment

The hazard quotients for the ineffective use of personal protective equipment (i.e., the center section of Table 9) are a substantial concern, with HQs of 11 (0.5 to 73), based on the standard Forest Service method and HQs of 3 (1.4 to 6), based on the deposition method used by U.S. EPA/OPP. As discussed in Section 3.3.5 (Dose-Severity Assessment), the LOAELs from the subchronic neurotoxicity studies in mice involving exposure to the plant metabolite of emamectin benzoate (Gerson 1992g) as well as to emamectin benzoate itself (Gerson 1992e) are relatively close to the corresponding NOAELs. In addition, the LOAELs are based on relatively severe signs of neurotoxicity as well as mortality or morbidity. While there are no data on dose-severity relationships in humans, the neurotoxicity studies in mice suggest that HQs slightly greater than 1 could be associated with severe toxic effects in workers. Thus, the effective use of personal protective equipment, as required on the product label for Tree-äge, is critical for workers who inject trees with emamectin benzoate.

3.4.2.4. Accidental Exposures

The accidental exposures for workers (i.e., the upper section of Table 9) are also of substantial concern across the range of scenarios and estimated levels of exposure. This is not unusual. The accidental exposure scenarios used in Forest Service risk assessments often exceed the level of concern.

Two types of accidental exposure scenarios are used, contaminated gloves (based on zero-order absorption kinetics) and accidental spills (based on first-order absorption kinetics). As detailed in Section 3.1.3.2.2, there is very low confidence in the estimated zero-order absorption rate for emamectin benzoate. The estimate of the zero-order dermal absorption rate is based on an algorithm developed by the EPA (U.S. EPA 1992, 2007). The EPA algorithm is relatively well-documented and credible, however,the molecular weight of emamectin benzoate exceeds the molecular weights of the

compounds on which the algorithm is based. Conversely, the exposure estimates for the accidental spill scenarios (Section 3.1.3.2.1) are based on an experimental first-order dermal absorption rate in primates (Wrzesinski et al. 1997). Consequently, confidence in the HQs for the accidental spill scenarios is relatively high. For these scenarios, the HQs are 6 (3 to 12) for spills onto the hands and 15 (8 to 31) for spills onto the lower legs.

The qualitative interpretation of the HQs for the accidental spill scenarios is relatively simple. Any spill of emamectin benzoate onto to the skin or clothing should be regarded as a serious event. Prompt action should be taken to decontaminate the skin and clothing. Any signs of toxicity or indication of abnormally high levels of exposure warrants prompt medical attention.

As noted in Section 3.1.11, emamectin benzoate is a severe eye irritant. Few details are available on the eye irritation studies, and there is some confusion concerning the irritancy of emamectin benzoate technical versus emamectin benzoate technical II. Nonetheless, U.S. EPA/OPP (2008a) indicates that both of these materials may cause severe irritation to the eyes. The product label for Tree-äge indicates that protective eyewear should be used when handling or applying Tree-äge.

Two types of labels were located for Tree-äge, special local needs labels for various states and a more detailed label for Tree-äge, which is available at the Arborjet web site (http://www.arborjet.com/products/injectables.htm). The latter product label provides the following recommendation for first aid in the event of eye contamination:

> *Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.*

Given the available information on the irritant effects of emamectin benzoate to the eyes, the use of protective eyewear should be ensured in any application of Tree-äge.

3.4.3. General Public

While the risk characterization for workers is more elaborate than those in most Forest Service risk assessments, the risk characterization for members of the general public is much more limited than those in most Forest Service risk assessments. As discussed in Section 3.2.3, this limitation is imposed by the lack of data on the kinetics of emamectin benzoate in trees, which precludes the development of meaningful assessments of non-accidental exposures for members of the general public.

3.4.3.1. Accidental Spill Scenarios

Based on an approach taken in a recent EPA ecological risk assessment (U.S. EPA/OPP 2009a), the current Forest Service risk assessment develops several exposure scenarios associated with an accidental spill of emamectin benzoate into a pond (Section 3.2.3.4). The HQs developed for these accidental exposure scenarios are summarized in Table 10. The upper bounds of exposure scenarios for the consumption of water by a small child and for the consumption of fish by a typical member of the general public do not exceed

the level of concern (HQ=1). Modest excursions above the level of concern are apparent at the upper bounds of the HQs for the consumption of contaminated fish by subsistence populations and for a young woman swimming in contaminated water for 1 hour.

As discussed in Section 3.3.5, relatively modest excursions above the RfD for emamectin benzoate may be of concern because of the proximity of the LOAELs to the NOAELs as well as the severity of the LOAELs in the neurotoxicity studies on mice. Given the lack of any data on the effects of emamectin benzoate in humans, however, the dose-severity relationships cannot be overly interpreted. The simplest qualitative interpretation of the HQs for the accidental exposure scenarios is that it would be prudent to limit human exposures to contaminated water in the event of an accidental spill of emamectin benzoate.

Apart from stating the obvious with respect to an accidental spill, the risk characterization for the accidental exposure scenarios may have some limited use in at least semi-quantitatively considering plausible risks to the general public in the normal use of emamectin benzoate for the injection of ash trees. In other words, the highest HQ is 3. If a large ash tree located next to a 20 million liter pond—i.e., the EPA standard farm pond—is injected with emamectin benzoate, one-third of the emamectin benzoate would have to be transported simultaneously by some mechanism into the pond in order for the HQ to reach a level of concern. It is difficult to envision how this would occur. The most likely event is that most of the injected emamectin benzoate would remain in the tree. This is the basic benefit of tree injection. Some transport to surface water might occur; however, the loss would be gradual and would most likely be associated with incidental loss of leaves from the ash tree with some deposition of the leaves into surface water. While the kinetics of this process cannot be quantified, it does not seem reasonable to assert that one-third of the emamectin benzoate would be in the pond at any given time.

The above discussion is not intended to be dismissive of potential risk. If a large number of high value ash trees near a small body of water were treated with emamectin benzoate injections, the risks would be higher than the scenario discussed above. Whether or not the exposures would reach a level of concern cannot be determined. On the other hand, if several large ash trees not near a body of water were treated emamectin benzoate injections, risks associated with the contamination of surface water could be negligible.

3.4.3.2. Consumption of Vegetation (Semi-quantitative)

While no formal exposure assessment is conducted in the current Forest Service risk assessment for exposure scenarios other than an accidental spill of emamectin benzoate into surface water, Section 3.2.3.6 does discuss a very atypical exposure scenario in which a child might place 1 gram of leaves from a downed limb of a treated ash tree into his or her mouth. In this case, the estimated dose to the child would range from approximately 0.00004 to approximately 0.0002 mg a.i./kg bw (i.e., $4x10^{-5}$ mg/kg bw to $2x10^{-4}$ mg/kg bw. The lower bound of the estimated dose for this scenario ($4x10^{-5}$ mg/kg bw) is similar to the central estimates of concentrations associated with the accidental spill scenarios —i.e., from about $2x10^{-5}$ to $8x10^{-5}$ from Worksheet E03—and is below the acute RfD of 0.00025 mg/kg bw. The upper bound of dose for the scenario based on contaminated leaves ($2x10^{-4}$ mg/kg bw) is modestly below the upper bound of the

scenario associated with the consumption of contaminated water following an accidental spill (i.e., $2.4x10^{-5}$ mg/kg bw). Using the acute RfD of 0.00025 mg/kg bw, the dose of $2x10^{-4}$ mg/kg bw would lead to an HQ of 0.8, approaching but below the level of concern. Thus, the minor elaboration of the exposure assessment involving contaminated leaves adds little to the risk characterization. Nonetheless, this elaboration does suggest that it would be prudent to dispose properly of any branches of treated ash trees that might accidently be lost from incidental damage (e.g., high wind or lightning strikes) to treated trees.

While semi-quantitative discussions of risk given in this risk characterization are not satisfying, data on which to base a definitive risk characterization for members of the general public (i.e., the kinetics of emamectin benzoate in ash trees) are currently unavailable. In any specific program involving the injection of ash trees with emamectin benzoate, some common sense will need to be exercised in considering and responding to the potential risks associated with the contamination of surface water or ash leaves.

3.4.4. Sensitive Subgroups

As discussed in Section 3.3, children are the most obvious group of individuals at risk from exposures to emamectin benzoate. Given the adverse effects of emamectin benzoate on offspring in the developmental study by Wise (Wise 1993a; Wise et al. 1997) as well as the decrease in fecundity observed in the reproduction study by Lankas (1992c), concern for effects in children may be extended to women of childbearing age. Nonetheless and as detailed in Section 3.3, concerns for adverse effects in children exposed to emamectin benzoate are addressed specifically in U.S. EPA/OPP (2008a) with the application of the Food Quality Protection Act (FQPA) uncertainty factors for the acute and chronic RfDs.

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

As discussed in detail in Sections 3.1.14 (Inerts and Adjuvants) and 3.1.15 (Impurities and Metabolites), emamectin benzoate formulations contain inert components, and the metabolism of emamectin benzoate may involve the formation of numerous other compounds, some of which may be more toxic than emamectin benzoate itself. In some respects, concern for toxic metabolites is encompassed by the U.S. EPA/OPP RfDs for emamectin benzoate, which are based on the most toxic metabolite of emamectin benzoate. As noted in Section 3.3., the RfDs proposed by U.S. EPA/OPP are adopted and used in the current Forest Service risk assessment.

Inerts are a much more difficult issue to address, and it is beyond the scope of this risk assessment to address the subject in detail. This is a general issue in all Forest Service risk assessments. For emamectin benzoate, however, the inerts appear to consist primarily of nonspecific neurotoxins —i.e., CNS depressants. As discussed in Section 3.1.14, the highly specific and highly potent neurotoxicity of emamectin benzoate suggests that emamectin benzoate is the toxic agent of primary concern in the current Forest Service risk assessment.

3.4.6. Cumulative Effects

Similar to the issues involved in assessing the use of inerts, 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 emamectin benzoate. 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 recent EPA human health risk assessment on emamectin benzoate states:

> *… EPA has not made a common mechanism of toxicity finding as to emamectin benzoate and any other substances and emamectin benzoate 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 emamectin benzoate has a common mechanism of toxicity with other substances..*
>
> – U.S. EPA/OPP, 2008a, p. 34.

Notwithstanding the above statement, emamectin benzoate is a chloride channel activator, and other pesticides in this group (e.g., abamectin and milbemectin) are likely to have the same mechanism of action as emamectin benzoate (Section 3.1.2). Consequently, combined exposures to these other pesticides as well as other GABA inhibitors are likely to lead to additive effects.

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

4. ECOLOGICAL RISK ASSESSMENT

4.1. HAZARD IDENTIFICATION

4.1.1. Overview

Emamectin benzoate is an effective insecticide to which insects appear to be far more sensitive than most other organisms. In the honey bee, the contact LD_{50} is about 0.035 mg/kg bw, more than 600 times lower than the oral LD_{50} of 22 mg/kg bw in mice. Most of the toxicity data for other insects are expressed in units of LC_{50} values for either oral or contact exposures or in units of application rate (i.e., kg a.i./ha). While these toxicity values are not directly comparable to the LD_{50} in bees, the equivalent LD_{50} values in sensitive populations of lepidopterans are about 0.001 mg/kg bw. There is substantial variability in dietary LC_{50} values for different populations of lepidopterans, ranging from 0.001 to 2.4 mg/L. While resistance to emamectin benzoate among populations of lepidopterans might account for some of the apparent differences in sensitivity, studies specifically designed to assess the development of resistance in insect populations report resistance factors of no greater than 5. Thus, it seems that the highly variable LC_{50} values reported in insect studies may reflect differences in the methods used to conduct the studies. While studies are available on the efficacy emamectin benzoate against some coleopteran species, no studies were identified on the toxicity of emamectin benzoate to the emerald ash borer.

Emamectin benzoate is much less toxic to mammals and birds than to insects. As noted above, the lowest mammalian LD_{50} is 22 mg/kg bw. The lowest avian LD_{50} is 46 mg/kg bw. These differences are relatively modest and suggest that sensitivities in mammals and birds are similar. Data are available on only few species of mammals and birds, and any generalizations regarding sensitivity are tenuous. Nonetheless, the available data suggest that in mammals, small animals (i.e., mice) are somewhat more sensitive than larger animals. In birds, the opposite relationship is apparent.

Data are not available on the effects of emamectin benzoate on reptiles, terrestrial-phase amphibians, or terrestrial microorganisms. Emamectin benzoate does not appear to be toxic to terrestrial plants. The injection of emamectin benzoate into trees is associated with injection site injury.

Information on the toxicity of emamectin benzoate to aquatic species consists of a standard set of bioassays in fish, aquatic invertebrates, and aquatic plants as well as some unusual studies associated with the use of emamectin benzoate in the control of sea lice in farmed Atlantic salmon. Based on standard acute toxicity studies, emamectin benzoate is highly toxic to freshwater fish and invertebrates. In saltwater/estuarine species, emamectin benzoate is very highly toxic to invertebrates but only moderately toxic to fish. Data on aquatic plants are limited to a very simple Tier 1 study that identifies NOAELs but not LOAELs.

4.1.2. Terrestrial Organisms

4.1.2.1. Mammals

As discussed in the human health risk assessment (Section 3.1), virtually all of the information available on the toxicity of emamectin benzoate to mammals comes from standard toxicity studies submitted to the U.S. EPA in support of the registration of emamectin benzoate. These studies are also relevant to the assessment of potential hazards to mammalian wildlife. Based on an acute oral LD_{50} value of 22 mg/kg bw in mice (MRID 42743612), U.S. EPA/OPP (2008b, Table D4, p.74) classifies emamectin benzoate as highly toxic to mammals in terms of acute oral toxicity.

The ecological risk assessment attempts to identify subgroups of mammals that may display greater or lesser sensitivity to a particular pesticide. These differences may be based on allometric scaling (e.g., Boxenbaum and D'Souza 1990) or differences in physiology. As discussed in Section 3.1.4, mice appear to be more sensitive than rats to the acute toxicity of emamectin benzoate. Mice were also more sensitive than either rats or dogs in repeated dose toxicity studies (Section 3.1.5). The data on mammals, however, are insufficient to determine whether these differences in sensitivity are related to body size, physiological differences, or simply to random variability among different studies conducted at different times in different laboratories. For some compounds, particularly weak acids, dogs are somewhat more sensitive than rodents. There is no indication, however, that dogs are more sensitive than rodents to emamectin benzoate. Thus, for the current Forest Service risk assessment, separate toxicity values are not derived for canids (Section 4.3.2). In addition, in the absence of a clear relationship between body weight and toxicity across a range of mammalian species, separate toxicity values are not derived for small and large non-canid mammals.

As in the human health risk assessment, neurotoxicity is the endpoint of concern for emamectin benzoate. An EPA ecological risk assessment (U.S. EPA/OPP 2008b, p. 2), expresses concern that risks to mammals may be … *underestimated because emamectin benzoate has been shown to induce neurotoxic effects that could result in decreased survival at sublethal doses. The acute risk assessment, however, was based on lethality*. As detailed further in the dose-response assessment (Section 4.3.2), the current Forest Service risk assessment differs from the EPA ecological risk assessments (U.S. EPA/OPP 2008b, 2009a) in that the toxicity values used the current Forest Service risk assessment are based on NOAELs for neurotoxicity rather than lethality. While there are substantial uncertainties in the current Forest Service risk assessment, these uncertainties relate primarily to the exposure assessment for mammals (Section 4.2.2).

4.1.2.2. Birds

Studies on the toxicity of emamectin benzoate to birds are summarized in Appendix 3. These studies are limited to the standard toxicity studies in mallards (*Anas platyrhynchos*) and bobwhite quail (*Colinus virginianus*) required by the U.S. EPA for pesticide registration: acute gavage studies (Appendix 3, Table 1), acute dietary studies (Appendix 3, Table 2), and reproductive studies (Appendix 3, Table 3). These studies are summarized in the EPA ecological risk assessments (U.S. EPA/OPP 2008b, 2009a, MRIDs 42743601 and 42868905). In addition, the acute toxicity studies (Chukwudebe et

al. 1998) the reproductions studies (O'Grodnick et al. 1998a) are published in the open literature. The literature on emamectin benzoate does not include field studies concerning its potential impact on birds.

Based on the acute gavage toxicity studies, mallards appear to be substantially more sensitive (LD_{50} = 46 mg/kg bw) than quail (LD_{50} = 264 mg/kg bw). Mallards are substantially larger than quail; thus, the apparent differences in sensitivity of birds to emamectin benzoate, albeit based on only two species, suggest a pattern different from that observed in mammals. As discussed in the previous subsection, mice appear to be more sensitive than rats or dogs to emamectin benzoate (i.e., smaller mammals appear to be more sensitive than larger mammals). In any event, the LD_{50} of 46 mg/kg bw for mallard ducks is only modestly greater than the LD_{50} of 22 mg/kg bw for mice (Section 4.1.2.2). Thus, at least in terms of the lowest available gavage LD_{50} values, the sensitivities of birds and mammals to emamectin benzoate do not appear to differ substantially.

As indicated in Appendix 3 (Table 1), the U.S. EPA/OPP (2008b, 2009a) summary of the gavage study in quail (MRID 42868905) is consistent with the gavage toxicity data on quail in the publication by Chukwudebe et al. (1998). For mallards, however, the EPA summary (MRID 42743601) is not consistent with the mallard data in the publication by Chukwudebe et al. (1998). The U.S. EPA/OPP (2008b, 2009a) summary of the acute gavage toxicity study in mallards indicates an LD_{50} of 46 (30-69) mg/kg bw; whereas, the publication by Chukwudebe et al. (1998) indicates an LD_{50} of 76 (56-102) mg/kg bw. It is not uncommon for the U.S. EPA/OPP to reanalyze toxicity data submitted by the registrant, and the differences in the toxicity values could be related to differences in the statistical methods used to calculate the LD_{50} values. Nonetheless, U.S. EPA/OPP (2008b, Table 12, p. 15) indicates that the NOAEC in the mallard study is <12 mg/kg bw in MRID 42743601. In the publication by Chukwudebe et al. (1998), however, the authors indicate that the lowest dose tested in mallards was 25 mg/kg bw. As indicated in Appendix 1 (i.e., the list of studies submitted to the U.S. EPA/OPP) only one acute oral gavage toxicity study in mallards was submitted to the EPA. Furthermore, there is no DER for, or cleared review of, this study. Consequently, the reason for the discrepancies between the summaries of the mallard studies in U.S. EPA/OPP (2008b, 2009a) and the information presented in the Chukwudebe et al. (1998) publication cannot be identified.

The summaries of the acute dietary studies in mallards and quail (Appendix 3, Table 2), are identical or nearly so in the EPA ecological risk assessments (U.S. EPA/OPP 2008b, 2009a) and Chukwudebe et al. (1998). The only minor difference is that the Chukwudebe et al. (1998) study rounds the slopes of the concentration-response curves to one significant digit and the EPA reports the slopes with two significant digits. As with the acute gavage studies, mallards (LC_{50} = 570 ppm) are more sensitive than bobwhite quail (LC_{50} = 1318 ppm). As detailed in Appendix 3 (Table 2), the mallards in the 20 ppm dose group consumed about 0.33 kg food/bw. Thus, the dietary NOEC of 20 ppm corresponds to a dose of 6.6 mg a.i./kg bw/day [20 mg a.i./kg food/day x 0.33 kg food per kg bw]. In the study on bobwhite, food consumption was about 0.3 kg food/kg bw, and

the dietary NOEC of 125 ppm corresponds to about 38 mg a.i./kg bw/day [125 mg a.i./kg food/day x 0.3 kg food per kg bw = 37.5 mg a.i./kg bw/day].

The subchronic reproduction studies suggest that birds are somewhat less sensitive than mammals to emamectin benzoate. The standard reproduction studies in birds fail to note any signs of toxicity at dietary concentrations of up to 40 ppm (mg emamectin benzoate/kg food) in mallard ducks (MRID 44007910) or 125 mg/kg bw in bobwhilte quail (MRID 44007911). Neither the U.S EPA/OPP summaries of these studies (U.S. EPA/OPP 2008b, 2009a) nor the open literature publication by O'Grodnick et al. (1998a) provides information on body weights or food consumption rates for the adult birds. As indicated in a previous Forest Service risk assessment for which both body weights and food consumption rates were available for quail and mallards (SERA 2007b), approximate food consumption rates during reproduction studies are about 0.07 kg food/kg bw. Using this factor, the dietary reproduction NOAELs correspond to doses of about 2.8 mg a.i./kg bw/day for mallards [40 mg a.i./kg food x 0.07 kg food/kg bw/day] and about 9 mg a.i./kg bw/day for quail [125 mg a.i./kg food x 0.07 kg food/kg bw/day = 8.75 mg a.i./kg bw/day]. These doses are higher than the reproduction NOAEL in rats of 0.6 mg/kg bw/day (Lankas 1992c as discussed in Section 3.1.9.2) by a factor of about 5 for mallards [2.8 mg a.i./kg bw/day ÷ 0.6 mg/kg bw/day ≈ 4.66] and a factor of about 15 for quail [8.75 mg a.i./kg bw/day ÷ 0.6 mg/kg bw/day ≈ 14.58].

Wrzesinski et al. (1998) studied the metabolism of emamectin benzoate in chickens, specifically leghorn hens (*Gallus domesticus*). The chickens in this study, were given 7 daily doses of dual labeled (^{3}H- and ^{14}C-) emamectin benzoate at 1 mg/kg bw/day. Radioactivity was assayed at about 20 hours after the last dose. In chickens, as in mammals, emamectin benzoate appears to be excreted rapidly with about 92% of the administered dose recovered in the excreta; however, emamectin benzoate was metabolized in hens much more extensively than in mammals—i.e., about 34-38% of the administered dose. Also unlike mammals, the major metabolite (33% of the administered dose) was a 24-hydroxy derivative of the $B1_a$ component in emamectin benzoate. As noted above, the limited toxicity data in birds suggest that larger birds are more sensitive than smaller birds to emamectin benzoate; whereas, the pattern in mammals appears to be exactly opposite. Speculatively, the sensitivity differences observed in mammals and birds (i.e., larger and smaller animals) may be owing to the more extensive metabolism of emamectin benzoate in birds— i.e., xenobiotics are generally metabolized more rapidly by smaller animals than by larger animals.

4.1.2.3. Reptiles and Amphibians (Terrestrial-Phase)

Data regarding the toxicity of emamectin benzoate to reptiles or terrestrial-phase amphibians are not available. The database maintained by Pauli et al. (2000) on reptiles and amphibians does not include toxicity data for emamectin benzoate. Furthermore, there are no sources of such information in the open literature. The EPA ecological risk assessment on emamectin benzoate indicates that data regarding the toxicity of emamectin benzoate to terrestrial-phase amphibians or reptiles were not submitted by the registrant. Following standard Agency practice, U.S. EPA/OPP (2008b, p. iii) states that *… birds were used as a surrogate for reptiles and terrestrial-phase amphibians*.

4.1.2.4. Terrestrial Invertebrates

The studies on the toxicity of emamectin benzoate to terrestrial invertebrates is summarized Appendix 4 with laboratory toxicity studies summarized in Table 1 and field or field simulation studies summarized in Table 2. Appendix 4, Table 1 is sorted by the following groups of invertebrates: honey bees, lepidopterans, other insects, and other invertebrates. The following discussion parallels this organization.

4.1.2.4.1. Honey Bees

The honeybee is the standard test species used by the U.S. EPA to assess toxicity to nontarget terrestrial invertebrates. Typically, both contact and oral toxicity studies in bees are available. For emamectin benzoate, however, only one contact bioassay is available which reports an LD_{50} of 3.5 ng/bee, equivalent to 0.0035 µg/bee (MRID 42851530, as summarized in U.S. EPA/OPP 2009, Table D6). Body weights of the bees are somewhat variable, with typical body weights of worker bees ranging from about 81 to 151 mg (Winston 1987, p. 54). Taking a typical body weight as 100 mg (0.1 g or 0.0001 kg), the contact LD_{50} of 0.0035 µg/bee would correspond to doses of about 0.035 mg/kg bw [0.0000035 mg ÷ 0.0001 kg]. As discussed in Section 4.1.2.1, the lowest LD_{50} of emamectin benzoate in mammals is 22 mg/kg in mice (MRID 42743612). Based on this comparison, emamectin benzoate is more than 600 times more toxic to bees than to mice [22 mg/kg bw ÷ 0.035 mg/kg bw ≈ 628.57].

The only other toxicity study on bees is the foliar contact bioassay by Chukwudebe et al. (1997b). In this study, substantial mortality was noted in bees in contact with alfalfa treated with emamectin benzoate at an application rate of 0.0168 kg a.i./ha (≈0.14 lb a.i/acre). This type of bioassay is designed to assess the residual toxicity of a pesticide following foliar applications. This type of bioassay has little relevance to the current Forest Service risk assessment which considers only the injection of ash trees with emamectin benzoate.

4.1.2.4.2. Lepidopterans

As reviewed by Lasota and Dybas (1991), emamectin benzoate is highly toxic to lepidopterans. A direct comparison of the sensitivity of lepidopterans and honey bees to emamectin benzoate is difficult to make. As noted in the previous subsection, emamectin benzoate is highly toxic to bees with a contact LD_{50} of 0.0035 µg/bee or about 0.035 mg/kg bw. As summarized in Appendix 4 (Table 1), no comparable contact bioassay is available in lepidopterans. The available toxicity studies in lepidopterans can be roughly classified as dip bioassays (Ahmad and Arif 2009; Ahmad et al. 2006; Ioriatti et al. 2009), dietary studies (Ahmad et al. 2002; Argentine et al. 2002; Jansson et al. 1997; Lopez et al. 2010; Mascarenhas et al. 1998), and foliar contact studies (Argentine et al. 2002; Ioriatti et al. 2009; Jansson et al. 1997). In all of these studies, exposures are expressed as the concentration of emamectin benzoate in a solution or in the diet (e.g., mg/L) rather than as doses to the insect (e.g., mg/insect or mg/kg bw). In addition to these laboratory studies, fields studies have been conducted on the effects of emamectin benzoate to fall armyworms (Adamczyk et al. 1999) and tobacco budworms (Gore et al. 1998). In these studies, summarized in Appendix 4, Table 2, exposures are characterized as application rates—i.e., kg a.i./ha.

The dietary studies on emamectin benzoate are probably the most relevant to the current Forest Service risk assessment in terms of assessing the potential risks to nontarget insects feeding on the leaves of treated ash trees. The oral studies, however, are difficult to compare to each other because of differences in experimental details as well as differences in the ways that the data are reported. For example, Argentine et al. (2002) report LC_{50} values for several species of Lepidoptera but the LC_{50} values appear to reflect the concentrations in 50 µL aliquots that were added to the diets of the test species. The volumes of the diets, however, are not specified and thus a concentration on emamectin benzoate in the diet cannot be estimated. Within the context of the study by Argentine et al. (2002), the inability to estimate the concentration of emamectin benzoate in the diet is not important but this does limit comparisons of this study to other dietary studies.

As summarized in Appendix 4, Table 1, the dietary studies by Ahmad et al. (2002), Jansson et al. (1997), Lopez et al. (2010), and Mascarenhas et al. (1998) do provide either direct data on concentrations in the diet or information that permit the calculation of dietary concentrations. Nonetheless, direct comparisons of the results of these studies are difficult because of differences in experimental design. For example, while Lopez et al. (2010) report 24-hour to 96-hour LC_{50} values, the durations refer only to the period of observation while the during of feeding was only 30 minutes. At the other extreme, the 120-hour LC_{50} values reported by Mascarenhas et al. (1998) are based on a feeding period of 120 hours.

The lowest LC_{50} value for dietary exposure (96-hours) is 0.001 mg/L for the beet armyworm larvae from the study by Jansson et al. (1997). Jansson et al. (1997) also report a low LC_{50} of 0.004 mg/L for the tobacco budworm. These LC_{50} values appear to reflect the concentration of emamectin benzoate in the test solution used to treat the diet. Jansson et al. (1997) note at 500 µL of diet was treated with 50 µL aliquots of emamectin benzoate. Thus, the LC_{50} of 0.001 mg/L appears to correspond to a total dietary concentration appears to be about 0.0001 mg/L. Similarly low 6-day dietary LC_{50} values—i.e., reported LC_{50}s of 0.0014 to 0.0055 mg/L—for these species as well as three other species of lepidopteran larvae are reported by Argentine et al. (2002). These authors also report using 50 µL aliquots to treat the diet but the volume of the treated diet is not specified.

The dietary studies in lepidopterans do not report the food consumption of the insects. Consequently, LD_{50} values expressed in units of mg/kg bw cannot be estimated directly. As discussed in Section 4.2.2.3, herbivorous insects generally consume vegetation at a rate of about 0.5 to 2 of their body weight per day. Taking a food consumption rate of 1 kg food/kg insect bw and assuming a density of 1 kg/L for the test solutions used in insect bioassays, the estimated dietary LC_{50} of 0.0001 mg/L for the whole diet for the bioassay of the beet armyworm larvae from the study by Jansson et al. (1997) would correspond to a dose of 0.0001 mg/kg bw [0.001 mg/L x 1 L food/kg food x 1 kg food/kg bw].

While the dietary studies by Argentine et al. (2002) and Jansson et al. (1997) suggest that beet armyworms are highly sensitive to emamectin benzoate, the highest reported LC_{50}

among the dietary studies in lepidopteran larvae is also for the beet armyworm—i.e., a 5-day LC_{50} of 2.4 mg/L for a tolerant population from the study by Mascarenhas et al. (1998). Note, however, that the study by Mascarenhas et al. (1998) reports LC_{50} values as concentrations of emamectin benzoate in 0.1 mL aliquots that were added to 3 mL of artificial diet. Thus, the concentration in the diet corresponding to a 0.1 mL aliquot of 2.4 mg/L would be about 0.08 mg/L [2.4 mg/L x (0.1 mL ÷ 3 mL)]. Nonetheless, this LC_{50}s expressed as a total dietary concentration is a factor of 800 [0.08 mg/L ÷ 0.0001 mg/L] higher than corresponding LC_{50} from Jansson et al. (1997). The lowest LC_{50} reported by Mascarenhas et al. (1998) is 0.2 mg/L. Correcting for mixing rate of 0.1 mL to 3 mL, this would correspond to a total dietary LC_{50} of about 0.007 mg/L [0.2 mg/L x (0.1 mL ÷ 3 mL) ≈ 0.00666 mg/L], a factor of about 70 greater than the whole dietary LC50 of 0.0001 mg/L reported by Jansson et al. (1997).

As noted above, there may be many reasons for the large differences in LC_{50} values reported in the same species by different investigators. Unlike the standardized tests required by the U.S. EPA/OPP for pesticide registration, open literature studies do not use standardized bioassay protocols, and even minor differences in experimental conditions (e.g., differences in the vehicle or food used in the bioassay) may affect the outcomes of the different studies. One obvious source of variability is the different populations of organisms used in the studies which may have differing levels of susceptibility or resistance to emamectin benzoate.

The development of resistance in different insect populations is an obvious source of variability which could affect the results of bioassays reported in the open literature. Using leaf dip bioassays, Ahmad and Arif (2009) assayed the development of resistance to emamectin benzoate in populations of the spotted bollworm in Pakistan. Over a 6-year period, 48-hour LC_{50} values in wild-caught populations increased from 0.22 to 1.11 mg/L for a resistance factor of about 5. Waldstein and Reissig (2000) assayed resistance in different populations of the obliquebanded leafroller in New York and estimated relatively modest resistance factors—i.e., 2.3 with a confidence interval of 1.2 to 5. Note that in the Mascarenhas et al. (1998) study discussed above, there is close to a 10-fold difference in sensitivity among various populations of beet armyworms. In this study, however, the most tolerant population was laboratory reared and the most sensitive populations were wild-caught. Thus, sensitivity differences among different populations of beet armyworms in the Mascarenhas et al. (1998) study do not appear to be associated with the development of resistance. A greater sensitivity in field populations relative to laboratory populations was not noted for other insecticides assayed by Mascarenhas et al. (1998)—i.e., chlorpyrifos, spinosad, thiodicarb, chlorfenapyr, methoxyfenozide, and tebufenozide.

Although most of the studies on the toxicity of emamectin benzoate to lepidopterans are focused on measures of acute lethal potency, Lopez et al. (2010) assayed both the acute lethal potency as well as the reproductive effects of dietary exposures of corn earworms to emamectin benzoate. In both sets of studies, the LC_{50} values reported in Lopez et al. (2010) appear to reflect the actual concentration of emamectin benzoate in the diet. Based on acute lethal potency, the populations of corn earworms were relatively tolerant

to emamectin benzoate with 24, 48-, and 96-hour LC_{50} values of 0.718, 0.525, and 0.182 mg/L, respectively. Two sets of reproduction assays were conducted, the first test using concentrations ranging from 0.0125 to 0.1 mg/L and a second test using concentrations ranging from 0.05 to 1 mg/L. In the first assay, a transient decrease in egg production was observed on Day 1 at concentrations of 0.0125-0.05 mg/L but not at higher concentrations (i.e., 0.075 and 0.1 mg/l). No significant effects on egg production were noted on Days 2 or 3 of the study (Lopez et al. 2010, Table 2, p. 6). In the second assay, a general concentration-related trend in decreased egg production was noted over the range of concentrations assays —i.e., from 0.05 to 1 mg/L. Oddly, however, no significant effects on egg production were noted at the mid concentration of 0.2 mg/L (Lopez et al. 2010, Table 3, p. 10). Egg hatching, however, evidenced a significant concentration-related decrease in both assays. Based on the total number of eggs hatching over the 3-day period in Test 1, the lowest concentration assayed (0.0125 mg/L) resulted in a significant ($p<0.05$) and substantial (44%) reduction (Table 4, p. 10). Finally, all concentrations of emamectin benzoate resulted in a significant ($p<0.0001$) reduction in the survival of hatched larvae (Figure 8, p. 12). Thus, using the 96-hour LC_{50} of 0.182 mg/L as a reference point, adverse sublethal effects occurred at concentrations that were a factor of about 15 below the acute LC_{50} [0.182 mg/L ÷ 0.0125 mg/L = 14.56]. This relationship is discussed further in the dose-response assessment (Section 4.3.2.4).

4.1.2.4.3. Other Insects

While studies indicate that emamectin benzoate is highly toxic to honey bees and at least some populations of lepidopterans, there are no studies on the toxicity of emamectin benzoate to the emerald ash borer, a coleopteran and the target species considered in the current Forest Service risk assessment. Grossman and Upton (2006) examined the efficacy of emamectin benzoate as well as other injectable insecticides for protecting loblolly pine from attack by southern pine engraver beetles and wood bores, both of which are coleopterans. As detailed further in Section 4.1.2.5, doses of emamectin benzoate used in the study by Grossman and Upton (2006) are somewhat lower than those recommended for the emerald ash borer. Nonetheless, the doses used in the study by Grossman and Upton (2006) were effective in protecting pine from both species of coleopterans. This study, however, does not provide any specific toxicity data (e.g., LC_{50} values) on the effects of emamectin benzoate on the target species.

As summarized in Appendix 4 (Table 1), Boyd and Beothel (1998) conducted a series bioassays in various species of beneficial heteropteran insects in which Proclaim, an agricultural formulation of emamectin benzoate, was applied to soybeans at a rate equivalent to 0.008 kg a.i./ha or about 0.007 lb a.i./acre with or without a surfactant. This study was designed to assay residual toxicity, primarily through contact with the contaminated vegetation, over periods of 4-72 hours. The metric for the exposure is not comparable to the studies available on honeybees or lepidopterans, and, for that reason, is not comparable to the studies discussed in the previous subsections.

Similarly, Chukwudebe et al. (1997b) conducted an assay on *Diglyphus isaea*, a beneficial predator on leafminers, in which a 0.16 EC formulation was applied to alfalfa at a rate equivalent to 0.0168 kg a.i./ha (≈0.14 lb a.i/acre). As discussed in Section

4.1.2.4.1, this study also involved bioassays on honeybees. As with honeybees, high rates of mortality were noted in *Diglyphus isaea*, shortly after treatment of the foliage. As also noted in Section 4.1.2.4.1, however, this type of bioassay, which mimics foliar broadcast applications, has little relevance to the current Forest Service risk assessment which considers only the injection of ash trees with emamectin benzoate.

4.1.2.4.4. Other Invertebrates

As discussed in Sections 3.2.3.4 and 3.2.3.6, Takai et al. (2004) characterized the movement of emamectin benzoate in pine trees as part of an effort to evaluate the efficacy of emamectin benzoate in protecting Japanese pine trees from pine wilt disease caused by the pine wood nematode (*Bursaphelenchus xylophilus*). As part of this effort, Takai et al. (2004) report an LC_{50} of 0.017 µg/g tree tissue and an LC_{90} of 0.031 µg/g tree tissue in the pine wood nematode. This is the only available study on the toxicity of emamectin benzoate to terrestrial invertebrates other than insects.

4.1.2.5. Terrestrial Plants (Macrophytes)

There is very little indication that emamectin benzoate is toxic to plants. In broadcast applications of an unspecified formulation of emamectin benzoate onto tomatoes at application rates of up to 5 kg formulation/ha (≈4.5 lb formulation/acre), no signs of phytotoxicity were apparent (Fanighiulo and Sacchetti 2008).

In the study by Takai et al. (2001), some components used in the emamectin benzoate formulation were associated with discoloration or necrosis of the cambium at the injection site. In tests using the final 4% emamectin benzoate formulation developed in Japan, tree injections at doses of up to 20 g emamectin benzoate/m^3 of tree biomass were associated with necrosis of the cambium at the injection site. The development of injection site damage is not an unusual occurrence in tree injections, and the damage at the injection site was not apparent at 2 years after injection.

Grosman and Upton (2006) evaluated the phytotoxicity of emamectin benzoate in tree injections of Denim. As summarized in Table 2, Denim is an agricultural formulation of emamectin benzoate labeled for broadcast application, and the study by Grosman and Upton (2006) appears to have been a preliminary efficacy study prior to the development of Tree-äge. Denim was injected into 16 loblolly pines (with a mean DBH of 19 cm or about 7.5 inches) at a rate of 0.08 g a.i. per cm DBH. Taking the mean DBH of 19 cm, the dose was about 600 mg a.i./tree. As indicated in Table 4, this dose is only somewhat lower than low dose of 864 mg a.i./tree recommended for 8 inch DBH ash trees. Similar injections were also made with formulations of dinotefuran, fipronil, and imidacloprid. All of the pesticides were associated with injection site lesions, but the lesions caused by emamectin benzoate were longer and more persistent than lesions caused by the other formulations (Grosman and Upton 2006, Table 1, p. 97). Citing an apparently unpublished study by Arborjet, Grosman and Upton (2006, p. 100) suggest that the lesions following injections with Denim are probably associated with the petroleum components in the Denim formulation. As summarized in Table 3 of the current Forest Service risk assessment, both Denim and Tree-äge contain petroleum distillates. Nonetheless, the term *petroleum distillates* designates a very broad class of agents, and it is not clear if the damage observed with tree injections of Tree-äge would be more or less

severe than those observed with Denim. In a subsequently study on the efficacy of an experimental formulation of emamectin benzoate in protecting pine from bark beetle infestations, Grosman et al. (2010) provide a brief note indicating that no external signs of phytotoxicity were observed.

From a practical perspective, the potential damage to treated trees associated with the tree injection of Tree-äge is more of an issue of efficacy than toxicity to nontarget plants in that the damage to the tree associated with tree injection of emamectin benzoate or any other pesticides must be weighed against the benefits of protecting the tree from the pest (i.e., target) species.

Emamectin benzoate appears to be metabolized extensively in plants, with radiolabelled material incorporated into both extractable and non-extractable components of plant tissue (Allen et al. 1997; Crouch et al. 1997; Feely and Crouch 1997). As discussed in Section 3.4.6, one plant metabolite has been identified that is more toxic than emamectin benzoate. Toxicity data on this metabolite, 4"-epi-(N-formyl-N-methyl)-amino-4"-deoxyavermectin B1 (also designated as L-660,599), serves as the basis for the RfDs on emamectin benzoate (Section 3.3).

4.1.2.6. Terrestrial Microorganisms

No information has been encountered on the toxicity of emamectin benzoate to terrestrial microorganisms.

4.1.3. Aquatic Organisms

Relatively little information is available on the effect of emamectin benzoate on aquatic organisms. The U.S. EPA/OPP recently conducted risk assessments on the effects of a number of pesticides on the California Red-legged frog (http://www.epa.gov/espp/litstatus/effects/redleg-frog/). Emamectin benzoate, however, is not covered in these assessments. Emamectin benzoate is used for the control of sea lice, a copepod that parasitizes salmon in commercial fish farms (Armstrong et al. 2000; Ramstad et al. 2002). While this use leads to some unusual types of studies on the oral toxicity of emamectin benzoate to fish, as discussed below, this information has little impact on the current Forest Service risk assessment.

4.1.3.1. Fish

Information on the toxicity of emamectin benzoate to fish is summarized in Appendix 5. Standard acute toxicity studies in three species of freshwater fish—i.e., rainbow trout, fathead minnows, and bluegill sunfish—as well as one estuarine species, the sheepshead minnow (Appendix 5, Table 1) were submitted to the U.S. EPA in support of the registration of emamectin benzoate. Based on 96-hour LC_{50} values ranging from 0.174 to 0.194 mg/L in the freshwater species, emamectin benzoate is classified as highly toxic to freshwater fish (U.S. EPA/OPP 2008b, p. ii). The LC_{50} in sheepshead minnow is 1.43 mg/L, about a factor of 10 higher than the corresponding values in freshwater fish. As discussed further in Section 4.1.3.3, the opposite pattern is apparent with aquatic invertebrates, in which saltwater species appear to be much more sensitive than freshwater species.

Summaries of the acute toxicity studies are taken from the EPA risk assessments (U.S. EPA/OPP 2008b, 2009a); cleared reviews of these studies are not available. Slopes of the concentration response curves are reported in the EPA documents for only two species—i.e., a slope of 7.0 in trout and 7.9 in sheepshead minnows. These slopes are very steep and suggest that response rates will diminish rapidly as the concentration of emamectin benzoate decreases. For example, assuming that the slopes are based on common logarithm transformations of the concentration, a slope of 7 indicates that the response rate at a concentration of 10 below the LC_{50} would be equivalent to 7 standard deviations below the mean —i.e., a response rate of about $1.3x10^{-12}$ using the approximation from the EXCEL NORMSDIST(x) function with x=-7). The implications of the steep concentration-response relationships are discussed further in Section 4.3.3.1, the dose-response assessment for fish.

Only one chronic toxicity study in fish is available, and, as with the acute studies, this study was submitted to the U.S. EPA/OPP in support of the registration of emamectin benzoate, and the only information about this study is available from the EPA risk assessments on emamectin benzoate (U.S. EPA/OPP 2008b, 2009a). The chronic study is a standard early life-stage study in fathead minnows in which the NOAEC is reported as 0.0065 mg/L with an LOAEC of 0.012 mg/L based on decreases in survival and growth of fish larvae.

As noted at the start of Section 4.1.3, emamectin benzoate is used as an oral treatment for sea lice in farmed Atlantic salmon. Sea lice are copepod parasites (e.g., *Lepeophtheirus salmonis* and *Caligus elongates*) in salmonids. Severe outbreaks of sea lice infections can occur, particularly in dense populations of salmonids in fish farms. A 0.2% pellet formulation of emamectin benzoate, designated as SLICE, is administered orally by broadcast application to Atlantic salmon to reduce sea lice infestations (e.g., Ramstad et al. 2002). To assess the potential effects of this use of emamectin benzoate on fish, Armstrong et al. (2000) conducted an oral toxicity study in Atlantic salmon and estimated an oral LD_{50} of 0.05 mg/kg bw.

Fish appear to be much more sensitive than the most sensitive mammals to emamectin benzoate, and are almost as sensitive as insects. As discussed in Section 3.1.4, the lowest mammalian LD_{50} is 22 mg/kg bw, a factor of about 440 above the oral LD_{50} in Atlantic salmon. As discussed in Section 4.1.2.4.1, the contact LD_{50} for emamectin benzoate in honeybees is 0.035 mg/kg bw. Based on this LD_{50}, Atlantic salmon (LD_{50} of 0.05 mg/kg bw) and honeybees appear to be about equally sensitive to emamectin benzoate.

Other studies pertaining to the use of emamectin benzoate to control sea lice involve palatability to fish (Armstrong et al. 2000) and residues in fish following oral exposures (Kim-Kang et al. 2004; Roy et al. 2006; Sevatdal et al. 2005). Given the uses of emamectin benzoate covered in the current Forest Service risk assessment, which involves the injection of ash trees, these studies on salmon are peripheral.

4.1.3.2. Amphibians (Aquatic-Phase)

As with reptiles and terrestrial-stage amphibians (Section 4.1.2.3), there is no information available on the toxicity of emamectin benzoate to aquatic-phase amphibians. The U.S.

EPA/OPP (2008b) also notes the lack of information on the toxicity of emamectin benzoate to aquatic-phase amphibians. This risk assessment follows the standard EPA approach: …*freshwater fish were used as a surrogate for aquatic-phase amphibians* (U.S. EPA/OPP 2008b, p. iii).

4.1.3.3. Aquatic Invertebrates

As with fish, the most relevant information on the toxicity of emamectin benzoate to aquatic invertebrates comes from standard studies submitted to the U.S. EPA/OPP in support of the registration of emamectin benzoate. Also as with fish, these studies as well as internal EPA reviews of these studies were available for use in the current Forest Service risk assessment, and the information on the toxicity studies in aquatic invertebrates is taken from risk assessments conducted by the U.S. EPA/OPP (2008b, 2009a). Some studies on emamectin benzoate are available in the open literature, but these studies relate to the use of emamectin benzoate to control sea lice in salmonids. As detailed below, the data from the open literature are somewhat tangential to the current Forest Service risk assessment in that the most sensitive endpoints are provided in the unpublished studies submitted to the U.S. EPA.

Information on the toxicity of emamectin benzoate to aquatic invertebrates is summarized in Appendix 6. As noted in Section 4.1.3.1, estuarine fish appear to be about 10 times more sensitive than freshwater fish to emamectin benzoate. For aquatic arthropods, the opposite pattern is apparent, although the comparisons are based on very limited data. In *Daphnia magna*, a freshwater invertebrate and standard test species in aquatic toxicity studies, the 48-hour EC_{50} is 1 µg/L. In mysid shrimp, a standard estuarine species used in aquatic toxicity studies, the 96-hour EC_{50} is 0.04 µg/L. In both of these very small species, the toxicity values are given as EC_{50} values for immobility, which in these small species is treated as lethality.

The only other acute toxicity study is the shell deposition assay in the Eastern oyster in which the EC_{50} for the inhibition of shell deposition was 490 µg/L. The inhibition of shell deposition is a sublethal effect, although the effect does have important implications for survival. Nonetheless, these very limited data suggest that mollusks may be much less sensitive than aquatic arthropods to emamectin benzoate.

The only standard chronic toxicity data available on aquatic invertebrates is the life-cycle/reproduction study in *Daphnia magna* (MRID 43393004). In this study, the NOAEC was 0.088 µg a.i./L with an LOAEC of 0.16 µg a.i./L, based on decreased egg production as well as decreased survival and growth in offspring.

In a field study on the potential effects of using emamectin benzoate to control sea lice, Willis et al. (2005) noted that standard applications of emamectin benzoate to control sea lice resulted in average concentrations of 0.01 ng/L (0.00001 µg/L) emamectin benzoate in sea water, and that these concentrations were not associated with any remarkable changes in invertebrate abundance. The concentration of 0.01 ng/L (0.00001 µg/L) is below the 0.088 µg/L NOAEC in daphnids by a factor of over 8000 and below the EC_{50} of 0.04 µg/L in mysid shrimp by a factor of 4000. Thus, the field observations by Willis

et al. (2005) are consistent with the experimental reproduction study in daphnids and acute toxicity data on mysids.

Other studies associated with the use of emamectin benzoate to control sea lice include two gavage studies in lobsters (Waddy et al. 2002, 2007). These studies investigate the effects of emamectin benzoate on molting. Emamectin benzoate can induce premature molting in lobsters. The early study by Waddy et al. (2002) reports a NOAEL for premature molting of 0.12 mg/kg bw with an LOAEC of 0.22 mg/kg bw. Given the clear and relatively well understood neurotoxicity of emamectin benzoate, it is interesting that no signs of neurotoxicity are noted in the study. In a later publication, Waddy et al. (2007) specifically note that no signs of neurotoxicity were observed at 0.12 mg/kg bw and no signs of neurotoxicity are noted at any higher doses. Given the very high toxicity of emamectin benzoate to small aquatic arthropods, the apparent tolerance of lobsters to gavage doses of emamectin benzoate is not intuitive. As discussed by Waddy et al. (2002, 2007) and reviewed further by Rodriquez et al. (2007), the mechanism for the effect on molting may involve the interference with neuroendocrine receptors in the eyestalks of lobsters. Like the studies involving the use of emamectin benzoate to control sea lice in fish, the lobster studies are relevant to marine applications of emamectin benzoate but peripheral to the current Forest Service risk assessment on the injection of ash trees with emamectin benzoate.

4.1.3.4. Aquatic Plants

Very little information is available on the toxicity of emamectin benzoate to aquatic plants. As summarized in U.S. EPA/OPP (2008b, Table 11, p. 13), Tier 1 toxicity studies on one species of algae (*Selenastrum capricornutum*) and one species of aquatic macrophyte (*Lemna gibba*) were submitted to the EPA. Tier 1 studies are relatively crude screening assays in which the agent, in this case emamectin benzoate, is tested at only a single concentration. In the study on algae, the 5-day NOAEC for cell density was 3.9 µg a.i./L (MRID 43850108). In the study on duckweed (*Lemna gibba*), the 14-day NOAEC for frond biomass was 94 µg a.i./L (MRID 43850109). No further details of these studies are available in the EPA risk assessment (U.S. EPA/OPP 2008b).

Neither of the studies in aquatic plants defines a LOAEC, which limits their usefulness in both the hazard identification and dose-response assessment in that concentrations which might be associated with adverse effects in aquatic plants are undetermined.

4.1.3.5. Aquatic Microorganisms

In an open literature study, Hernando et al. (2007) assayed emamectin benzoate along with several other pesticides for toxicity to *Vibrio fischeri*, a marine bacterium. *Vibrio fischeri* is a commonly used test species in toxicity screening studies because it is capable of bioluminescence, and adverse effects in this organism may be assayed as a reduction in bioluminescence. Emamectin benzoate at a concentration of 6.3 mg/L had no effect on bioluminescence.

4.2. EXPOSURE ASSESSMENT

4.2.1. Overview

As with the exposure assessment for the general public (Section 3.2.3), exposures to emamectin benzoate in surface water associated with typical applications by tree injection cannot be estimated because of the lack of information on the transport of emamectin benzoate in treated ash trees. Based on the limited information of the transport of emamectin benzoate in some species of pine, it seems reasonable to assert that concentrations of emamectin benzoate in surface waters will be low. The only exposures via contaminated surface water that are quantified, however, are those associated with an accidental spill. As discussed further in the risk characterization (Section 4.4), the exposures associated with an accidental spill are far below levels of concern for all ecological receptors, except sensitive species of aquatic invertebrates.

The most likely exposures in nontarget species following the injection of ash trees with emamectin benzoate involve the consumption of bark, stem tissue, seeds, or leaves. With the exposure assessment for surface water, the lack of information on the movement of emamectin benzoate within ash trees following tree injection precludes reliable exposure assessments associated with the consumption of bark, stem tissue, and seeds. As a surrogate for these exposures, estimates are developed for exposures of herbivorous insects consuming the leaves of treated ash trees. Because of the number of uncertainties associated with these estimates, two sets of exposure assessments are made, one assuming uniform distribution of emamectin benzoate within the treated ash tree and the other assuming limited distribution to the leaves of the treated ash tree. The estimated exposures for herbivorous insects are extended to small mammals and birds under the assumption that the herbivorous insects may be consumed by mammals and birds. **All of these exposure scenarios are tenuous and limitations in the use of these exposure assessments are discussed further in the risk characterization.** When information becomes available on the transport of emamectin benzoate in ash trees, refinements to these exposure scenarios could be made which might reduce uncertainties in the current risk assessment.

4.2.2. Mammals and Birds

An overview of the exposure assessments for mammals and birds is given in Worksheet G01 of the EXCEL workbook that accompanies this risk assessment. Forest Service risk assessments typically derive exposure assessments for direct spray contact with contaminated vegetation, the ingestion of contaminated vegetation or prey, as well as the ingestion of contaminated water. All of these exposure scenarios are relevant to and can be developed for pesticides applied by broadcast application methods. The current risk assessment, however, considers only the injection of ash trees with emamectin benzoate. Thus, as in the human health risk assessment, many of the standard exposure scenarios typically used for mammals and birds cannot be developed for or do not apply to the injection of ash trees with emamectin benzoate.

4.2.2.1. Direct Spray

For tree injections, the direct spray of a mammal or bird is not a reasonable exposure scenario.

4.2.2.2. Dermal Contact with Contaminated Vegetation

Mammals or birds may come into contact with surfaces of treated trees; however there are no methods for estimating the magnitude of such exposures. For tree injection, risks associated with contacting the surfaces of treated trees are not likely to be substantial, relative to other exposure scenarios considered in the following subsections.

4.2.2.3. Ingestion of Contaminated Vegetation or Prey

For broadcast applications, standard exposure scenarios are developed for the consumption of treated vegetation, specifically the leaves, by several groups of mammals and birds. The direct ingestion of the leaves of treated ash trees does not appear to be a plausible route of exposure for most mammals and birds. Nonetheless, several species of mammals (e.g., beaver, rabbit, and porcupines) will consume the bark and/or stem tissue of ash trees; furthermore, the seeds of ash trees may be consumed by several species of birds (song birds, game birds, and ducks) as well as small mammals (Dieter and McCabe 1989; Gould and Bauer 2010; Marshall 2008; Nature Conservancy 2010).

If adequate information were available on plausible concentrations of emamectin benzoate in tree tissue, several exposure scenarios might be developed for specific nontarget species that are not routinely considered in Forest Service risk assessments. While information is available that could be used to develop exposure scenarios for species such as beaver (e.g., Aldous 1938; Baker and Hill 2003; Martin et al. 1951), specific exposure scenarios are not developed for each of the organisms that might consume the bark, stem tissue, or seeds of ash trees. As detailed in Section 2.3, no information is available on the movement and kinetics of emamectin benzoate in ash trees. Takai et al. (2004) investigated concentrations of emamectin benzoate in species of Japanese pine. These limited data do not support the development of quantitative exposure scenarios for mammals or birds consuming bark, stem tissue, or seeds of ash trees.

The consumption of contaminated insects by a small mammal and a small bird is a standard exposure scenario in most Forest Service risk assessments. As an alternative to developing specific exposure scenarios for the consumption of bark, stem tissue, and seed in ash trees, the exposure scenarios for the consumption of contaminated insects are modified and adapted to the consumption of contaminated insects that consume the leaves of treated ash trees. The exposure assessments for the consumption of contaminated insects are detailed in Worksheet F14a for a small mammal and F14b for a small bird.

For pesticides that are relatively nontoxic to insects, the exposure scenarios for the consumption of contaminated insects by a small mammal or bird are based on the estimated doses to insects consuming contaminated vegetation. This approach, however, is not appropriate for emamectin benzoate. As discussed in Section 4.2.3.2.1 (Exposure Assessment for Herbivorous Insects), the estimated exposures to insects exceed the LD_{50} values for insects by factors ranging from about 20 to 40,000, and it is not plausible to assert that insects would actually consume this much emamectin benzoate. The most reasonable interpretation of the exposure scenarios for herbivorous insects is that insects consuming vegetation from a treated tree would sicken and die after the consumption of

sufficient amounts of emamectin benzoate. Consequently, the potential exposure of insectivorous mammals and birds to emamectin benzoate is limited by the toxicity of emamectin benzoate to insects.

As discussed in Section 4.3.2.4, the estimated LD_{50} values for insects range from 0.0001 to 0.08 mg/kg bw. For the exposure scenarios for insectivorous mammals and birds, the assumption is made that concentrations of emamectin benzoate in insects would range from 0.0001 mg/kg bw (the LD_{50} for sensitive species of insects) to 0.16 mg/kg bw (twice the LD_{50} for tolerant species of insects). The central estimate of the concentration of emamectin benzoate is taken as 0.004 mg/kg bw, the geometric mean of the range [(0.0001 mg/kg bw x 0.16 mg/kg bw)$^{0.5}$]. These estimated concentrations are likely to be conservative in that it seems reasonable to suggest that some insects would be consumed by mammals or birds prior to the consumption of a lethal dose of emamectin benzoate by the insect.

Other aspects of the exposure scenarios for a small mammal and a small bird consuming contaminated insects are standard in Forest Service risk assessments. The amount of food that the mammal and bird will consume is based on allometric relationships for the caloric requirements of small mammals and birds cited in U.S. EPA/ORD (1993). For both mammals and birds, the proportion of the diet that is contaminated is taken as 0.1 (0.01 to 1). The upper bound of this range —i.e., the assumption is that the mammal or bird consumes only contaminated insects —would reflect an obviously extreme circumstance, such as an outbreak of an insect population that consumes only leaves from treated ash trees.

4.2.2.4. Ingestion of Contaminated Water

The methods for estimating emamectin benzoate concentrations in water are identical to those used in the human health risk assessment (Section 3.2.3.4). The only major differences in the estimates of exposure involve the weight of the animal and the amount of water consumption. As in the exposure assessment for human health, only accidental spills are considered because the concentrations of emamectin benzoate likely to occur in surface water as a result of the injection ash trees cannot be estimated. As discussed further in Section 4.4.2, this limitation has little impact on the risk characterization because the concentrations of emamectin benzoate in water following an accidental spill are substantially below the level of concern.

4.2.3. Terrestrial Invertebrates

4.2.3.1. Direct Spray and Drift

As with the corresponding exposure scenario for mammals and birds (Section 4.2.2.1), the direct spray of terrestrial invertebrates is not a reasonable exposure scenario for pesticides applied by tree injection.

4.2.3.2. Ingestion of Contaminated Vegetation or Prey

4.2.3.2.1. Herbivorous Insects

As noted in Section 4.2.2.3, two different exposure scenarios are developed for exposures involving terrestrial insects. The first scenario is detailed in Worksheet G07a under the

assumption of uniform distribution of emamectin benzoate following tree injection. The second scenario is detailed in Worksheet G07a under the assumption of limited distribution of emamectin benzoate to leaves.

As discussed in Section 3.2.3.6 and illustrated in Figure 7, the dosing instructions for injecting emamectin benzoate into ash trees lead to a wide range of estimated concentrations of emamectin benzoate in ash trees under the assumption of uniform distribution. As detailed in Worksheet B07 of the EXCEL workbook that accompanies this risk assessment, the estimated concentrations of emamectin benzoate range from 0.37 mg a.i./kg tree (trees with a 71 inch diameter at breast height at the medium dose rate) to 18.61 mg a.i./kg tree (trees with a 5 inch diameter at breast height at the medium dose rate). Note that the medium dose rate defines the range, because medium dose rates are given for trees over the entire range of diameters included on the product label; whereas, low dose rates are given for only smaller trees and high dose rates are given for only larger trees.

Under the assumption of uniform distribution, the concentrations that may occur in the leaves of ash trees following tree injection are taken as 3 (0.4 to 19) mg a.i./kg. The upper and lower bounds are the range of values discussed above rounded to one significant digit. The central estimate of 3 mg a.i./kg is the geometric mean of this range, also rounded to one significant digit [$(0.4 \times 19)^{0.5} \approx 2.76$]. These concentrations are used in Worksheets G07a and G07b. The only difference between Worksheets G07a and G07b concerns the distribution of emamectin benzoate in leaves that might be consumed by an herbivorous insect. In Worksheets G07a, the distribution factor of 1 is used. Thus, the concentration of emamectin benzoate in leaves is identical to the concentration in the tree, based on the assumption of uniform distribution. In Worksheets G07b, the distribution factor of 0.1 is used, and the concentration of emamectin benzoate in leaves is estimated at one-tenth the concentrations given in Worksheet G07a.

In addition to the concentration of emamectin benzoate in the leaves, estimates of food consumption by foraging herbivorous insects are necessary to calculate dose levels. Food consumption rates by insects vary greatly, depending on the caloric requirements in a given life stage or activity of the insect and the caloric value of the food that is consumed. Nevertheless, general food consumption values, based on estimated food consumption per unit body weight, are available.

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

For two reasons, the estimated doses in Worksheets G07a and G07a are likely to overestimate the actual amount of emamectin benzoate that an insect might ingest. First, the doses to the insect are estimated at about 4 (0.2 to 40) mg a.i./kg bw in Worksheet G7a and about 0.4 (0.02 to 4) mg a.i./kg bw in Worksheet G07b. As discussed in Section 4.3.2.4, the LD_{50} values for emamectin benzoate in terrestrial insects range from about 0.001 to 0.08 mg/kg bw. Note that the range of LD_{50} values are below the upper bound estimated dose of 40 mg a.i./kg bw by factors of 500 to 40,000. For sensitive species of insects, the lower bound dose of 0.02 mg a.i./kg bw is below the lower bound LD_{50} of 0.001 mg/kg bw by a factor of 20. It is not likely that concentrations of 0.02 mg a.i./kg bw could occur in sensitive insects—i.e., those with LD_{50} values of about 0.001 mg/kg bw—because the insects would probably sicken and cease eating at doses in the range of the LD_{50}. Similarly, even for tolerant species of insects with an LD50 of about 0.08 mg/kg bw, the upper bound dose of 40 mg/kg bw would probably not actually occur because the insect would sicken and die longer before it could ingest a dose that is 500 times that of the LD_{50}. As discussed further in Section 4.4.2.4 (Risk Characterization for Terrestrial Invertebrates), these very high estimated doses relative to the LD_{50} values simply indicate that insects feeding extensively on treated trees would die. These potential overestimates of exposures to herbivorous insects have an impact on the exposure assessment for small mammals and birds, as discussed in Section 4.2.2.3.

Another factor that may lead to overestimates of exposures in herbivorous insects is the assumption of uniform distribution. As discussed in Section 2.3, a relatively substantial difference is apparent between the nominal doses of emamectin benzoate used in the study by Takai et al. (2004)—i.e., 29 µg/g dry weight—and the average concentrations of emamectin benzoate monitored in sapwood—i.e., about 0.15 to 2 µg/g. Thus, the use of the assumption of uniform distribution could overestimate plausible exposures by a factor of about 10 or more. Note that this potential overestimate is not adjusted by the factor of 0.1 for the assumption of limited distribution to in leaves. The assumption of limited distribution to leaves is based on the extremely low concentrations of emamectin benzoate in leaves—i.e., about 0.011 to 0.025 mg/kg—reported in the study by Takai et al. (2004).

4.2.3.2.2. Honeybees

No exposure assessment for honeybees is conducted, because ash trees are wind pollinated (e.g., http://www.treecaretips.org/Diseases/About_EAB.htm).

4.2.3.2.3. Other Terrestrial Invertebrates

No exposure assessments are conducted for other terrestrial invertebrates. As discussed in Section 2.3, the limited data from the studies by Takai et al. (2001, 2003, and 2004) do not identify detectable concentrations of emamectin benzoate in the soil around treated pine trees. It is possible that some soil invertebrates, like earthworms, could be exposed to emamectin benzoate on fallen leaves from treated ash trees during autumn. No data, however, are available on the toxicity of emamectin benzoate to soil invertebrates.

4.2.4. Terrestrial Plants

No exposure assessments are made for nontarget terrestrial plants. As noted in Section 4.1.2.5, the injection of trees may result in damage at the injection site. A mechanism for significant exposures to nontarget trees, however, is not apparent.

4.2.5. Aquatic Organisms

The methods for estimating emamectin benzoate concentrations in water are identical to those used in the human health risk assessment (Section 3.2.3.4) as well as the exposure assessments for birds and mammals (Section 4.2.2.4). As with these other groups, exposures of aquatic organisms are estimated only for an accidental spill. As discussed in some detail in Section 3.2.3.4, there is not sufficient information about movement of emamectin benzoate in ash trees to permit a reasonable assessment of its expected concentrations in surface water following tree injection.

Except for sensitive species of aquatic invertebrates, the inability to estimate surface water concentrations of emamectin benzoate following the application of emamectin benzoate by injection into ash trees has little impact on the current risk assessment. As discussed further in risk characterization for aquatic organisms (Section 4.4.3), sensitive species of aquatic invertebrates appear to be the only group at risk following an accidental spill.

4.3. DOSE-RESPONSE ASSESSMENT

4.3.1. Overview

The toxicity values used in this risk assessment are summarized in Table 11. The derivation of each of these values is discussed in the following subsections. Different units of exposure are used for different groups of organisms, depending on the nature of exposure and the way in which the toxicity data are expressed. As discussed in the exposure assessment (Section 4.2), only acute exposure scenarios are derived in the ecological risk assessment. Nonetheless, both acute and longer-term toxicity values for emamectin benzoate are derived. This approach is taken to support longer-term exposure scenarios, in the event that the Forest Service considers other application methods for emamectin benzoate for which longer-term exposure assessments could be derived.

Available toxicity data support separate dose-response assessments in seven classes of organisms: terrestrial mammals, birds, terrestrial insects, fish, aquatic invertebrates, aquatic algae, and aquatic macrophytes. As would be expected for an effective insecticide, the lowest terrestrial toxicity value is for insects.

Only one toxicity value is derived for mammals, 0.075 mg/kg bw/day. This approach parallels the dose-response assessment for human health effects—i.e., the NOAEL of 0.075 mg/kg bw/day, which is associated with a plant metabolite of emamectin benzoate, is applied to both acute and longer-term exposures.

The toxicity values for birds—i.e., an acute NOAEL of 4.6 mg/kg bw and a chronic NOAEL of 2.8 mg/kg bw— are substantially greater than the NOEAL for mammals. This large difference may be an artifact of the differences in types of available data on birds and mammals. As detailed in Section 3.1, several subchronic neurotoxicity studies are available on emamectin benzoate and its metabolites. Subchronic neurotoxicity studies in birds, which are not required for pesticide registration, are not available. Standard developmental studies in mammals yield NOAECs of 2-3 mg/kg bw/day (Manson 1992b,c), which are very similar to the longer-term NOAEL of 2.8 mg/kg bw/day in birds. These differences in the types of available data on birds and mammals are considered further in the risk characterization (Section 4.4.2).

Toxicity data directly relevant to the dose-response assessment on aquatic animals are relatively sparse, consisting of standard acute toxicity studies in a few species of fish and aquatic invertebrates, a single longer-term toxicity study in fish (minnows) and another single longer-term toxicity study in a single species of aquatic invertebrates (*Daphnia*). No data are available in terrestrial-phase amphibians. The only consistent toxicity pattern is that invertebrates are more sensitive than fish to emamectin benzoate. This difference is consistent with differences in the toxicity of emamectin benzoate to terrestrial organisms as well as differences often seen in the toxicity of insecticides to aquatic organisms. While the data on fish and aquatic invertebrates are limited, separate toxicity values can be derived for sensitive and tolerant species in both groups for acute and longer-term exposure. Toxicity data in aquatic plants are limited to free-standing NOAECs which are of limited use in risk characterization.

4.3.2. Toxicity to Terrestrial Organisms

4.3.2.1. Mammals

Forest Service risk assessments will generally base the dose-response assessment for mammalian wildlife on the NOAECs used for the acute and chronic RfDs. Different approaches may be taken if the available data suggest that some groups of mammals (e.g., canids) are more sensitive or more tolerant than mammalian species on which the RfD is based or if ecological risk assessments conducted by U.S. EPA/OPP suggest that basing the mammalian dose-response assessment on the studies used for the RfDs might not be appropriate.

As summarized in Table 8 and discussed in Section 3.3 (Dose-Response Assessment for human health), U.S. EPA/OPP (2008a) bases both the acute and chronic RfDs on the NOAEL of 0.075 mg/kg bw from the 15-day neurotoxicity study by Gerson (1992g) on the plant metabolite of emamectin benzoate—i.e., 4"-epi-(N-formyl-N-methyl)-amino-4"-deoxyavermectin B1, also designated as L-660,599. Arguably, as discussed in Section 3.3, this study may not be relevant to some human exposure scenarios—i.e., workers applying emamectin benzoate. A similar argument may be made for mammalian wildlife. As detailed in Section 4.2.2, the only quantitative exposure assessments for emamectin benzoate are associated with an accidental spill of emamectin benzoate. As with the exposure assessment for members of the general public (Section 3.2.3), exposures associated with the normal use of emamectin benzoate in Forest Service programs—i.e., the injection of ash trees—will probably be very low; however, there is not sufficient information on the fate and movement of emamectin benzoate after injection into ash trees to quantify typical exposures. Since the exposure assessments quantified for the accidental spill are not likely to involve plant metabolites, the somewhat higher NOAEL of 0.1 mg/kg bw/day from the 15-day neurotoxicity study on emamectin benzoate (Gerson 1992e) could be viewed as a more reasonable NOAEL for the current Forest Service risk assessment.

Accidental spills could involve exposure to aqueous photolysis degradates of emamectin benzoate. U.S. EPA/OPP (2008b, p. 5) identifies one aqueous photolysis degradate of emamectin benzoate referenced as the 8,9-Z MA or (8,9-Z)-4”-epimethylamino-4”deoxy avermectin B1, which appears to be the same metabolite illustrated in Figure 5 and referenced as L-695,638. As summarized in Appendix 2, Table 6, the NOAEL for this metabolite is 0.3 mg/kg bw/day in the 14-day neurotoxicity study in mice by Gerson (1992h). Relative to emamectin benzoate, which has a NOAEL of 0.1 mg/kg bw/day in a 16-day neurotoxicity study in mice, aqueous photolysis would be regarded as a detoxicification process.

In the EPA ecological risk assessment of emamectin benzoate (U.S. EPA/OPP 2008b), LD_{50} values are used to characterize acute risks; the 2-generation reproductive NOAEL of 0.6 mg/kg bw is used to characterize longer-term risks. U.S. EPA/OPP (2008b, p. iii) cites the mouse LD_{50} of 22 mg a.i./kg bw as the lowest LD_{50}. As summarized in Appendix 2, Table 1, this LD_{50} is taken from MRID 42743612 and is the lowest reported mammalian LD_{50} for emamectin benzoate. In implementing the acute dose-response

assessment for mammals, U.S. EPA/OPP (2008b, Table 20, p. 23) uses the following allometric equation to scale a reference LD_{50} based on animal body weight:

Equation 1

$$Estimated\ LD_{50} = \text{Reference}\ \text{LD}_{50}\left(\frac{TW}{AW}\right)^{0.25}$$

where ***TW*** is body weight of the animal on which the Reference LD_{50} is available and ***AW*** is the body weight of the animal for which the LD_{50} is estimated. For example, using the LD_{50} of 22 mg/kg in mice and using 20 g as the body weight of the reference mouse, U.S. EPA/OPP (2008b) estimates the LD_{50} for a 1000 gram mammal as 8.3 mg/kg bw:

Equation 2

$$Estimated\ LD_{50} = 22\,mg/kg\,bw\left(\frac{20\,g}{1000\,g}\right)^{0.25} = 8.273\,mg/kg\,bw$$

The allometric equation for estimating the LD_{50} is referenced to Mineau et al. (1996); however, a full citation for this reference is not provided in U.S. EPA/OPP (2008b). Mineau et al. (1996), which is a common reference in ecological risk assessments, provides allometric scaling factors for estimating chemical specific LD_{50} values for birds. The equation used in U.S. EPA/OPP (2008b) is not presented in Mineau et al. (1996), which does not present any equations for mammals.

Another issue with the approach used in U.S. EPA/OPP (2008b) involves the data on emamectin benzoate. As discussed in Section 4.1.2.1 and summarized in Appendix 2, Table 1, the definitive acute oral LD_{50} values for emamectin benzoate in rats range from 53 to 88 mg/kg bw, suggesting that larger animals are less rather than more sensitive to emamectin benzoate. Based on the algorithm used in U.S. EPA/OPP (2008b), the expected LD_{50} in a 350 g rat, the reference weight used in U.S. EPA/OPP (2008b, p. 25), would be about 11 mg/kg bw:

Equation 3

$$Estimated\ LD_{50} = 22\,mg/kg\,bw\left(\frac{20\,g}{350\,g}\right)^{0.25} = 10.756\,mg/kg\,bw$$

While definitive LD_{50} values are available on only two species, mice and rats, these data indicate that rats are less sensitive than mice. Consequently, the algorithm used in U.S. EPA/OPP (2008b) does not appear to be appropriate for emamectin benzoate.

For chronic exposures, U.S. EPA/OPP (2008b, p. 24) uses a NOAEL of 0.6 mg/kg bw/day. As summarized in Appendix 2, Table 3, this NOAEL is from the 2-generation reproduction study in rats. As with the acute LD_{50} values, U.S. EPA/OPP (2008b, Table 22, p. 24) uses the same equation attributed to Mineau et al. (1996) to adjust the NOAEL for animals weighing from 15 grams (i.e., an adjusted NOAEL of 1.3 mg/kg bw) to animals weighing 1000 grams (i.e., an adjusted NOAEL of 0.46 mg/kg bw). As discussed above, the reference to Mineau et al. (1996) is questionable.

None of the toxicity values used for mammalian wildlife in the EPA ecological risk assessment of emamectin benzoate (U.S. EPA/OPP 2008b) are more conservative (i.e., lower) than the NOAEL of 0.1 mg/kg bw/day from the 16-day neurotoxicity study in mice (Gerson 1992e) as well as the NOAEL of 0.075 mg/kg bw/day for the plant

metabolite (Gerson 1992g). The current Forest Service risk assessment uses the NOAEL of 0.075 mg/kg bw/day for both the acute and chronic toxicity value. Although this approach, which is consistent with standard practices in Forest Service risk assessments, may be viewed as somewhat overly conservative, the difference between the NOAELs of 0.1 mg/kg bw/day for emamectin benzoate and 0.075 mg/kg bw/day for the plant metabolite is insubstantial. The impact of this somewhat more conservative approach is discussed further in the risk characterization (Section 4.4.2.1).

4.3.2.2. Birds

The only substantial uncertainty in developing the dose-response assessment for birds involves the acute gavage toxicity study in mallard ducks. As discussed in Section 4.1.2.2 and summarized in Appendix 3, Table 1, it appears that only one acute toxicity study in mallard ducks was submitted to U.S. EPA/OPP. Based on summaries of this study in EPA ecological risk assessments (U.S. EPA/OPP 2008b, 2009a), the LD_{50} in mallards is reported as 46 mg/kg bw with an NOAEL of <12 mg/kg bw. In the publication by Chukwudebe et al. (1998), however, the LD_{50} in mallards is reported as 76 mg/kg bw with a NOAEL of <25 mg/kg bw. The reason(s) for the discrepancy between the data summaries in U.S. EPA/OPP (2008b, 2009a) and Chukwudebe et al. (1998) cannot be determined. Consequently, the current Forest Service risk assessment uses the lower LD_{50} of 46 mg/kg bw for mallards from the EPA risk assessments.

Acute toxicity values for birds may be based either on the acute gavage studies or acute dietary studies using the most sensitive species on which data are available. As noted above, the lowest acute gavage LD_{50} in birds is 46 mg/kg bw with a NOAEL of <12 mg/kg bw for mallards. In the absence of a defined NOAEL, Forest Service risk assessments typically multiply the LD_{50} in birds and other terrestrial species by a factor of 0.1 to approximate a NOAEL. As discussed in SERA (2007a), this approach is consistent with the U.S. EPA/OPP approach of using a level of concern of 0.1 for RQs based on LD_{50} values. Thus, based on the gavage LD_{50} of 46 mg/kg bw, the NOAEL is estimated at 4.6 mg/kg bw. Mallards are also the most sensitive species in the acute dietary studies in birds, with a dietary NOAEC of 20 ppm (Chukwudebe et al. 1998). Based on measured food consumption and body weight, the dietary concentration of 20 ppm corresponds to a daily dose of about 6.6 mg/kg bw/day. The estimated NOAEL of 4.6 mg/kg bw from the gavage toxicity study is only modestly below the dietary NOAEL of 6.6 mg/kg bw/day. For the current Forest Service risk assessment, the lower NOAEL of 4.6 mg/kg bw is used to characterize acute risks in birds.

As discussed in Section 4.1.2.2, no adverse effects on reproduction are noted at dietary concentrations of up to 40 ppm in mallards and 125 ppm in quail (O'Grodnick et al. 1998a). Using a food consumption rate of 0.07 kg food/kg bw, these dietary concentrations correspond to estimated doses of 2.8 mg/kg bw/day in mallards and 8.75 mg/kg bw/day in quail. These estimated doses for the reproduction studies are consistent with the estimated dose of 6.6 mg/kg bw/day from the acute dietary toxicity studies. The lower reproduction NOAEL of 2.8 mg/kg bw/day could be used to characterize risks of longer-term term exposures in sensitive species of birds. Because the reproduction studies did not define an LOAEC, the consequences of exceeding the chronic NOAEL of 2.8 mg/kg bw/day cannot be well characterized.

4.3.2.3. Reptiles and Amphibians (Terrestrial-Phase)

As noted in Section 4.1.2.3, no information is available on the toxicity of emamectin benzoate to reptiles or terrestrial-phase amphibians. Consequently, no dose-response assessment is given for this group. Following the approach taken in U.S. EPA/OPP (2008b), risks to reptiles and terrestrial-phase amphibians are characterized based on risks to birds.

4.3.2.4. Terrestrial Invertebrates

While there is little doubt that emamectin benzoate is highly toxic to insects, the toxicity values from the open literature are highly variable. This variability is substantial even within a single species. This variability is most clearly evident for beet armyworms for which reported dietary LC_{50} values range from 0.001 mg/L (Jansson et al. 1997) to 2.4 mg/L (Mascarenhas et al. 1998). As discussed in Section 4.1.2.4.2, these reported LC_{50} values are not directly comparable because of differences in the ways that the experiment diets were prepared. Adjusting for these differences, the dietary LC_{50} values expressed as average concentrations in the total diet are 0.0001 mg/L in the study by Jansson et al. (1997) and 0.08 mg/L in the study by Mascarenhas et al. (1998). Using a food consumption rate of 1 kg food/kg insect bw as a crude approximation of food consumption (Section 4.2.3), the estimated LD_{50} values range from 0.0001 to 0.08 mg/kg bw. For comparison, the LD_{50} for honeybees, based on a contact study, is about 0.035 mg/kg bw.

For assessing risks to sensitive populations of insects, the lowest estimated LD_{50} of 0.0001 mg/kg bw from the study by Jansson et al. (1997) is multiplied by 0.1 to approximate an acute NOAEC of 0.00001 mg/kg bw. As with mammals and birds, the factor of 0.1 is adopted from the general approach used by U.S. EPA/OPP of setting the level of concern at 0.1, when LD_{50} values are used for risk characterization. The estimated NOAEC of 0.00001 mg/kg bw is applied to sensitive populations of insects.

For tolerant species of insects, the adjusted LC_{50} of 0.08 mg/L from the study by Mascarenhas et al. (1998), corresponding to an estimated LD_{50} of about 0.08 mg/kg bw, is used with the 0.1 factor to estimate an NOAEC of 0.008 mg/kg bw for tolerant populations of insects. As detailed in Section 4.1.2.4.2, the LC_{50} of 0.08 mg/L is derived from the reported LC_{50} of 2.4 mg/L in Mascarenhas et al. (1998) adjusted for the mixing of a 0.1 mL aliquot of the emamectin benzoate solution into 3 mL of artificial diet.

4.3.2.5. Terrestrial Plants (Macrophytes)

No dose-response assessment is proposed for nontarget terrestrial plants. Given the application method considered in this risk assessment (i.e., the injection of ash trees), significant exposures to nontarget plants are not anticipated.

4.3.2.6. Terrestrial Microorganisms

As noted in Section 4.1.2.6, data are not available on the toxicity of emamectin benzoate to terrestrial microorganisms. Consequently, no dose-response assessment for this group of organisms is proposed.

4.3.3. Aquatic Organisms

4.3.3.1. Fish

Forest Service risk assessments generally attempt to derive NOAECs associated with both acute and chronic exposures in both sensitive and tolerant species of fish. For acute exposures, the only relevant data are acute LC_{50} values summarized in the EPA risk assessments (U.S. EPA/OPP 2008b, 2009a). Freshwater fish appear to be much more sensitive than estuarine species of fish to emamectin benzoate. The lowest LC_{50} is 0.174 mg/L in rainbow trout (MRID 42851529), which is only modestly lower than the LC_{50} of 0.180 mg/L in sunfish (MRID 42743602) and the LC_{50} of 0.194 mg/L in minnows (MRID 43850106).

In the absence of information on the NOAEC, LC_{50} values are typically multiplied by a factor of 0.05. As with the use of LD_{50} values to approximate NOAECs in terrestrial species, the factor of 0.05 is based on the U.S. EPA/OPP practice of setting the level of concern at 0.05 for threatened and endangered aquatic species, when the risk characterization is based on an LC_{50} for an aquatic species.

For emamectin benzoate, the use of the factor of 0.05 may be grossly conservative. As discussed in Section 4.1.3.1, the available information on the slope of the concentration-response relationship in fish indicates a very steep slope. Thus, as the concentration decreases, risks will rapidly diminish. Nonetheless, in the absence of details on the studies used to derive the fish LC_{50} values, the standard factor of 0.05 is applied to the lowest LC_{50} of 0.174 mg/L. Thus, the estimated NOAEC is estimated at 0.0087 mg/L [0.174 mg/L x 0.05 = 0.0087 mg/L].

The highest acute LC_{50} is 1.43 mg/L for sheepshead minnows (MIRDs 43393003 and 44007914). This LC_{50} is multiplied by 0.05 to estimate the NOAEC in tolerant species at 0.072 mg/L [1.43 mg/L x 0.05 = 0.0715 mg/L $\approx$ 0.072 mg/L]. While this LC_{50} is based on an estuarine species, it is not clear that all estuarine/marine species are tolerant to emamectin benzoate. As discussed in Section 4.1.3.1, the oral LD_{50} of emamectin benzoate in Atlantic salmon (Armstrong et al. 2000) is 50 µg/kg bw/day.

The only chronic toxicity study in fish is the egg-and-fry study in fathead minnows (MRID 43850107, as summarized in U.S. EPA/OPP 2008b) in which the NOAEC is reported as 0.0065 mg/L. As discussed above, fathead minnows appear to be a species that is sensitive to emamectin benzoate. Thus, the concentration of 0.0065 mg/L is taken as a longer-term NOAEC for sensitive species of fish. For tolerant species of fish, the NOAEC for sensitive species is adjusted by the ratio of the LC_{50} for tolerant species to the LC_{50} for sensitive species—i.e., 1.43 mg/L $\div$ 0.174 mg/L $\approx$ 8.2. Thus, the longer-term NOAEC for tolerant species of fish is estimated at 0.053 mg/L [0.0065 mg/L x 8.2 = 0.0533].

4.3.3.2. Amphibians (Aquatic-Phase)

As noted in Section 4.1.3.2, no information is available on the toxicity of emamectin benzoate to aquatic-phase amphibians. Consequently, no dose-response assessment is

given for this group. Following the approach used in U.S. EPA/OPP (2008b), risks to aquatic-phase amphibians are characterized based on risks to fish.

4.3.3.3. Aquatic Invertebrates

The dose-response assessment for aquatic invertebrates is similar to that for fish in that acute NOAECs for aquatic invertebrates are not available and must be estimated from acute EC_{50} values. Unlike the case with fish, however, the lowest EC_{50} is associated with immobility in an estuarine/marine species, *Americamysis bahia* (a mysid shrimp), rather than in a freshwater species. The acute EC_{50} for the mysid shrimp is 0.04 µg/L (0.00004 mg/L). The estimated NOAEC is derived by multiplying this EC_{50} by a factor of 0.05. As discussed in Section 4.3.3.1, this approach is based on the U.S. EPA/OPP approach for setting a level of concern for threatened and endangered species at 0.05, when the risk characterization is based on an LC_{50} in an aquatic species. Thus, the acute NOAEC for sensitive species of invertebrates is estimated at 0.000002 mg/L [0.00004 mg/L x 0.05]. While this NOAEC is based on an estuarine/marine species, the NOAEC is applied to potentially sensitive freshwater species. This approach is taken because acute toxicity data are available on only a few aquatic invertebrates (Appendix 6, Table 1). Given these limited data, generalizations concerning the relative sensitivities of freshwater and saltwater arthropods are not warranted.

The highest EC_{50} is 0.49 mg/L. This EC_{50} is associated with the inhibition of shell deposition in an estuarine mollusk, the Eastern oyster. Again, given the very limited toxicity data available on emamectin benzoate, no generalizations are made or warranted concerning general differences in sensitivity between freshwater and estuarine mollusks or between aquatic arthropods and mollusks. The NOAEC for tolerant species is estimated as 0.025 mg/L [0.49 mg/L x 0.05 = 0.0245 mg/L].

Only one chronic toxicity study is available in aquatic invertebrates, a standard life-cycle assay in *Daphnia magna* which yielded an NOAEC of 0.088 µg/L (0.000088 mg/L). Based on the acute toxicity studies, *Daphnia magna* is intermediate in sensitivity to emamectin benzoate with an acute EC_{50} of 0.001 mg/L. Consequently, it does not seem reasonable to directly use the chronic NOAEC in *Daphnia* for either tolerant or sensitive species. As an alternative, the chronic NOAEC of sensitive species could be estimated by multiplying the chronic daphnid NOAEC by the ratio of the acute NOAEC in mysid shrimp to the acute NOAEC in daphnids—i.e., 0.000088 mg/L x 0.00004 mg/L ÷ 0.001 mg/L = 0.00000352 mg/L. This estimate of the longer-term NOAEC, however, is modestly greater than the estimate of the acute NOAEC of 0.000002 mg/L. Consequently, the acute NOAEC for sensitive species is maintained as the toxicity value for longer-term exposures.

The chronic NOAEC of tolerant species could be estimated by multiplying the chronic daphnid NOAEC by the ratio of the acute NOAEC in oysters to the acute NOAEC in daphnids—i.e., 0.000088 mg/L x 0.49 mg/L ÷ 0.001 mg/L = 0.04312 mg/L. Again, however, this estimate of the chronic NOAEC for tolerant species is somewhat greater than the estimate of the acute NOAEC of 0.025 mg/L for tolerant species. Consequently, as with sensitive species of aquatic invertebrates, the acute NOAEC of 0.025 mg/L is maintained as the estimate of the NOAEC for longer-term exposures.

4.3.3.4. Aquatic Plants

As detailed in Section 4.1.3.4, the only toxicity values available for aquatic plants are free-standing NOAECs of 0.0039 mg/L in algae and 0.094 mg/L in an aquatic macrophyte. In other words, there are studies on concentrations that do not cause adverse effects but no studies on concentrations that do cause adverse effects. As discussed further in the risk characterization, HQs associated with free-standing NOAECs provide little information of the potential consequences of exposures that exceed the NOAECs.

While Forest Service risk assessments typically derive toxicity values for sensitive and tolerant species of algae and aquatic macrophytes, the available toxicity data on aquatic plants exposed to emamectin benzoate do not support the development of a dose-response assessment.

4.4. RISK CHARACTERIZATION

4.4.1. Overview

The ecological risk assessment for emamectin benzoate is dominated by uncertainties in the exposure assessment. Because of limited information on the transport of emamectin benzoate in trees following tree injection and the lack of information on the transport of emamectin benzoate in ash trees, reliable estimates of exposures in nontarget species associated with the injection of emamectin benzoate into ash trees cannot be made. **The inability to estimate expected exposures of nontarget species limits confidence in the risk characterization for nontarget species.**

Uncertainties in the exposure assessments associated with the potential contamination of surface water in the normal use of emamectin benzoate for the injection of ash trees are addressed with an accidental spill scenario. Based on the accidental spill scenario, no risks are apparent for mammals, birds, fish, aquatic plants, or tolerant species of aquatic invertebrates. The lack of risk in the accidental spill scenarios for these groups of organisms suggest that the contamination of surface water associated with the normal use of emamectin benzoate is not likely to adversely affect these organisms. Risks to sensitive species of aquatic invertebrates, however, are apparent in the accidental spill scenario with an upper bound HQ of 120. Thus, in the event of an accidental spill of a significant amount of emamectin benzoate into a pond, adverse effects, including mortality, are anticipated. The high HQs for sensitive species of aquatic invertebrates associated with the accidental spill scenario also prevents a clear risk characterization for this group of organisms in the normal use of emamectin benzoate. At least in situations in which high doses of emamectin benzoate are used or a relatively large number of trees are treated near surface water, risks to sensitive species of aquatic invertebrates can neither be discounted nor characterized clearly.

While uncertainties associated with contaminated surface water can be addressed reasonably well, other exposure pathways are problematic. The most likely exposures for mammals and birds involve the consumption of bark, stem tissue, or seeds of ash trees as well as the consumption of herbivorous insects that may feed on ash leaves. Only the pathway involving the consumption of herbivorous insects is developed quantitatively. Under worst-case exposure assumptions, risks to mammals are marginal (an upper bound HQ of 1.1) and risks to birds are negligible (an upper bound HQ of 0.03). For herbivorous insects, however, the risk characterization is well-defined. Both tolerant and sensitive species or populations of herbivorous insects are likely to be adversely affected if they feed on ash trees injected with effective doses of emamectin benzoate.

While the risk characterization for emamectin benzoate is dominated by uncertainties in the exposure assessments, it is worth noting that the most relevant toxicity studies on aquatic organisms and birds are limited to relatively standard bioassays on relatively few species of organisms, relative to other more fully studied pesticides. In addition, no data are available on reptiles, amphibians, or soil invertebrates exposed to emamectin benzoate.

4.4.2. Terrestrial Organisms

4.4.2.1. Mammals

The HQs for mammals are summarized in Worksheet G02 of the EXCEL workbook that accompanies this risk assessment. Two sets of exposure scenarios are provided, one set associated with accidental spills and the other set associated with the consumption of contaminated insects.

While the exposure assessments for mammals as well as other nontarget species are limited, risks to mammals associated with the potential contamination of surface water appear to be negligible. The highest HQ for the consumption of contaminated water following an accidental spill is about 0.004—i.e., the upper bound of the HQ for a small mammal. This HQ is below the level of concern (HQ=1) by a factor of 250.

Accidental exposure scenarios can always be made more extreme. As detailed in Section 3.2.3.4, the upper bound of the dose for the accidental spill scenario is equivalent to the exposure scenario used in the EPA ecological risk assessment (U.S. EPA/OPP 2009a) and involves a spill of 42,600 mg a.i. into a small pond. For the Tree-äge formulation (4% a.i.), this amount is equivalent to 1,065,000 mg formulation [42,600 mg a.i. ÷ 0.04 a.i./formulation] or a little more than 2 lbs of Tree-äge [1,065,000 mg ÷ (1000 mg/g x 453.6 g/lb) ≈ 2.35 lbs], which is the upper bound of the dose of emamectin benzoate for a large ash tree. For the accidental exposure scenario to reach a level of concern, the amount of the spill would have to be nearly 600 lbs of Tree-äge [2.35 lbs formulation x 250 = 587.5 lbs formulation], the amount needed to treat 250 large trees.

While it is not possible to estimate the amount of emamectin benzoate that might reach surface waters in the normal course of tree injections, the very low HQs associated with the accidental spill scenarios suggest that non-accidental (i.e., expected) concentrations of emamectin benzoate in surface water are not likely to pose any risks to mammals in the normal use of Tree-äge for the injection of ash trees.

As discussed in Section 4.2, the most likely exposures for mammals involve the consumption of bark, stem tissue, or seeds of ash trees. The potential risks associated with these types of exposures cannot be well characterized because of the lack of information on the movement of emamectin benzoate in ash trees following tree injection.

The exposure scenarios for the consumption of contaminated insects by a small mammal leads to hazard quotients of 0.003 (0.000007 to 1.1). As detailed in Section 4.2.2.3, this wide range of HQ values reflects two factors, differences in the toxicity of emamectin benzoate to insects and differing assumptions concerning the proportion of the diet of the mammal that consists of contaminated insects. The upper bound HQ of 1.1 reflects the consumption of insects that are tolerant to emamectin benzoate, specifically insects that had consumed twice the highest estimated insect LD_{50} of 0.08 mg/kg bw. In addition, the upper bound HQ of 1.1 reflects the assumption that the mammal consumes only contaminated insects. Given these extreme assumptions, the modest excursion about the

level of concern (HQ=1) suggests that mammals consuming insects that have fed on treated trees are not likely to be at substantial risk.

A simple verbal interpretation of the risk characterization for mammals is that risks associated with the consumption of surface water appear to be minimal and risks associated with the consumption of contaminated insects range are marginal. Risks associated with other exposure pathways, however, cannot be determined without additional information on the movement of emamectin benzoate within treated ash trees.

4.4.2.2. Birds

As with the HQs for mammals, the HQs for birds are summarized in Worksheet G02 of the EXCEL workbook that accompanies this risk assessment. Also, an attempt is made to characterize risks associated with exposure scenarios for accidental spills and the consumption of contaminated insects.

The only substantial differences in the risk characterization for birds and mammals involve the differences in the toxicity values—i.e., the NOAEL of 0.075 mg/kg bw for mammals and the estimated NOAEL of 4.6 mg/kg bw for birds. As discussed in Section 4.3.2.2, the much higher estimated NOAEL for birds, relative to mammals, may simply reflect the differences in the types of available toxicity studies for the two groups of animals. For mammals, acute neurotoxicity studies are required by the U.S. EPA/OPP to support the human health risk assessment. For neurotoxins, studies specifically designed to assess neurotoxic endpoints often yield lower NOAECs than standard toxicity studies, as is the case with emamectin benzoate. If the neurotoxicity studies in mammals are excluded, the standard acute and reproduction studies in mammals and birds do not suggest substantial differences in the sensitivity of mammals and birds to emamectin benzoate. Thus, a case could be made for applying the neurotoxicity NOAEL in mammals to the risk characterization for birds.

For emamectin benzoate, however, this would not have a substantial impact on the risk assessment, because the uncertainties associated with the risk assessment on emamectin benzoate are primarily associated with the exposure assessments for both mammals and birds. As with mammals, the risk characterization for birds suggests that exposures via the contamination of surface water are not likely to pose risks – i.e., the highest HQ is the upper bound of HQ of 0.0001 for a small bird which is below the level of concern by a factor of 10,000.

The HQs for the consumption of contaminated insects by a small bird are 0.00007 (0.0000002 to 0.03). As with the corresponding HQs for mammals, the very wide range of HQs reflects differences in the toxicity of emamectin benzoate to insects which is the limiting factor for exposure as well as differences in the proportion of the diet that consists of contaminated insects. Unlike the case with mammals, however, the upper bound HQ for this exposure scenario is below the level of concern by a factor of about 33.

One minor qualitative difference between birds and mammals involves concerns for mammals that may consume the bark of ash trees. This exposure pathway does not apply to birds.

4.4.2.3. Reptiles and Amphibians (Terrestrial Phase)

As noted in Section 4.3.2.3, no data are available on the toxicity of emamectin benzoate to reptiles or terrestrial-phase amphibians. U.S. EPA/OPP (2008b) suggests that risks to reptiles and terrestrial-phase amphibians should be characterized based on risks to birds. This is a standard recommendation in ecological risk assessments conducted by U.S. EPA/OPP.

4.4.2.4. Terrestrial Invertebrates

Risks to nontarget insects are summarized in the EXCEL workbook that accompanies this risk assessment. Worksheet G07a summarizes risks based on the assumption of uniform distribution within the ash tree, and Worksheet G07b summarizes risks under the assumption of restricted distribution to leaves. The rationale for these two sets of assumptions is detailed in Section 4.2.3.2.1; furthermore, the uncertainties associated with these assumptions are discussed in Section 4.4.2.1, the risk characterization for mammals.

While the uncertainties and limitations in the exposure assessments for herbivorous insects are essentially identical to those for mammals and birds, these uncertainties have little impact on the risk characterization for emamectin benzoate because of the very high toxicity of emamectin benzoate to insects.

Emamectin benzoate is an effective insecticide. If emamectin benzoate is injected into ash trees at effective doses to control the emerald ash borer, sensitive species of herbivorous insects feeding on the leaves of treated trees could easily ingest lethal doses of emamectin benzoate. Uncertainties in amount of leaves consumed and the concentrations of emamectin benzoate in the leaves have relatively little impact on the risk characterization for sensitive or tolerant species, with HQs ranging from 3 (the lower bound of the HQ for tolerant species under the assumption of restricted distribution) to over 4 million (the upper bound of the HQ for sensitive species under the assumption of uniform distribution). It must be emphasized that the extremely high HQs are not realistic in the sense that an insect would sicken and die longer before sufficient amount of emamectin benzoate could be consumed to reach some of the very high HQs given in Worksheets G07a and G07b. A more reasonable verbal interpretation of these HQs is simply that the effective treatment of a tree with emamectin benzoate could and probably would lead to fatal exposures in herbivorous insects.

Potential risks to other terrestrial invertebrates are not quantified. As discussed in Section 4.2.3.2.2, risks to honeybees are not anticipated because ash trees are wind pollinated. Risks to soil invertebrates, like earthworms, are not quantified because exposures cannot be reliably estimated and toxicity data are not available (Section 4.2.3.2.3).

4.4.2.5. Terrestrial Plants

Risks to terrestrial plants are not quantified. Nonetheless, given that Forest Service uses of emamectin benzoate covered in the current risk assessment involve only the injection of ash trees, there is no basis for asserting that damage to other types of terrestrial plants is likely to occur.

4.4.3. Aquatic Organisms

The HQs for aquatic organisms are summarized in Worksheet G03 of the EXCEL workbook that accompanies the current Forest Service risk assessment. The risk characterization for aquatic species is limited by the inability to estimate concentrations of emamectin benzoate likely to occur in surface water as a result of its injection into ash trees. For the most part, however, these limitations have only a minor impact on the risk characterization.

As summarized in Worksheet G04, the HQs for most groups of aquatic organisms associated with the accidental spill scenario are very low, with upper bound HQs ranging from 0.003 to 0.06—i.e., below the level of concern (HQ=1) by factors ranging from about 17 to more than 300. As discussed in Section 4.4.2.1, the accidental scenarios can always be made more severe; however, this would involve increasing the quantity of Tree-äge that is spilled to amounts unlikely to occur at a single application site. More importantly, the very low HQs associated with the accidental spill scenario for most groups of aquatic organisms suggest that the normal injection of emamectin benzoate into ash trees is not likely to cause adverse effects in most groups of aquatic organisms.

Sensitive species of aquatic invertebrates comprise the only group for which there is an exception to the above risk characterization. For this group of organisms, the accidental spill scenario leads to HQs of 9 (0.7 to 120). As detailed in Section 3.2.3.4, the range of HQs is related directly to the range of emamectin benzoate doses injected into individual trees. Thus, in the accidental spill of a high dose of emamectin benzoate into a small pond, the HQ of 120 suggests the potential for significant mortality in sensitive species of aquatic invertebrates. Conversely, the spill of a low dose of emamectin benzoate might not be associated with any detectable adverse effects.

While the accidental spill scenario can be used to suggest that the normal injection of emamectin benzoate into ash trees is not likely to present a risk to most species of aquatic organisms, such is not the case for sensitive species of aquatic invertebrates. At least in situations in which high doses of emamectin benzoate are used or a relatively large number of trees are treated near surface water, risks to sensitive species of aquatic invertebrates cannot be discounted. In the absence of data that might permit a reliable estimate of concentrations of emamectin benzoate in surface water following the injection of emamectin benzoate into ash trees, potential risks to sensitive species of aquatic invertebrates cannot be characterized clearly.

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.

ClRev1	**Internal EPA documents from cleared reviews available at: http://www.epa.gov/pesticides/chemical/foia/cleared-reviews/reviews/122806/122806.htm.**
DER1	**DERs from cleared reviews available at: http://www.epa.gov/pesticides/chemical/foia/cleared-reviews/reviews/122806/122806.htm.**
FOAI01	**Initial FOIA to EPA (HQ-FOI-00787-10) for EPA risk assessments and bibliography of registrant submitted studies.**
FOAI02	**A second request to U.S. EPA/OPP (HQ-FOI-01225-10, May 10, 2010) for three studies which are listed at the start of this section.**
E-Docket01	**Initial screen [59 listings in various Docket IDs – e.g., EPA-HQ-OPP-2005-0212, EPA–HQ–OPP–2008–0261].**
Internet	**References obtained from various sites on the Internet.**
MRID01	**Key references to be requested from registrant or U.S. EPA.**
PeerRev	**Papers obtained during peer review.**
SET00	**Papers from preliminary scoping.**
SET01-TOXL	**Preliminary TOXLINE literature search.**
SET02	**References identified from SET01**
Sec	**Summary of citation from a secondary source.**
Std	**Standard references used in most Forest Service risk assessments.**

Special Note: The studies listed below were not available in the preparation of this risk assessment. These studies are cited in the text of this risk assessment. This list is followed by the standard open literature references and DERs that were available for the preparation of this risk assessment.

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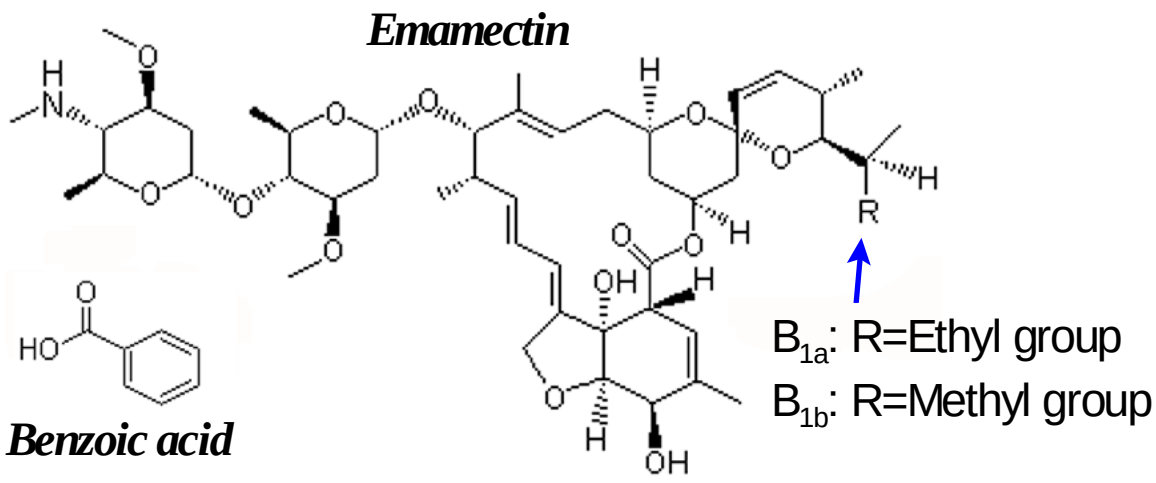


Figure 1: Chemical Structure of Emamectin benzoate

Source: www.chemblink.com
See discussion in Section 2.2.

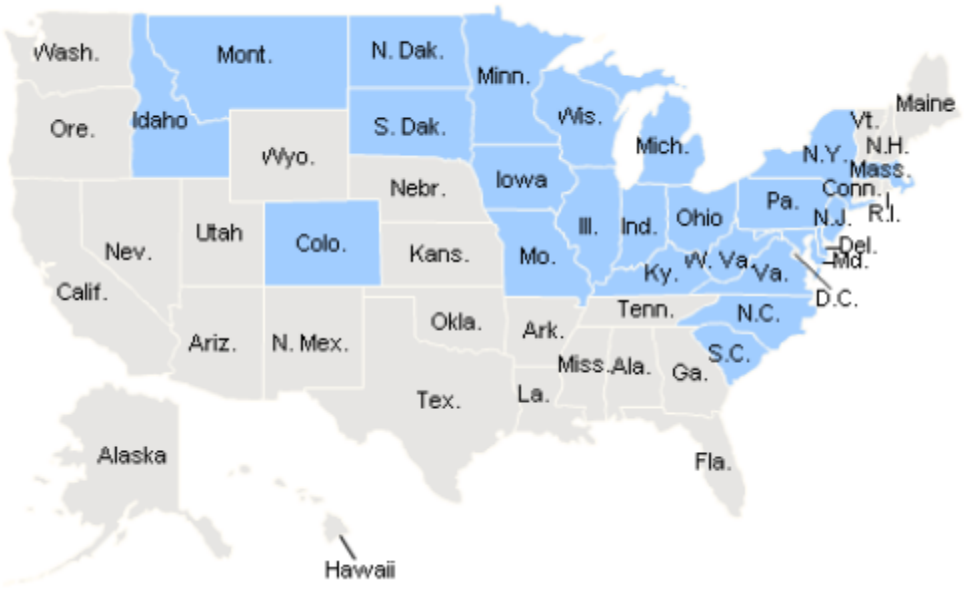


Figure 2: States in which Tree-äge is Registered

Source: Arborjet 2010

See Sections 2.2 and 2.5 for discussion.

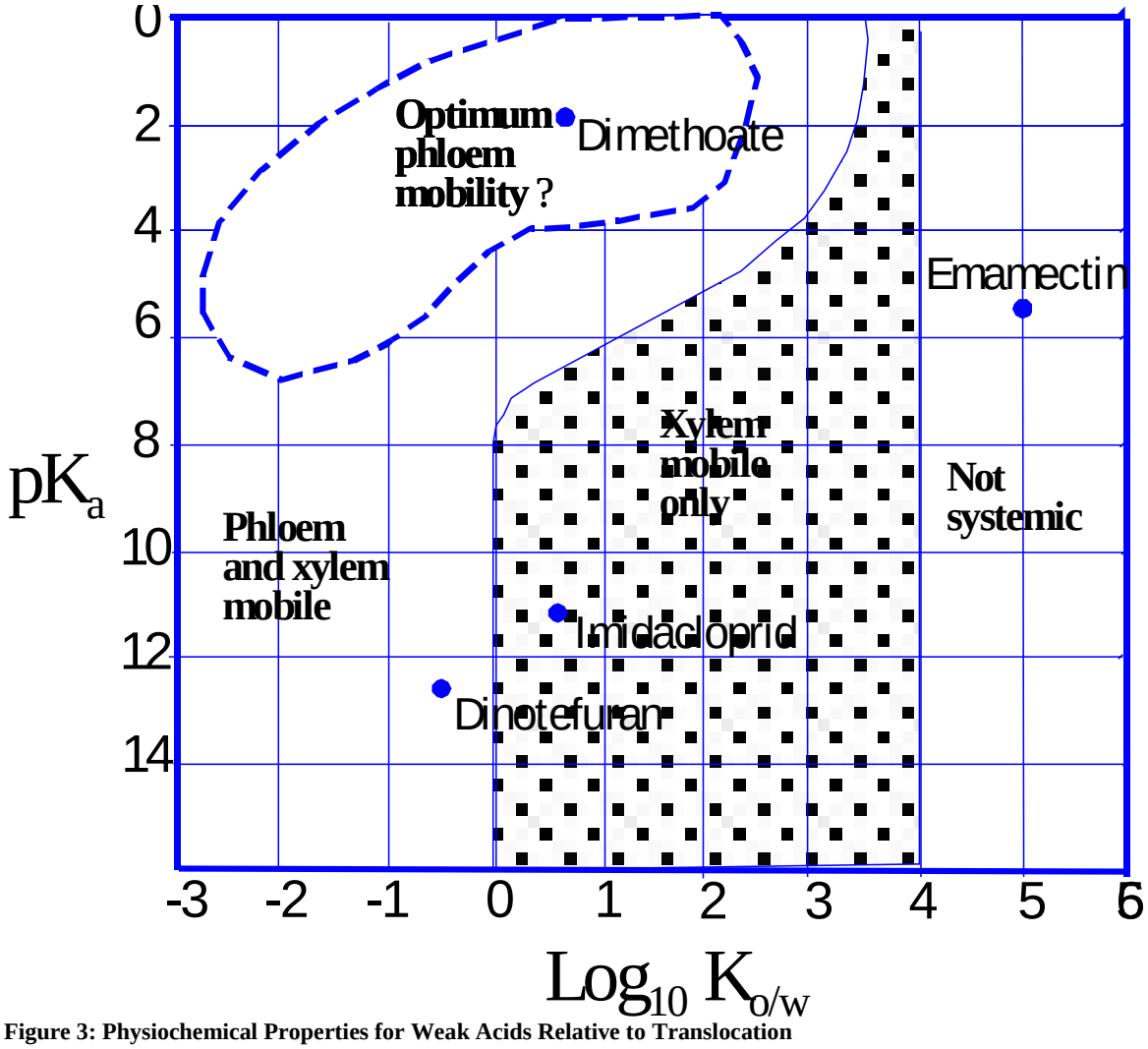


Figure 3: Physiochemical Properties for Weak Acids Relative to Translocation

Source: Redrawn from Bromilow et al. 1990, Figure 5, p. 313 and modified to illustrate the data on emamectin, dinotefuran, imidacloprid, dimethoate.

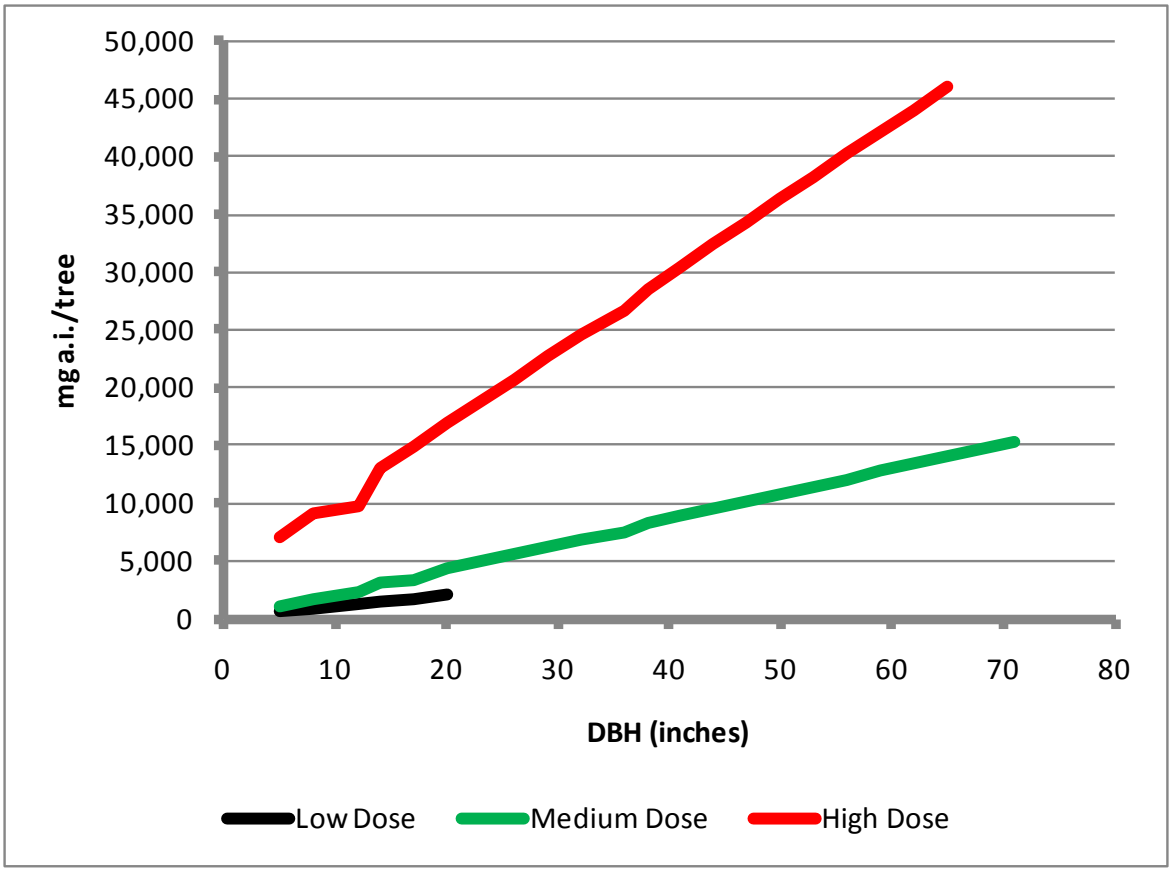
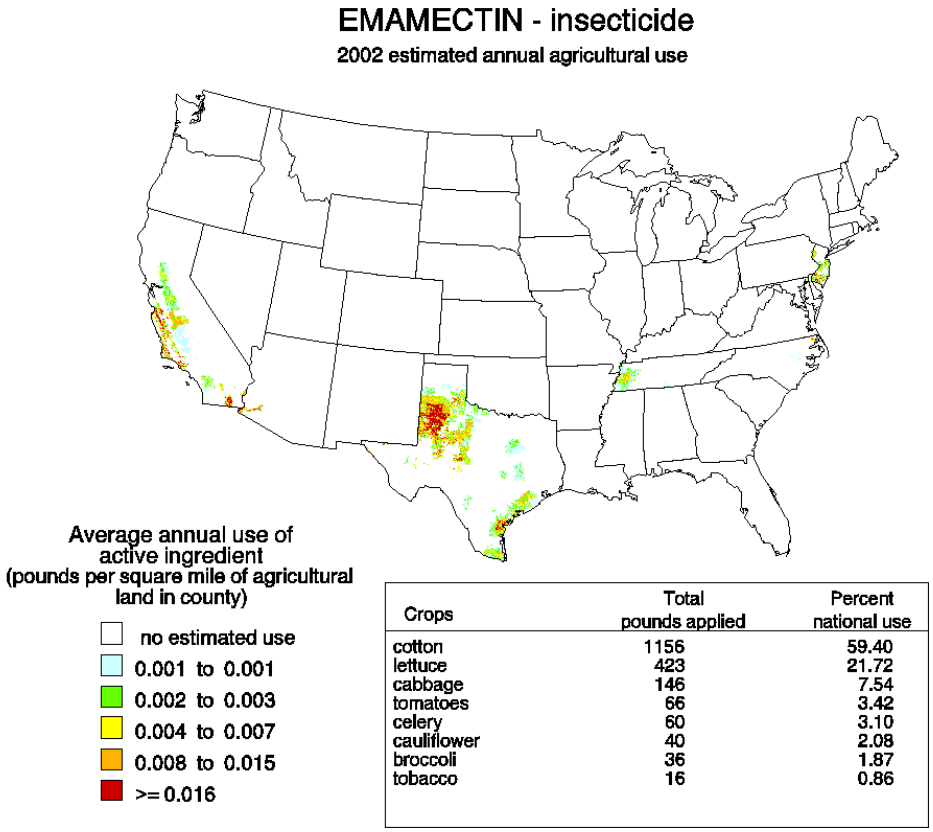


Figure 4: Doses of Tree-äge for Tree Injections

See Table 4 for data.
See Section 2.4 for discussion.



Crops	Total pounds applied	Percent national use
cotton	1156	59.40
lettuce	423	21.72
cabbage	146	7.54
tomatoes	66	3.42
celery	60	3.10
cauliflower	40	2.08
broccoli	36	1.87
tobacco	16	0.86

Figure 5: Agricultural Uses of Emamectin

Source: USGS 2003a

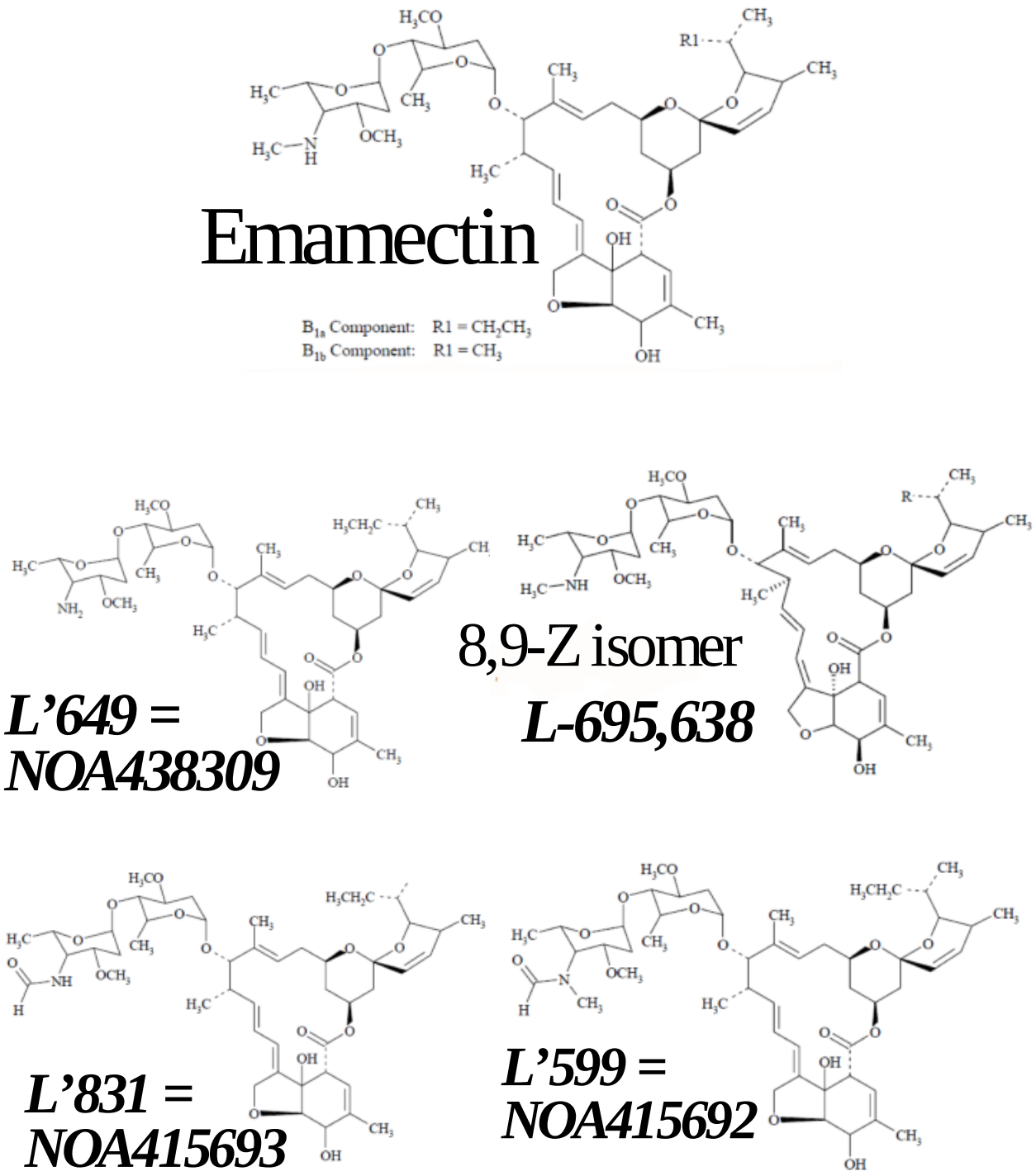


Figure 6: Emamectin and Metabolites

Adapted from U.S. EPA/OPP (2008a), Appendix B.
See Section 3.1.15 for discussion.

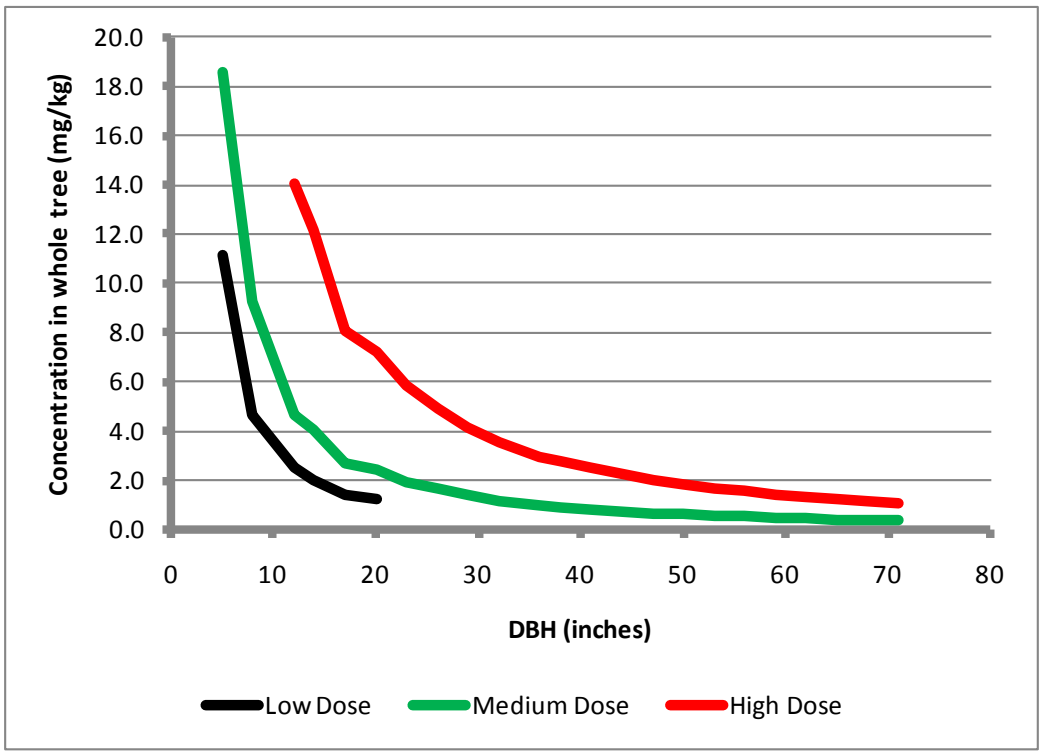


Figure 7: Estimated Concentrations of Emamectin Benzoate in Whole Ash Trees

See Worksheet B07 for data.
See Section 3.2.3.6 for discussion.

Table 1: EPA Guideline Studies for Emamectin benzoate

No	Guideline	No	Guideline
123-2	**Aquatic plant growth**	**81-5**	**Primary dermal irritation**
132-1	Dissipation of Dislodgeable Foliar & Soil Residues	**81-6**	**Dermal sensitization**
133-3	Dermal passive dosimetry exposure	**81-7**	**Neurotoxicity study in hens**
133-4	Inhalation. passive dosimetry exposure	**81-8**	**Acute neurotoxicity screen study in rats**
141-1	**Honey bee acute contact**	**82-1**	**Subchronic Oral Toxicity: 90-Day Study**
141-2	**Honey bee residue on foliage**	**82-2**	**21-day dermal-rabbit/rat**
161-1	Hydrolysis	**82-5**	**Subchronic Neurotoxicity: 90-Day Study**
161-2	Photodegradation-water	**82-7**	**Subchronic Neurotoxicity**
161-3	Photodegradation-soil	830.1550	Product Identity and composition
161-4	Photodegradation-air	830.1600	Description of materials used to produce the product
162-1	Aerobic soil metabolism	830.1620	Description of production process
162-2	Anaerobic soil metabolism	830.1650	Description of formulation process
163-1	Leach/adsorption/desorption	830.1670	Discussion of formation of impurities
164-1	Terrestrial field dissipation	830.1700	Preliminary analysis
165-1	Confined rotational crop	830.1750	Certified limits
171-11	Tobacco Uses: Total Residues and Pyrolysis Products	830.1800	Enforcement analytical method
171-4A1	Characterization of Total Terminal Residue	830.6302	Color
171-4A2	Nature of the Residue in Plants	830.6303	Physical state
171-4A3	Nature of the Residue in Livestock	830.6304	Odor
171-4B	Residue Analytical Methods	830.6313	Stability to sunlight, normal and elevated temperatures
171-4C	Magnitude of the Residue [by commodity]	830.6314	Oxidizing or reducing action
61-1	Chemical Identity	830.6315	Flammability
61-2	Beginning Materials and Manufacturing Process	830.6316	Explodability
61-3	Discussion of Formation of Impurities	830.6317	Storage stability of product
62-1	Preliminary Analysis	830.6320	Corrosion characteristics
62-2	Certification of limits	830.7000	pH of water solutions or suspensions
62-3	Analytical Method	830.7050	UV/Visible absorption
63-0	Reports of Multiple physical/chemical properties	830.7100	Viscosity
63-10	Dissociation Constant	830.7200	Melting point/melting range
63-11	Octanol/Water partition Coefficient	830.7300	Density/relative density
63-12	pH	830.7370	Dissociation constant in water
63-13	Stability	830.7550	Partition coefficient (n-octanol/water), shake flask method
63-17	Storage stability	830.7840	Water solubility: Column elution method, shake flask method
63-20	Corrosion characteristics	830.7950	Vapor pressure
63-5	Melting Point	**83-1**	**Chronic Toxicity**
63-7	Density	**83-2**	**Oncogenicity**
63-8	Solubility	**83-3**	**Teratogenicity -- 2 Species**
63-9	Vapor Pressure	**83-4**	**2-generation repro.-rat**
71-1	**Avian Single Dose Oral Toxicity**	**84-2**	**Interaction with Gonadal DNA**
71-2	**Avian Dietary Toxicity**	**85-1**	**General metabolism**
71-4	**Avian Reproduction**	**85-3**	**Dermal Penetration/Absorption**
72-1	**Acute Toxicity to Freshwater Fish**	860.1000	Background
72-2	**Acute Toxicity to Freshwater Invertebrates**	860.1380	Storage stability data
72-3	**Acute Toxicity to Estuarine/Marine Organisms**	860.1500	Crop field trials
72-4	**Fish /Aquatic Invertebrate Life Cycle**	860.1520	Processed food/feed
72-6	**Aquatic org. accumulation**	**870.1100**	**Acute oral toxicity**
810.1000	Overview, Definitions, and General Considerations	**870.1200**	**Acute dermal toxicity**
810.3000	Efficacy of invertebrate control agents	**870.1300**	**Acute inhalation toxicity**

810.3500	Premises treatments	**870.2400**	**Acute eye irritation**
81-1	**Acute oral toxicity in rats**	**870.2500**	**Acute dermal irritation**
81-2	**Acute dermal toxicity in rabbits or rats**	**870.2600**	**Skin sensitization**
81-3	**Acute inhalation toxicity in rats**	**870.5100**	**Bacterial reverse mutation test**
81-4	**Primary eye irritation in rabbits**	N/A	Non-Guideline Study

Guidelines relevant to human health effects and ecological effects are given in bold typeface. See Section 1.1 for discussion.

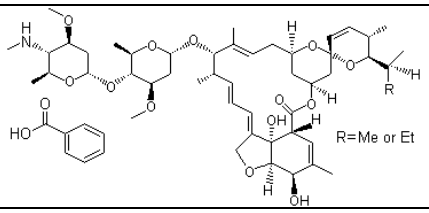
Table 2: Chemical and Physical Properties of Emamectin benzoate		
Property	**Value**	**Reference**
	Identifiers	
Common name:	Emamectin benzoate	
CAS Name	(4"R)-5-O-demethyl-4"-deoxy-4"-(methylamino)avermectin A1a + (4"R)-5-Odemethyl-25-de(1-methylpropyl)-4"-deoxy-4"-(methylamino)-25-(1-methylethyl)avermectin A1a (9:1)	Tomlin 2004
CAS No.	Emamectin: 155569-91-8	Tomlin 2004
	Emamectin benzoate: 155569-91-8	ChemIDplus Advanced 2010 Syngenta 2007
	Emamectin benzoate: 148477-71-8	U.S. EPA/OPP 2009a[1]
Previous CAS No.	Emamectin: 137512-74-4 and 179607-18-2	ChemIDplus Advanced 2010
U.S. EPA PC Code	122806	U.S. EPA FOIA 01
EPA Reg. No.	100-902	Syngenta 2004 MSDS
Development Codes	MK 244 (a.i.)	Tomlin 2004
	MK 243 (emulsifiable concentrate formulation)	Lasota and Dybas 1991
Mode of Action Class	IRAC 6, Chloride channel activators	IRAC 2009
Synonyms	Methylamino abamectin benzoate Sch 58854 UNII-HVM3G4A01W	ChemIDplus Advanced 2010
Structure		http://www.chemblink.com B_{1a}: Ethyl group B_{1b}: Methyl group
Composition	≥ 90%B_{1a}; ≤ 10% B_{1b}	Tomlin 2004
	Chemical Properties	
Kow	100,000 (pH 7) [log P = 5]	Tomlin 2004
	Emamectin B_{1a}: ≈501,000 [log P = 5.7] Emamectin B_{1b}: ≈158,000 [log P = 5.2]	
Melting Point	141-146 °C [Emamectin benzoate]	Tomlin 2004
Molecular weight (g/mole)	Emamectin B_{1a}: 886.1 B_{1b}: 972.1 Emamectin benzoate B_{1a}: 1008.3 B_{1b}: 994.2 Benzoic acid: 122.12	Tomlin 2004 Tomlin 2004 Budavari 1989
pKa	4.2 (benzoic acid) 5.2 (methyl-amino group on emamectin benzoate)	U.S. EPA/OPP 2008a, Table 2.3
Source	Fermentation byproduct from *Streptomyces avermitilis* (Actinomycete)	Tomlin 2004
Specific gravity	1.2 (23°C) [Emamectin benzoate]	Tomlin 2004
Vapor pressure	$4x10^{-3}$ mPa (21 °C) [Emamectin benzoate]	Tomlin 2004
Water solubility	0.024 g/L (pH 7, 25°C)	Tomlin 2004

Table 2: Chemical and Physical Properties of Emamectin benzoate		
Property	**Value**	**Reference**
	Environmental Properties	
Bioconcentration Factor	Whole fish: 80 Fillet: 30 Viscera: 116	Chukwudebe et al. 1996a
	Whole fish: 69 Fillet: 31 Viscera: 98	U.S. EPA/OPP 1995, MRID 43393005
Foliar half-life	10 to 15 hours (0.4 to 0.6)	Chukwudebe et al. 1997b
Hydrolysis	pH 5: stable pH 7: stable pH 9: 20 weeks	Peterson et al. 1994b
Koc	25,363 to 730,000	U.S. EPA/OPP 2008a
	25,000 to 729,000	Mushtaq et al. 1996a
Photolysis	Half-lives in natural pond water: Fall: 6.9 days (10 h light) Winter: 10.9 days (estimated) Summer: 3.6 days (estimated)	Mushtaq et al. 1998
Soil aerobic degradation, laboratory	$t_{1/2}$ of 193.4 days (sandy loam)	U.S. EPA/OPP 2008a
	Biphasic Initial half-life: 74 days (sorption processes) Terminal half-life: 349 days (degradation)	Chukwudebe et al. 1997a
Soil anaerobic degradation	Very slow	Chukwudebe et al. 1997a

[1] This appears to be an error. CAS No. 148477-71-8 is assigned to Spirodiclofen.

Table 3: Emamectin Benzoate Formulations

Formulation/ Registrant	Composition	Application Information
Formulations considered in Forest Service risk assessment		
Tree-äge/ Syngenta EPA Reg. No.: 100-1309-74578 (product label from http://arborjet.com. 100-RGNO (U.S. EPA/OPP 2008a)	4.0% emamectin benzoate 96% other ingredients including tetrahydrofurfuryl alcohol, petroleum distillates. Density: 1.08 g/mL at 68°F. 0.36 lbs emamectin per gallon	Applied by tree injection 2 to 3 weeks prior to likely infestation period. Application dose per tree dependant on size of tree: 15 to 1065 mL/tree ≈ 0.630 to 46 g/tree ≈ 0.0014 to 0.10 lb/tree [1 lb = 453.6 g] Diluted in 1 to 3 volumes of water 3 to 30 injection sites See Section 2.3 for discussion and Table 4 for more detailed application rates. Figure 2 illustrates the states in which Tree-äge is registered.
Other Formulations		
Denim/ Syngenta EPA No. 100-903 Initial EPA label on May 19, 1999 Most recent EPA label on May 15, 2009	2.5% emamectin benzoate (liquid) 97.85% other ingredients including organic solvent (petroleum distillate) and butylated hydroxytoluene. 0.9 g/mL at 77°F. 0.16 lb a.i./gallon	Restricted use pesticide. Labeled only for application to cotton and tobacco for the control of a variety of insect pests. Broadcast foliar applications at rates of 6 to 12 fl oz/acre (equivalent to ≈ 0.0075 to 0.015 lb a.i./acre).
Proclaim/ Syngenta EPA No. 100-904 Initial EPA label on May 19, 1999 Most recent EPA label on September 30, 2009	5% emamectin benzoate (soluble granules) 95% other ingredients including organic solvent (petroleum distillate) and butylated hydroxytoluene. 0.9 g/mL at 77°F.	Restricted use pesticide. Labeled for applications to various fruits and vegetables for the control of lepidopterans, leafminers, and spider mites. Broadcast foliar applications (in 5 to 40 gallons/acre) at rates of 0.8 to 4.8 oz/acre (equivalent to ≈ 0.0025 to 0.015 lb a.i./acre).

Table 4: Tree Injection Rates for Tree-äge

	Dose as mL Tree-äge Per Tree			Dose as mg a.i. Per Tree		
Mid-Point DBH (Inches)	Low Dose	Medium Dose	High Dose	Low Dose	Medium Dose	High Dose
5	15	25		648	1080	
8	20	40		864	1728	
11	30	55	165	1296	2376	7128
14	35	70	210	1512	3024	9072
17	40	75	225	1728	3240	9720
20	50	100	300	2160	4320	12960
23		115	345		4968	14904
26		130	390		5616	16848
29		145	435		6264	18792
32		160	480		6912	20736
35		175	525		7560	22680
38		190	570		8208	24624
41		205	615		8856	26568
44		220	660		9504	28512
47		235	705		10152	30456
50		250	750		10800	32400
53		265	795		11448	34344
56		280	840		12096	36288
59		295	885		12744	38232
62		310	930		13392	40176
65		325	975		14040	42120
68		340	1020		14688	44064
71		355	1065		15336	46008

Source: Tree-äge Product label from http://www.arborjet.com/products/injectables.htm.
The above table is included in Worksheet B07 of Attachment 1.
See Section 2.4 for discussion.

Table 5: Summary of PHED Exposure Rates

Scenario	mg/lb a.i. handled[1]			
	No clothing	**Single Layer, No gloves**	**Single layer, Gloves**	**Inhalation**
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	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	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] Note that the above values are in mg a.i./lb handled and not mg a.i./kg bw per lb a.i. handled.

Source: Keigwin 1988

Table 6: Exposure Rates Based on Biomonitoring

Worker Group	Rate (mg/kg bw/day per lb applied)		
	Central	Lower	Upper
Directed foliar	0.003	0.0003	0.01
Broadcast foliar	0.0002	0.00001	0.0009
Aerial	0.00003	0.000001	0.0001

Source: SERA 2007a, Table 3-3

Table 7: Summary of Typical Exposure Scenarios for Differing Application Methods

Scenario	Person	Application Method: Broadcast Foliar	Broadcast Soil	Bark	Soil Injection	Tree Injection	Worksheet
Accidental Acute Exposures							
Direct Spray of Child, whole body	Child	■		■			D01a
Direct Spray of Woman, feet and lower legs	Female	■		■			D01b
Water consumption (spill)	Child	■	■	■	■	■	D05
Fish consumption (spill)	Male	■	■	■	■	■	D08a
Fish consumption (spill)	SP	■	■	■	■	■	D08b
Swimming, 1 hour	Female					■*	D11*
Non-Accidental Acute Exposures							
Vegetation Contact, shorts and T-shirt	Female	■		■			D02
Contaminated Fruit	Female	■	■				D03a
Contaminated Vegetation	Female	■	■				D03b
Swimming, one hour	Female	■	■	■	■		D11
Water consumption	Child	■	■	■	■		D06
Fish consumption	Male	■	■	■	■		D09c
Fish consumption	SP	■	■	■	■		D09d
Chronic/Longer Term Exposures							
Contaminated Fruit	Female	■	■				D04a
Contaminated Vegetation	Female	■	■				D04b
Water consumption	Male	■	■	■	■		D07
Fish consumption	Male	■	■	■	■		D09a
Fish consumption	SP	■	■	■	■		D09b

SP: Subsistence Populations

*The scenario for swimming following an accidental spill is not used in most Forest Service risk assessments. This scenario is used for emamectin benzoate only to elaborate the characterization of risk.

Table 8: Summary of Toxicity Values Used for Human Health

Duration	Derivation of RfD	Reference	Comment
Acute – single exposure			
NOAEL Dose	0.075 mg/kg bw/day	Gerson 1992g [1] MRID 42851503	The uncertainty factor is composed of 10 (animal-to-human), 10 (sensitive individuals), 3 (concern for infants and children for acute exposures)
LOAEL Dose	0.1 mg/kg bw/day		
LOAEL Endpoint(s)	Neurotoxicity		
Species, sex	Mice (M&F)		
Uncertainty Factor	300	U.S. EPA/OPP 2008a	
RfD	0.00025 mg/kg bw/day		
Chronic – lifetime exposure			
NOAEL Dose	0.075 mg/kg bw/day	Gerson 1992g[1] MRID 42851503	The uncertainty factor is composed of 10 (animal-to-human), 10 (sensitive individuals), 10 (concern for infants and children for longer-term exposures)
LOAEL Dose	0.1 mg/kg bw/day		
Species, sex	Neurotoxicity		
LOAEL Endpoint(s)	Mice (M&F)		
Uncertainty Factor	1000	U.S. EPA/OPP 2008a	
RfD	0.000075 mg/kg bw/day		
Occupational, Dermal – 1 to 30 day exposure periods			
NOAEL Dose	0.075 mg/kg bw/day	Gerson 1992g[1] MRID 42851503	The uncertainty factor is composed of 10 (animal-to-human), 10 (sensitive individuals), 3 (steepness of dose-response, severity of effect). Use with absorption factor of 1.8%.
LOAEL Dose	0.1 mg/kg bw/day		
LOAEL Endpoint	Neurotoxicity		
Species, sex	Mice (M&F)		
Uncertainty Factor/MOE	300	U.S. EPA/OPP 2008a	
Equivalent RfD	0.00025 mg/kg bw/day		
Occupational – 1 to 6 month exposure periods			
NOAEL Dose	0.075 mg/kg bw/day	Gerson 1992g[1] MRID 42851503	The uncertainty factor is composed of 10 (animal-to-human), 10 (sensitive individuals), 10 (steepness of dose-response, severity of effect, use of short-term study). Use with absorption factor of 1.8%.
LOAEL Dose	0.1 mg/kg bw/day		
LOAEL Endpoint	Neurotoxicity		
Species, sex	Mice (M&F)		
Uncertainty Factor/MOE	1000	U.S. EPA/OPP 2008a	
Equivalent RfD	0.000075 mg/kg bw/day		

[1]The duration of this study is 15 days.

Table 9: Summary of Risk Characterization for Workers

Scenario	Receptor	Hazard Quotients			Toxicity Value[1]
		Central	Lower	Upper	
Accidental/Incidental Exposures					
Contaminated Gloves, 1 min.	Worker	**6**	0.8	**35**	**0.00025**
Contaminated Gloves, 1 hour	Worker	**332**	**48**	**2,074**	**0.00025**
Spill on Hands, 1 hour	Worker	**6**	**3**	**12**	**0.00025**
Spill on lower legs, 1 hour	Worker	**15**	**8**	**31**	**0.00025**
General Exposures - Ineffective Use of PPE					
Longer-term					
Absorbed dose rate	Worker	**11**	0.5	**73**	**0.000075**
EPA/PHED Method	Worker	**3**	**1.4**	**6**	**0.000075**
Shorter-term					
Absorbed dose rate	Worker	**3**	0.2	**22**	**0.00025**
EPA/PHED Method	Worker	0.8	0.4	**1.7**	**0.00025**
General Exposures - Effective Use of PPE					
Longer-term					
Absorbed dose rate	Worker	8E-02	4E-03	0.6	**0.000075**
EPA/PHED Method	Worker	8E-02	4E-02	0.2	**0.000075**
Shorter-term					
Absorbed dose rate	Worker	3E-02	1E-03	0.2	**0.00025**
EPA/PHED Method	Worker	2E-02	1E-02	5E-02	**0.00025**

[1] Toxicity values in units of mg/kg bw/day.

The above table is a copy of Worksheet E02 in the EXCEL workbook that accompanies this risk assessment. See Section 3.4.2 for discussion.

Table 10: Summary of Risk Characterization for the General Public

Scenario	Receptor	Hazard Quotients			Toxicity Value[1]
		Central	Lower	Upper	
Accidental Acute Exposures (dose in mg/kg/event)					
Direct Spray of Child, whole body	Child	No exposure assessment			
Direct Spray of Woman, feet and lower legs	Adult Female	No exposure assessment			
Water consumption (spill)	Child	8E-02	6E-03	1.0	**0.00025**
Fish consumption (spill)	Adult Male	7E-02	8E-03	0.6	**0.00025**
Fish consumption (spill)	Subsistence Populations	0.3	4E-02	**3**	**0.00025**
Swimming, one hour	Adult Female	8E-02	3E-03	**2**	**0.00025**
Non-Accidental Acute Exposures (dose in mg/kg/event)					
Vegetation Contact, shorts and T-shirt	Adult Female	No exposure assessment			
Contaminated Fruit	Adult Female	No exposure assessment			
Contaminated Vegetation	Adult Female	No exposure assessment			
Swimming, one hour	Adult Female	No exposure assessment			
Water consumption	Child	No exposure assessment			
Fish consumption	Adult Male	No exposure assessment			
Fish consumption	Subsistence Populations	No exposure assessment			
Chronic/Longer Term Exposures (dose in mg/kg/day)					
Contaminated Fruit	Adult Female	No exposure assessment			
Contaminated Vegetation	Adult Female	No exposure assessment			
Water consumption	Adult Male	No exposure assessment			
Fish consumption	Adult Male	No exposure assessment			
Fish consumption	Subsistence Populations	No exposure assessment			

[1] Toxicity values in units of mg/kg bw/day.

The above table is a copy of Worksheet E04 in the EXCEL workbook that accompanies this risk assessment. See Section 3.4.3 for discussion.

Table 11:Summary of Toxicity Values Used in the Ecological Risk Assessment

Group/Duration Organism		Endpoint	Toxicity Value (a.i.)	Reference
Terrestrial Animals				
Acute				
Non-canine Mammals		NOAEC	0.075 mg/kg bw	Section 4.3.2.1.
Canine Mammals		NOAEC	0.075 mg/kg bw	Section 4.3.2.1.
Birds		LD_{50} x 0.1	4.6 mg/kg bw	Section 4.3.2.2
Insects (sensitive)		LD_{50} x 0.1	0.00001 mg/kg bw	Section 4.3.2.4
Insects (tolerant)		LD_{50} x 0.1	0.008 mg/kg bw	Section 4.3.2.4
Longer-term				
Small Mammal		NOAEC (acute)	0.075 mg/kg bw	Section 4.3.2.1
Large Mammal		NOAEC(acute)	0.075 mg/kg bw	Section 4.3.2.1
Bird		Dietary NOAEC (reproduction)	2.8 mg/kg bw	Section 4.3.2.2.
Aquatic Organisms				
Acute				
Amphibians	Sensitive	No toxicity data	N/A	Section 4.3.3.2
	Tolerant	No toxicity data	N/A	Section 4.3.3.2
Fish	Sensitive	LC_{50} x 0.05	0.0087 mg/L	Section 4.3.3.1
	Tolerant	LC_{50} x 0.05	0.072 mg/L	Section 4.3.3.1
Invertebrates	Sensitive	EC_{50} x 0.05	0.000002 mg/L	Section 4.3.3.3
	Tolerant	EC_{50} x 0.05	0.025 mg/L	Section 4.3.3.3
Plants	Algae	NOAEC	0.0039 mg/L	Section 4.3.3.4
	Macrophytes	NOAEC	0.094 mg/L	Section 4.3.3.4
Longer-term				
Amphibians	Sensitive	No toxicity data	N/A	Section 4.3.3.2
	Tolerant	No toxicity data	N/A	Section 4.3.3.2
Fish	Sensitive	Chronic NOAEC	0.0065 mg/L	Section 4.3.3.1
	Tolerant	Estimated Chronic NOAEC	0.053 mg/L	Section 4.3.3.1
Invertebrates	Sensitive	Use acute NOAEC	0.000002 mg/L	Section 4.3.3.3
	Tolerant	Use acute NOAEC	0.025 mg/L	Section 4.3.3.3

Appendix 1: Studies Submitted to U.S. EPA/OPP

EPA OPP HQ-FOI # 0787-10
EPA OPP Freedom of Information Act Request
Emamectin benzoate (Pc code 122806)
Guideline Bibliography
N = 402

Guideline: 61-1 Chemical Identity

MRID: 42743644
Demchak, R.; Egan, R. (1993) MK-0244. 0.16 lb/gallon Emulsifiable Concentrate: Product Identity and Composition: Lab Project Number: 93265/91-002F: 618-244-PC61. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 56 p.

MRID: 43824001
Peterson, R.; Arenas, R. (1995) Product Chemistry Data for the End-Use Product PROCLAIM 5SG: Lab Project Number: 618-244-PC 61/62. Unpublished study prepared by Merck Research Labs. 42 p.

MRID: 45420801
Phelps, L. (2001) Manufacturing Process Description and Supporting Data for Emamectin Benzoate Technical: Lab Project Number: PC-01-014. Unpublished study prepared by Syngenta Crop Protection, Inc. 302 p. {OPPTS 830.1550, 830.1600, 830.1620, 830.1670, 830.1700, 830.1750, 830.1800}

Guideline: 61-2 Description of Beginning Materials and Manufacturing Proces

MRID: 42743644
Demchak, R.; Egan, R. (1993) MK-0244. 0.16 lb/gallon Emulsifiable Concentrate: Product Identity and Composition: Lab Project Number: 93265/91-002F: 618-244-PC61. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 56 p.

MRID: 43824001
Peterson, R.; Arenas, R. (1995) Product Chemistry Data for the End-Use Product PROCLAIM 5SG: Lab Project Number: 618-244-PC 61/62. Unpublished study prepared by Merck Research Labs. 42 p.

MRID: 44883701
Phelps, L. (1999) Emamectin Benzoate Technical Product Chemistry Group A Data Requirements: Lab Project Number: PC-99-016. Unpublished study prepared by Novartis Crop Protection, Inc. 14 p. {OPPTS 830.1620}

MRID: 45420801
Phelps, L. (2001) Manufacturing Process Description and Supporting Data for Emamectin Benzoate Technical: Lab Project Number: PC-01-014. Unpublished study prepared by Syngenta Crop Protection, Inc. 302 p. {OPPTS 830.1550, 830.1600, 830.1620, 830.1670, 830.1700, 830.1750, 830.1800}

Guideline: 61-3 Discussion of Formation of Impurities

MRID: 42743644
Demchak, R.; Egan, R. (1993) MK-0244. 0.16 lb/gallon Emulsifiable Concentrate: Product Identity and Composition: Lab Project Number: 93265/91-002F: 618-244-PC61. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 56 p.

MRID: 43393010
Ballard, J. (1994) Characterization of the Impurity Profile of MK-0244 Technical Grade Active Ingredient: Lab Project Number: 618-244-93908. Unpublished study prepared by Merck Research Labs. 56 p.

MRID: 43824001
Peterson, R.; Arenas, R. (1995) Product Chemistry Data for the End-Use Product PROCLAIM 5SG: Lab Project Number: 618-244-PC 61/62. Unpublished study prepared by Merck Research Labs. 42 p.

MRID: 45420801
Phelps, L. (2001) Manufacturing Process Description and Supporting Data for Emamectin Benzoate Technical: Lab Project Number: PC-01-014. Unpublished study prepared by Syngenta Crop Protection, Inc. 302 p. {OPPTS 830.1550, 830.1600, 830.1620, 830.1670, 830.1700, 830.1750, 830.1800}

Guideline: 62-1 Preliminary Analysis

MRID: 42743645
Egan, R.; Ellison, D. (1993) MK-0244. 0.16 lb/gallon Emulsifiable Concentrate: Analysis and Certification of Product Ingredients: Lab Project Number: 618-244-PC62. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 65 p.

MRID: 45420801
Phelps, L. (2001) Manufacturing Process Description and Supporting Data for Emamectin Benzoate Technical: Lab Project Number: PC-01-014. Unpublished study prepared by Syngenta Crop Protection, Inc. 302 p. {OPPTS 830.1550, 830.1600, 830.1620, 830.1670, 830.1700, 830.1750, 830.1800}

Guideline: 62-2 Certification of limits

MRID: 42743645
Egan, R.; Ellison, D. (1993) MK-0244. 0.16 lb/gallon Emulsifiable Concentrate: Analysis and Certification of Product Ingredients: Lab Project Number: 618-244-PC62. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 65 p.

MRID: 43824001
Peterson, R.; Arenas, R. (1995) Product Chemistry Data for the End-Use Product PROCLAIM 5SG: Lab Project Number: 618-244-PC 61/62. Unpublished study prepared by Merck Research Labs. 42 p.

MRID: 45420801
Phelps, L. (2001) Manufacturing Process Description and Supporting Data for Emamectin Benzoate Technical: Lab Project Number: PC-01-014. Unpublished study prepared by Syngenta Crop Protection, Inc. 302 p. {OPPTS 830.1550, 830.1600, 830.1620, 830.1670, 830.1700, 830.1750, 830.1800}

Guideline: 62-3 Analytical Method

MRID: 42743645
Egan, R.; Ellison, D. (1993) MK-0244. 0.16 lb/gallon Emulsifiable Concentrate: Analysis and Certification of Product Ingredients: Lab Project Number: 618-244-PC62. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 65 p.

MRID: 43824001
Peterson, R.; Arenas, R. (1995) Product Chemistry Data for the End-Use Product PROCLAIM 5SG: Lab Project Number: 618-244-PC 61/62. Unpublished study prepared by Merck Research Labs. 42 p.

MRID: 44007908
Pindar, J. (1995) Method Validation of 0.16 lb/gal Formulation MK-0244: Lab Project Number: 94005: 4005: 618-244-94005. Unpublished study prepared by Merck Research Labs. 50 p.

MRID: 44007909

Pindar, J. (1995) Method Validation of MK-0244 Technical Active Ingredient: Lab Project Number: 618-244-4001: 94001: 4001. Unpublished study prepared by Merck Research Labs. 124 p.

MRID: 45420801
Phelps, L. (2001) Manufacturing Process Description and Supporting Data for Emamectin Benzoate Technical: Lab Project Number: PC-01-014. Unpublished study prepared by Syngenta Crop Protection, Inc. 302 p. {OPPTS 830.1550, 830.1600, 830.1620, 830.1670, 830.1700, 830.1750, 830.1800}

Guideline: 63-0 Reports of Multiple phys/chem Characteristics
---
MRID: 42743646
Anderson, K., comp. (1993) MK-0244 0.16 lb/gallon Emulsifiable Concentrate: Summary Results of Physical and Chemical Characteristics Tests: Lab Project Number: 618-244-PC63SUM. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 10 p.

MRID: 42743647
Whetzel, J. (1992) Determination of Seven Product Chemistry Parameters for a 0.16 lb/gal EC Formulation of MK-244: Lab Project Number: 97/91-MER.2. Unpublished study prepared by Twin City Testing Corp. 27 p.

MRID: 42743649
Sweetapple, G. (1993) MK244--0.16 EC Formulation--Color, Physical State, Odor; Specific Gravity; pH; Oxidation-Reduction; Impact Explodability; Corrosion Characteristics: Lab Project Number: 4232-91-0424-AS: 618-244-PC63R4. Unpublished study prepared by Ricerca, Inc. 60 p.

MRID: 42743651
Anderson, K., comp. (1993) Additional Physical and Chemical Properties of MK0244: Lab Project Number: 618-244-PC63R6. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 11 p.

MRID: 43824002
Sweetapple, G. (1995) Emamectin Benzoate (L-656,748-088T 5 SG Formulation): Color, Physical State, Bulk Density, pH: Lab Project Number: 618-244-PC 63: 4232-95-0129-AS. Unpublished study prepared by Ricerca, Inc. 36 p.

MRID: 44883705
Phelps, L. (1999) Emamectin Benzoate Technical (Addendum to MRID #42794202) Product Chemistry Group B Data Requirements: Lab Project Number: PC-99-017: ASGSR-99-133. Unpublished study prepared by Novartis Crop Protection, Inc. 6 p.

Guideline: 63-5 Melting Point

MRID: 42794202
McCauley, J. (1992) Determination of Physical-Chemical Properties of MK-244: Lab Project Number: 001-618-244-PC63R2: PMLMK244001. Unpublished study prepared by Merck Research Labs. 197 p.

Guideline: 63-7 Density

MRID: 42794202
McCauley, J. (1992) Determination of Physical-Chemical Properties of MK-244: Lab Project Number: 001-618-244-PC63R2: PMLMK244001. Unpublished study prepared by Merck Research Labs. 197 p.

Guideline: 63-8 Solubility

MRID: 42794202

McCauley, J. (1992) Determination of Physical-Chemical Properties of MK-244: Lab Project Number: 001-618-244-PC63R2: PMLMK244001. Unpublished study prepared by Merck Research Labs. 197 p.

MRID: 43850102
McCauley, J. (1995) Determination of Some Solubility Properties of MK-244: Lab Project Number: 618-244-EX2: 94457: 4457. Unpublished study prepared by Merck Research Labs. 69 p.

MRID: 44883704
Phelps, L. (1999) Emamectin Benzoate Technical (Addendum to MRID #42794202) Product Chemistry Group B Data Requirements: Lab Project Number: 162-98: ASR-684: ASGSR-98-333. Unpublished study prepared by Novartis Crop Protection, Inc. 53 p. {OPPTS 830.7840}

Guideline: 63-9 Vapor Pressure

MRID: 42794202
McCauley, J. (1992) Determination of Physical-Chemical Properties of MK-244: Lab Project Number: 001-618-244-PC63R2: PMLMK244001. Unpublished study prepared by Merck Research Labs. 197 p.

Guideline: 63-10 Dissociation Constant

MRID: 42794202
McCauley, J. (1992) Determination of Physical-Chemical Properties of MK-244: Lab Project Number: 001-618-244-PC63R2: PMLMK244001. Unpublished study prepared by Merck Research Labs. 197 p.

Guideline: 63-11 Oct/Water partition Coef.

MRID: 42794202
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MRID: 44883703
Phelps, L. (1999) Emamectin Benzoate Technical (Addendum to MRID #42794202) Product Chemistry Group B Data Requirements: Lab Project Number: 163-98: ASR-658: ASGSR-98-265. Unpublished study prepared by Novartis Crop Protection, Inc. 42 p. {OPPTS 830.7570}

Guideline: 63-12 pH

MRID: 44883702
Phelps, L. (1999) Emamectin Benzoate Technical (Addendum to MRID #42794202) Product Chemistry Group B Data Requirements: Lab Project Number: 886-99: ASR-825: ASGSR-99-182. Unpublished study prepared by Novartis Crop Protection, Inc. 15 p. {OPPTS 830.7000}

Guideline: 63-13 Stability

MRID: 42743648
Egan, R. (1993) Stability Data for MK-0244 Technical Grade Active Ingredinet (sic): Lab Project Number: 618-244-PC63R3. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 4 p.

MRID: 43850103
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Guideline: 63-17 Storage stability

MRID: 42743646
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MRID: 42743650
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Guideline: 63-20 Corrosion characteristics

MRID: 42743646
Anderson, K., comp. (1993) MK-0244 0.16 lb/gallon Emulsifiable Concentrate: Summary Results of Physical and Chemical Characteristics Tests: Lab Project Number: 618-244-PC63SUM. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 10 p.

MRID: 42743649
Sweetapple, G. (1993) MK244--0.16 EC Formulation--Color, Physical State, Odor; Specific Gravity; pH; Oxidation-Reduction; Impact Explodability; Corrosion Characteristics: Lab Project Number: 4232-91-0424-AS: 618-244-PC63R4. Unpublished study prepared by Ricerca, Inc. 60 p.

Guideline: 71-1 Avian Single Dose Oral Toxicity

MRID: 42743601
Campbell, S.; Jaber, M. (1992) MK-244: An Acute Oral Toxicity Study with the Mallard: Lab Project Number: 105-144. Unpublished study prepared by Wildlife International Ltd. 33 p.

MRID: 42868905
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Guideline: 71-2 Avian Dietary Toxicity

MRID: 42851527
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MRID: 42851528
Campbell, S. (1993) MK-244: A Dietary LC50 Study with the Mallard: Lab Project Number: 105-141. Unpublished study prepared by Wildlife International, Ltd. 42 p.

Guideline: 71-4 Avian Reproduction

MRID: 43850104
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MRID: 43850105
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MRID: 44007910

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MRID: 44007911
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Guideline: 72-1 Acute Toxicity to Freshwater Fish

MRID: 42743602
Holmes, C.; Swigert, J. (1993) MK-244: A 96-Hour Flow-Through Acute Toxicity Test with the Bluegill (Lepomis macrochirus): Lab Project Number: 105A-105. Unpublished study prepared by Wildlife International Ltd. 53 p.

MRID: 42851529
Holmes, C.; Martin, K.; Swigert, J. (1993) MK-244: A 96-Hour Flow-Through Acute Toxicity Test with the Rainbow Trout (Oncorhynchus mykiss): Lab Project Number: 105A-106A. Unpublished study prepared by Wildlife International, Ltd. 56 p.

MRID: 43850106
Drottar, K. (1995) MK-0244: A 96-Hour Flow-Through Acute Toxicity Test with the Fathead Minnow (Pimephales promelas): Lab Project Number: WLI 105A-125A: 105A-125A: 94311. Unpublished study prepared by Wildlife International, Ltd. 42 p.

Guideline: 72-2 Acute Toxicity to Freshwater Invertebrates

MRID: 42743603
Holmes, C.; Swigert, J. (1993) MK-244: A 48-Hour Flow-Through Acute Toxicity Test with the Cladoceran (Daphnia magna): Lab Project Number: 105A-110. Unpublished study prepared by Wildlife International Ltd. 42 p.

MRID: 44007901
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Guideline: 72-3 Acute Toxicity to Estuarine/Marine Organisms

MRID: 43393001
Martin, K. (1994) (Hydrogen 3) MK-244: A 96-Hour Flow-through Acute Toxicity Test with the Saltwater Mysid (Mysidopsis bahia): Lab Project Number: 105A-109C. Unpublished study prepared by Wildlife International, Ltd. 53 p.

MRID: 43393002
Martin, K. (1994) MK-244: A 96-Hour Shell Deposition Test with the Eastern Oyster (Crassostrea virginica): Lab Project Number: 105A-107. Unpublished study prepared by Wildlife International, Ltd. 44 p.

MRID: 43393003
Martin, K. (1994) (Hydrogen 3)MK-244: A 96-Hour Flow-through Acute Toxicity Test with the Sheepshead Minnow (Cyprinodon variegatus): Lab Project Number: 105A-108. Unpublished study prepared by Wildlife International, Ltd. 46 p.

MRID: 44007912

Conner, B.; Martin, K.; Swigert, J. (1995) (Hydrogen 3)MK-244: A 96-Hour Flow-Through Acute Toxicity Test with the Saltwater Mysid (Mysidopsis bahia): Amended Final Report: Lab Project Number: 105A-109C: 93326: 3326. Unpublished study prepared by Wildlife International Ltd. 57 p.

MRID: 44007913
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MRID: 44007914
Martin, K.; Swigert, J. (1995) MK-244: A 96-Hour Flow-Through Acute Toxicity Test with the Sheepshead Minnow (Cyprinodon variegatus): Amended Final Report: Lab Project Number: 105A-108: 93327: 3327. Unpublished study prepared by Wildlife International Ltd. 50 p.

Guideline: 72-4 Fish Early Life Stage/Aquatic Invertebrate Life Cycle Study
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MRID: 43393004
Drottar, K. (1994) MK-244: A Flow-through Life-cycle Toxicity Test with the Cladoceran (Daphnia magna): Lab Project Number: 105A-122. Unpublished study prepared by Wildlife International, Ltd. 60 p.

MRID: 43850107
Drottar, K. (1995) MK-0244: An Early Life Stage Toxicity Test with the Fathead Minnow (Pimephales promelas): Lab Project Number: WLI 105A-123A: 105A-123A: 94312. Unpublished study prepared by Wildlife International, Ltd. 85 p.

MRID: 44305601
Boeri, R.; Magazu, J.; Ward, T. (1997) Chronic Toxicity of MK-244 to the Mysid, Mysidopsis bahia: Amended (Final) Report: Lab Project Number: 1013-ME: 4632. Unpublished study prepared by T.R. Wilbury Labs, Inc. 66 p.

MRID: 45833001
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Guideline: 72-6 Aquatic org. accumulation

MRID: 43393005
Drottar, K. (1994) MK-244: A Bioconcentration Test with the Bluegill (Lepomis macrochirus): Lab Project Number: 105A-119. Unpublished study prepared by Wildlife International, Ltd. 173 p.

Guideline: 81-1 Acute oral toxicity in rats

MRID: 42743605
Manson, J. (1992) MK-0243 0.16 lb./gal. EC Formulation: Acute Oral Toxicity Study in Rats: TT #89-121-0: Lab Project Number: 618-244-TOX01. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 53 p.

MRID: 42743612
Lankas, G. (1992) L-656,748: Acute Oral and Intravenous Toxicity Studies in Mice and Rats: TT #88-043-0, 88-2569, 88-2581, 88-2595: Lab Project Number: 618-244-TOX08. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 32 p.

MRID: 42743613

Gerson, R. (1992) MK-0244: Exploratory Acute Oral Toxicity in Female Mice and Rats: TT #90-2760, 90-2777: Lab Project Number: 618-244-TOX09. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 8 p.

MRID: 42851502
Lankas, G. (1992) L-656,748: Acute Oral and Intravenous Toxicity Studies in Mice and Rats: Lab Project Number: 618-244-TOX08A: TT #88-043-0: TT #88-2569. Unpublished study prepared by Merck Research Labs. 34 p.

MRID: 42851518
Bagdon, W. (1993) MK-0244: Fifteen-Day Acute Oral Bioequivalence Study in Female Rats (sic) (Mice): Lab Project Number: 618- 244-TOX56: TT #92-2746: AS-3600. Unpublished study prepared by Merck Research Labs. 54 p.

MRID: 42851519
Bagdon, W. (1993) MK-0244: Fifteen-Day Acute Oral Bioequivalence Study in Female Rats: Lab Project Number: 618-244-TOX57; TT #92-2747; AS-3600. Unpublished study prepared by Merck Research Labs. 56 p.

MRID: 43824003
Bagdon, W. (1995) MK-0244 5SG (Soluble Granules): Acute Oral Toxicity Study in Rats: Lab Project Number: 95-2666: TK 95-2666. Unpublished study prepared by Merck Institute for Therapeutic Research. 55 p.

MRID: 44007915
Lankas, G. (1994) L-656,748: Acute Oral Toxicity Study in Rats: Amended Report: Lab Project Number: 88-043-0. Unpublished study prepared by Merck Institute for Therapeutic Research. 29 p.

Guideline: 81-2 Acute dermal toxicity in rabbits or rats

MRID: 42743606
Manson, J. (1992) MK-0243 0.16 lb./gal. EC Formulation: Acute Dermal Toxicity Study in Rabbits: TT #89-122-0: Lab Project Number: 618-244-TOX02. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 42 p.

MRID: 43824004
Bagdon, W. (1995) MK-0244 5SG (Soluble Granules): Acute Dermal Toxicity Study in Rabbits: Lab Project Number: 95-2649: TT 95-2649. Unpublished study prepared by Merck Research Labs. 49 p.

MRID: 43850111
Bagdon, W. (1995) MK-0244 Emulsifiable Concentrate (E.C.) (0.16 Lbs./Gal.): Acute Dermal Neurotoxicity Study in Rabbits: Lab Project Number: TT #95-2574. Unpublished study prepared by Merck Research Labs. 52 p.

MRID: 43869401
Bagdon, W. (1994) MK-0244 (L-656,748-052S): Acute Dermal Toxicity Study in Rats: Lab Project Number: TT #94-2918. Unpublished study prepared by Merck Research Labs. 27 p.

Guideline: 81-3 Acute inhalation toxicity in rats

MRID: 42743608
Placke, M. (1992) MK-0243: Range-Finding and LC50 Inhalation Toxicity Study of MK-243, 0.16 EC in CD Rats: TT #90-9013: Lab Project Number: 618-244-TOX04. Unpublished study prepared by Battelle. 243 p.

MRID: 43868101

Labbe, R. (1994) MK-0244: An Acute Inhalation Range-Finding and Toxicity Study in the Albino Rat: Lab Project Number: TT #93-9011: 90642B. Unpublished study prepared by BioResearch Labs, Ltd. 187 p.

MRID: 43868102
Labbe, R. (1994) MK-0244: An Acute Inhalation Toxicity Study in the Albino Rat: Lab Project Number: TT #93-9017: 90901: 90642B. Unpublished study prepared by BioResearch Labs, Ltd. 147 p.

Guideline: 81-4 Primary eye irritation in rabbits

MRID: 42743615
Manson, J. (1992) MK-0243 (L-656,748): Primary Eye Irritation in Rabbits: TT #89-2696: Lab Project Number: 618-244-TOX11. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 18 p.

MRID: 43824005
Bailly, Y. (1995) MK-0244 5SG: Acute Ocular Irritation Study in Rabbits: Lab Project Number: 95-624-0: TT 95-624-0. Unpublished study prepared by Laboratoires Merck Sharp & Dohme-Chilbret. 55 p.

MRID: 43850112
Bagdon, W. (1994) MK-0244 EC (L-656,748-049C): Acute Ocular Irritation Study in Rabbits: Lab Project Number: TT# 94-2517. Unpublished study prepared by Merck Research Labs. 19 p.

Guideline: 81-5 Primary dermal irritation

MRID: 42743607
Manson, J. (1992) MK-0243 0.16 lb./gal. EC Formulation: Primary Dermal Irritation in Rabbits: TT #89-2720: Lab Project Number: 618-244-TOX03. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 25 p.

MRID: 42743616
Manson, J. (1992) MK-0243 (L-656,748): Primary Dermal Irritation in Rabbits: TT #89-2697: Lab Project Number: 618-244-TOX12: 618-244-TOX1. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 14 p.

Guideline: 81-6 Dermal sensitization

MRID: 42743609
Durand-Cavagna, G. (1992) MK-0244 0.16 EC: Guinea Pig Sensitization Test: TT #90-630-0: Lab Project Number: 618-244-TOX05. Unpublished study prepared by Laboratories Merck Sharp & Dohme-Chibret Centre de Recherche. 41 p.

MRID: 42743610
Durand-Cavagna, G. (1992) MK-0244 0.16 EC: Guinea Pig Open Epicutaneous Sensitization Test: TT #91-636-0: Lab Project Number: 618-244-TOX06. Unpublished study prepared by Laboratories Merck Sharp & Dohme-Chibret Centre de Recherche. 30 p.

MRID: 42743617
Durand-Cavagna, G. (1992) MK-0244: Guinea Pig Sensitization Test: TT #90-617-0: Lab Project Number: 618-244-TOX13. Unpublished study prepared by Laboratories Merck Sharp & Dohme-Chibret Centre de Recherche. 35 p.

Guideline: 81-7 Neurotoxicity study in hens

MRID: 42743611

Bagdon, W. (1992) MK-0243 0.16 lb./gal. EC Formulation: Acute Dermal Neurotoxicity Study in Male Rabbits: TT #90-024-0: Lab Project Number: 618-244-TOX07. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 64 p.

MRID: 42743614
Bagdon, W. (1992) MK-0243: Acute Dermal Neurotoxicity Study in Female Rabbits: TT #90-025-0: Lab Project Number: 618-244-TOX10. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 60 p.

MRID: 42743626
Lankas, G. (1992) MK-0243 (L656-748), L-682,901, L-653,648 L-653,649, L-655,372. Exploratory Comparative Neurotoxicity Study in Dogs: TT #88-134-0: Lab Project Number: 618-244-TOX23. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 33 p.

Guideline: 81-8 Acute neurotoxicity screen study in rats

MRID: 42743618
Manson, J. (1992) MK-0243: Acute Oral Neurotoxicity Study in Rats: TT #89-069-0: Lab Project Number: 618-244-TOX14. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 54 p.

MRID: 42743619
Manson, J. (1992) MK-0243 (L-656,748-038W): Acute Oral Neurotoxicity Study in Rats #2: TT #89-0129-0: Lab Project Number: 618-244-TOX15. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 69 p.

Guideline: 82-1 Subchronic Oral Toxicity: 90-Day Study

MRID: 42743620
Lankas, G. (1992) L-656,748: Three-Week Dietary Range-Finding Study in Rats: TT #88-046-0: Lab Project Number: 618-244-TOX16. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 109 p.

MRID: 42743621
Gerson, R. (1992) MK-0243: Thirteen-Week Dietary Toxicity Study in Mice: TT #90-061-0: Lab Project Number: 618-244-TOX18. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 198 p.

MRID: 42743622
Lankas, G. (1992) L-656,748: Three-Week Oral Range-Finding Study in Dogs: TT #88-047-0: Lab Project Number: 618-244-TOX19. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 192 p.

MRID: 42743623
Manson, J. (1992) L-656,748: Fourteen-Week Oral Toxicity Study in Dogs: TT #88-060-0: Lab Project Number: 618-244-TOX20. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 337 p.

MRID: 42794201
Lankas, G. (1992) L-656,748: Fourteen Week Dietary Toxicity Study in Rats: Lab Project Number: 618-244-TOX17: TT #88-059-0. Unpublished study prepared by Merck Research Labs. 685 p.

MRID: 43868103
Lankas, G. (1994) L-656,748: Fourteen-Week Oral Toxicity Study in Dogs: Amended Report: Lab Project Number: TT# 88-060-0. Unpublished study prepared by Merck Research Labs. 410 p.

Guideline: 82-2 21-day dermal-rabbit/rat

MRID: 42743625
Gillet, J. (1992) MK-0244 0.16 EC: 24-Day Dermal Toxicity Study in Rabbits: TT #90-631-0: Lab Project Number: 618-244-TOX22. Unpublished study prepared by Laboratories Merck Sharp & Dohme-Chibret Centre de Recherche. 157 p.

MRID: 44007902
Bagdon, W. (1996) MK-0244 E.C. (0.16) lbs/gal: Twenty-Two-Day Dermal Toxicity Study in Rabbits: Lab Project Number: 95-2656. Unpublished study prepared by Merck Research Labs. 155 p.

Guideline: 82-5 Subchronic Neurotoxicity: 90-Day Study

MRID: 42743627
Lankas, G. (1992) MK-0243 (L-656,748): Exploratory Five-Week Neurotoxicity Study in Dogs: TT #89-014-0: Lab Project Number: 618-244-TOX24. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 34 p.

Guideline: 82-7 Subchronic Neurotoxicity

MRID: 42743628
Gerson, R. (1992) MK-0244: Fourteen-Week Dietary Neurotoxicity Study in Rats: TT #91-006-0: Lab Project Number: 618-244-TOX25. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 970 p.

MRID: 42743629
Lankas, G. (1992) MK-0243 (L-656,748): Exploratory Two-Week Dietary Neurotoxicity Study in Mice: TT #89-023-0: Lab Project Number: 618-244-TOX26. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 51 p.

MRID: 42743630
Gerson, R. (1992) MK-0243: Sixteen-Day Dietary Neurotoxicity Study in the CF-1 Mouse: TT #90-101-0: Lab Project Number: 618-244-TOX27. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 93 p.

MRID: 42851503
Gerson, R. (1993) L-660, 599 Fifteen-Day Dietary Neurotoxicity Study in CF-1 Mice: Lab Project Number: 618-244-TOX39: TT #92-049-0: 3591. Unpublished study prepared by Merck Research Labs. 135 p.

MRID: 42851504
Gerson, R. (1993) L-695,638: Fifteen Day Dietary Neurotoxicity Study in CF-1 Mice: Lab Project Number: 618-244-TOX41: TT #92-072-0: 3690. Unpublished study prepared by Merck Research Labs. 118 p.

MRID: 42851505
Gerson, R. (1993) L-695,638: Fifteen Day Dietary Neurotoxicity Study in CF-1 Mice: Lab Project Number: 618-244-TOX42: TT #92-90-0: 3690. Unpublished study prepared by Merck Research Labs. 89 p.

MRID: 42851506
Gerson, R. (1993) L-660, 599: Fifteen Day Dietary Neurotoxicity Study in CF-1 Mice: Lab Project Number: 618-244-TOX43: TT #91-114-0: 3591. Unpublished study prepared by Merck Research Labs. 109 p.

MRID: 42851507
Gerson, R. (1993) L-930, 905: Fifteen Day Oral Neurotoxicity Study in CF-1 Mice: Lab Project Number: 618-244-TOX44: TT #92-082-0: AS-3696. Unpublished study prepared by Merck Research Labs. 74 p.

MRID: 42851508
Wise, D. (1993) MK-0244: Oral Developmental Neurotoxicity Study in Female Rats: Lab Project Number: 618-244-TOX45: TT #91-721-0: 3592. Unpublished study prepared by Merck Research Labs. 554 p.

MRID: 42851509
Gerson, R. (1992) MK-0244: Fourteen Week Dietary Neurotoxicity Study in Rats: Lab Project Number: 618-244-TOX46: TT #91-006-0. Unpublished study prepared by Merck Research Labs. 635 p.

Guideline: 83-1 Chronic Toxicity

MRID: 42743624
Gillet, J. (1992) MK-0244: 53-Week Oral Toxicity Study in Dogs: TT #90-612-0 & -1: Lab Project Number: 618-244-TOX21. Unpublished study prepared by Laboratories Merck Sharp & Dohme-Chibret Centre de Recherche. 297 p.

MRID: 42851510
Gillet, J. (1992) MK-0244: 53-Week Toxicity Study in Dogs: Lab Project Number: 618-244-TOX47: TT #90-612-0: TT #90-612-1. Unpublished study prepared by Laboratoires Merck Sharp & Dohme-Chibret, Centre de Recherche. 304 p.

MRID: 42868902
Gerson, R. (1992) MK-0244: Fifty Three Week Toxicity Study in Rats: Lab Project Number: TT #91-046-0: 618-244-TOX48: AS-3446. Unpublished study prepared by Merck Research Labs. 988 p.

MRID: 43868104
Lankas, G. (1994) MK-0244: One-Hundred-Five-Week Dietary Carcinogenicity/Toxicity Study in Rats: Lab Project Number: TT# 91-017-0: 91-017-0. Unpublished study prepared by Merck Research Labs. 2172 p.

Guideline: 83-2 Oncogenicity

MRID: 43868104
Lankas, G. (1994) MK-0244: One-Hundred-Five-Week Dietary Carcinogenicity/Toxicity Study in Rats: Lab Project Number: TT# 91-017-0: 91-017-0. Unpublished study prepared by Merck Research Labs. 2172 p.

MRID: 43868105
Lankas, G. (1994) MK-0244: Seventy-Nine-Week Dietary Carcinogenicity Study in Mice: Lab Project Number: TT# 91-033-0: 91-033-1: 91-033-2. Unpublished study prepared by Merck Research Labs. 1058 p.

Guideline: 83-3 Teratogenicity -- 2 Species

MRID: 42743631
Manson, J. (1992) MK-0243: Oral Range-Findig Study in Pregnant Rats: TT #89-716-2: Lab Project Number: 618-244-TOX28. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 79 p.

MRID: 42743632
Manson, J. (1992) MK-0243: Oral Developmental Toxicity Study in Rats: TT #89-716-0: Lab Project Number: 618-244-TOX29. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 133 p.

MRID: 42743634

Manson, J. (1992) MK-0243: Oral Range-Finding Study in Non-Pregnant Rabbits: TT #89-715-2: Lab Project Number: 618-244-TOX31. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 36 p.

MRID: 42743635
Manson, J. (1992) MK-0243: Oral Range-Finding Study in Pregnant Rabbits: TT #89-715-1: Lab Project Number: 618-244-TOX32. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 78 p.

MRID: 42743636
Manson, J. (1992) MK-0243: Oral Developmental Toxicity Study in Rabbits: TT #89-715-0: Lab Project Number: 618-244-TOX33. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 88 p.

Guideline: 83-4 2-generation repro.-rat

MRID: 42743633
Wise, L. (1992) MK-0243: Oral Range-Finding Reproduction Study in Female Rats: TT #90-724-9: Lab Project Number: 618-244-TOX30. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 232 p.

MRID: 42851511
Lankas, G. (1993) MK-0244: Two-Generation Dietary Reproduction Study in Rats: Lab Project Number: 618-244-TOX49: TT #91-715-0: AS-3446. Unpublished study prepared by Merck Research Labs. 927 p.

Guideline: 84-2 Interaction with Gonadal DNA

MRID: 42743637
Lankas, G. (1992) L-656,748: Microbial Mutagenesis Assay: TT #88-8013: Lab Project Number: 618-244-TOX34. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 54 p.

MRID: 42743638
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Guideline: 132-1 Dissipation of Dislodgeable Foliar & Soil Residues

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Guideline: 133-4 Inhal. passive dosimetry expo

MRID: 43943301
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Guideline: 141-1 Honey bee acute contact

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Guideline: 141-2 Honey bee residue on foliage

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Guideline: 161-1 Hydrolysis

MRID: 42743642
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Guideline: 161-2 Photodegradation-water

MRID: 43404301

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MRID: 43850114
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Guideline: 161-3 Photodegradation-soil

MRID: 43404302
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Guideline: 161-4 Photodegradation-air

MRID: 44007906
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Guideline: 162-1 Aerobic soil metabolism

MRID: 43235101
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MRID: 43404303
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Guideline: 162-2 Anaerobic soil metabolism

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MRID: 42743643
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Guideline: 164-1 Terrestrial field dissipation

MRID: 43404304
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Guideline: 165-1 Confined rotational crop

MRID: 43850119
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Guideline: 171-4B Residue Analytical Methods

MRID: 42868904
Wehner, T. (1993) Method Validation: HPLC-Flourescence Method to Determine the Total Toxic Residue of MK-244 and its Metabolites, on Vegetables, Including Leafy Vegetables and Cole Crops: Lab Project Number: 93670: 244-92-3: 618-244-93670. Unpublished study prepared by Merck Research Labs 1120 p.

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MRID: 43850125
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Guideline: 171-4C Magnitude of the Residue [by commodity]

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MRID: 43393011
Norton, J. (1994) Determination of the Magnitude of Residues of MK-244 and Its Metabolites in/on the Raw Agricultural Commodity Group, Leafy Vegetables, from MK-244 0.16 EC Applied with Non-ionic Surfactant by Ground Equipment: Lab Project Number: 618-244-92856: 92856: 001-90-0004R. Unpublished study prepared by Merck & Co., Inc. 2848 p.

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MRID: 43415301
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MRID: 43850122
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MRID: 44030602
Wehner, T.; Dunbar, D. (1996) Determination of the Magnitude of Residues of MK-244 and Its Metabolites in/on the Raw Agricultural Commodity Groups, Leafy Vegetables and Cole Crops, from MK-244 5 SG Applied with a Non-Ionic Surfactant by Ground Equipment: Lab Project Number: 618-244-94405: 94405: 4405. Unpublished study prepared by Merck & Co., Inc. 3359 p.

MRID: 44300101
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MRID: 44300106
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MRID: 44883707
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MRID: 44883708
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MRID: 44883716
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MRID: 45209802
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MRID: 45209803
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MRID: 45899801
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Guideline: 171-4A1 Characterization of Total Terminal Residue

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MRID: 44007904
Wehner, T. (1996) Method Validation: HPLC-Flourescence Method to Determine the Foliar Dislodgeable Total Toxic Residues of MK-0244 and Its Metabolites in Leaf Disk Extracts: Analytical Research Method 244-93-2: Lab Project Number: 618-244-93902: 93902: 3902. Unpublished study prepared by Merck Research Labs. 939 p.

Guideline: 171-4A2 Nature of the Residue in Plants

MRID: 42851522
Crouch, L. (1993) Metabolism of (carbon 14) MK-0244 in Lettuce: Lab Project Number: PLM6: PMES PLM6. Unpublished study prepared by Merck Research Labs and ABC Labs. 823 p.

MRID: 43850121
Crouch, L. (1995) Metabolism of (carbon 14)-MK-0244 in Cabbage: Lab Project Number: 3130: 93130: PMES-PLM7. Unpublished study prepared by ABC Labs. 475 p.

MRID: 43850122
Crouch, L. (1995) Metabolism of (carbon 14)-MK-0244 in Sweet Corn: Lab Project Number: 93583: PMES-PLM8: PLM8. Unpublished study prepared by ABC Labs. 340 p.

MRID: 44007906
Crouch, L. (1996) Assay and Characterization of Polar Photodegradates of MK244 and (carbon 14)-MK244: Lab Project Number: 93692 (PMES TCR-1). Unpublished study prepared by Merck Research Labs; Galbraith Labs, Inc.; and Ricerca, Inc. 128 p.

MRID: 44007907
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Guideline: 171-4A3 Nature of the Residue in Livestock

MRID: 44300107
Mushtaq, M. (1995) The Elimination, Tissue Distribution, and Metabolism of (3H)4"-Deoxy-4"-Epimethylaminoavermectin B1a (MAB1a) Benzoate and (3H/(carbon 14))MAB1a Benzoate in Lactating Goats: Final Report: Lab Project Number: ARM-9: 618-MK-0244-ARM-9: 93995. Unpublished study prepared by Merck Research Labs; Analytical Development Corp.; and Colorado State University. 490 p.

MRID: 44883710
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MRID: 44883711
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Guideline: 810.1000 Overview, Definitions, and General Considerations

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Guideline: 810.3500 Premises treatments

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Guideline: 830.1600 Description of materials used to produce the product
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MRID: 47002102
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Guideline: 830.1620 Description of production process

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Guideline: 830.1650 Description of formulation process

MRID: 47153904
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Guideline: 830.1670 Discussion of formation of impurities

MRID: 47002102
Sparrow, K. (2006) Emamectin Benzoate Technical II: (MK244G): Manufacturing Process Description and Supporting Data for Emamectin Technical. Project Number: PC/06/074, AW/212/1. Unpublished study prepared by Syngenta Crop Protection. 392 p.

MRID: 47153904
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Guideline: 830.1700 Preliminary analysis

MRID: 46044901
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MRID: 47002101
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MRID: 47002102
Sparrow, K. (2006) Emamectin Benzoate Technical II: (MK244G): Manufacturing Process Description and Supporting Data for Emamectin Technical. Project Number: PC/06/074, AW/212/1. Unpublished study prepared by Syngenta Crop Protection. 392 p.

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Guideline: 830.1750 Certified limits

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Guideline: 830.1800 Enforcement analytical method

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Guideline: 830.6302 Color

MRID: 47002103
Sparrow, K. (2006) Emamectin Benzoate Technical II: (MK244): Physical and Chemical Proerties of Emamectin Benzoate Technical II. Project Number: PC/06/126. Unpublished study prepared by Syngenta Crop Protection. 54 p.

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Guideline: 830.6303 Physical state

MRID: 47002103
Sparrow, K. (2006) Emamectin Benzoate Technical II: (MK244): Physical and Chemical Proerties of Emamectin Benzoate Technical II. Project Number: PC/06/126. Unpublished study prepared by Syngenta Crop Protection. 54 p.

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MRID: 47309302
Sparrow, K. (2007) Physical and Chemical Properties of Emamectin Benzoate ME (042.9) (A16297A). Project Number: PC/07/085. Unpublished study prepared by Syngenta Crop Protection, Inc. 34 p.

Guideline: 830.6304 Odor

MRID: 47153905
Phelps, L. (2006) Emamectin Benzoate RB (0.10) (A15276A): Physical and Chemical Properties of A15276A. Project Number: PC/06/085, T001646/06. Unpublished study prepared by Syngenta Crop Protection. 60 p.

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Sparrow, K. (2007) Physical and Chemical Properties of Emamectin Benzoate ME (042.9) (A16297A). Project Number: PC/07/085. Unpublished study prepared by Syngenta Crop Protection, Inc. 34 p.

Guideline: 830.6313 Stability to sunlight, normal and elevated temperatures, metals, and metal ions
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MRID: 47002103
Sparrow, K. (2006) Emamectin Benzoate Technical II: (MK244): Physical and Chemical Proerties of Emamectin Benzoate Technical II. Project Number: PC/06/126. Unpublished study prepared by Syngenta Crop Protection. 54 p.

Guideline: 830.6314 Oxidizing or reducing action

MRID: 47002103
Sparrow, K. (2006) Emamectin Benzoate Technical II: (MK244): Physical and Chemical Proerties of Emamectin Benzoate Technical II. Project Number: PC/06/126. Unpublished study prepared by Syngenta Crop Protection. 54 p.

MRID: 47153905
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MRID: 47309302
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Guideline: 830.6315 Flammability

MRID: 47002103
Sparrow, K. (2006) Emamectin Benzoate Technical II: (MK244): Physical and Chemical Proerties of Emamectin Benzoate Technical II. Project Number: PC/06/126. Unpublished study prepared by Syngenta Crop Protection. 54 p.

MRID: 47153905
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Guideline: 830.6316 Explodability

MRID: 47002103
Sparrow, K. (2006) Emamectin Benzoate Technical II: (MK244): Physical and Chemical Proerties of Emamectin Benzoate Technical II. Project Number: PC/06/126. Unpublished study prepared by Syngenta Crop Protection. 54 p.

MRID: 47153905
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MRID: 47309302
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Guideline: 830.6317 Storage stability of product

MRID: 47002103
Sparrow, K. (2006) Emamectin Benzoate Technical II: (MK244): Physical and Chemical Proerties of Emamectin Benzoate Technical II. Project Number: PC/06/126. Unpublished study prepared by Syngenta Crop Protection. 54 p.

MRID: 47153905
Phelps, L. (2006) Emamectin Benzoate RB (0.10) (A15276A): Physical and Chemical Properties of A15276A. Project Number: PC/06/085, T001646/06. Unpublished study prepared by Syngenta Crop Protection. 60 p.

MRID: 47309302
Sparrow, K. (2007) Physical and Chemical Properties of Emamectin Benzoate ME (042.9) (A16297A). Project Number: PC/07/085. Unpublished study prepared by Syngenta Crop Protection, Inc. 34 p.

Guideline: 830.6320 Corrosion characteristics

MRID: 47002103
Sparrow, K. (2006) Emamectin Benzoate Technical II: (MK244): Physical and Chemical Proerties of Emamectin Benzoate Technical II. Project Number: PC/06/126. Unpublished study prepared by Syngenta Crop Protection. 54 p.

MRID: 47153905
Phelps, L. (2006) Emamectin Benzoate RB (0.10) (A15276A): Physical and Chemical Properties of A15276A. Project Number: PC/06/085, T001646/06. Unpublished study prepared by Syngenta Crop Protection. 60 p.

MRID: 47309302
Sparrow, K. (2007) Physical and Chemical Properties of Emamectin Benzoate ME (042.9) (A16297A). Project Number: PC/07/085. Unpublished study prepared by Syngenta Crop Protection, Inc. 34 p.

Guideline: 830.7000 pH of water solutions or suspensions

MRID: 47002103
Sparrow, K. (2006) Emamectin Benzoate Technical II: (MK244): Physical and Chemical Proerties of Emamectin Benzoate Technical II. Project Number: PC/06/126. Unpublished study prepared by Syngenta Crop Protection. 54 p.

MRID: 47153905
Phelps, L. (2006) Emamectin Benzoate RB (0.10) (A15276A): Physical and Chemical Properties of A15276A. Project Number: PC/06/085, T001646/06. Unpublished study prepared by Syngenta Crop Protection. 60 p.

MRID: 47309302
Sparrow, K. (2007) Physical and Chemical Properties of Emamectin Benzoate ME (042.9) (A16297A). Project Number: PC/07/085. Unpublished study prepared by Syngenta Crop Protection, Inc. 34 p.

Guideline: 830.7050 UV/Visible absorption

MRID: 47002103
Sparrow, K. (2006) Emamectin Benzoate Technical II: (MK244): Physical and Chemical Proerties of Emamectin Benzoate Technical II. Project Number: PC/06/126. Unpublished study prepared by Syngenta Crop Protection. 54 p.

Guideline: 830.7100 Viscosity

MRID: 47309302
Sparrow, K. (2007) Physical and Chemical Properties of Emamectin Benzoate ME (042.9) (A16297A). Project Number: PC/07/085. Unpublished study prepared by Syngenta Crop Protection, Inc. 34 p.

Guideline: 830.7200 Melting point/melting range

MRID: 47002103
Sparrow, K. (2006) Emamectin Benzoate Technical II: (MK244): Physical and Chemical Proerties of Emamectin Benzoate Technical II. Project Number: PC/06/126. Unpublished study prepared by Syngenta Crop Protection. 54 p.

Guideline: 830.7300 Density/relative density

MRID: 47002103
Sparrow, K. (2006) Emamectin Benzoate Technical II: (MK244): Physical and Chemical Proerties of Emamectin Benzoate Technical II. Project Number: PC/06/126. Unpublished study prepared by Syngenta Crop Protection. 54 p.

MRID: 47153905
Phelps, L. (2006) Emamectin Benzoate RB (0.10) (A15276A): Physical and Chemical Properties of A15276A. Project Number: PC/06/085, T001646/06. Unpublished study prepared by Syngenta Crop Protection. 60 p.

MRID: 47309302
Sparrow, K. (2007) Physical and Chemical Properties of Emamectin Benzoate ME (042.9) (A16297A). Project Number: PC/07/085. Unpublished study prepared by Syngenta Crop Protection, Inc. 34 p.

Guideline: 830.7370 Dissociation constant in water

MRID: 47002103
Sparrow, K. (2006) Emamectin Benzoate Technical II: (MK244): Physical and Chemical Proerties of Emamectin Benzoate Technical II. Project Number: PC/06/126. Unpublished study prepared by Syngenta Crop Protection. 54 p.

Guideline: 830.7550 Partition coefficient (n-octanol/water), shake flask method
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MRID: 47002103
Sparrow, K. (2006) Emamectin Benzoate Technical II: (MK244): Physical and Chemical Proerties of Emamectin Benzoate Technical II. Project Number: PC/06/126. Unpublished study prepared by Syngenta Crop Protection. 54 p.

Guideline: 830.7840 Water solubility: Column elution method, shake flask method

MRID: 47002103
Sparrow, K. (2006) Emamectin Benzoate Technical II: (MK244): Physical and Chemical Proerties of Emamectin Benzoate Technical II. Project Number: PC/06/126. Unpublished study prepared by Syngenta Crop Protection. 54 p.

Guideline: 830.7950 Vapor pressure

MRID: 47002103
Sparrow, K. (2006) Emamectin Benzoate Technical II: (MK244): Physical and Chemical Proerties of Emamectin Benzoate Technical II. Project Number: PC/06/126. Unpublished study prepared by Syngenta Crop Protection. 54 p.

Guideline: 860.1000 Background

MRID: 46587001
Ediger, K.; Oakes, T. (2005) Emamectin Benzoate - Magnitude of the Residues in or on Crop Group 4: Leafy Vegetables, Except Brassica: Final Report. Project Number: T002301/03. Unpublished study prepared by Syngenta Crop Protection, Inc. 187 p.

MRID: 46587002
Ediger, K.; Oakes, T. (2005) Emamectin Benzoate - Magnitude of the Residues in or on Crop Group 8: Fruiting Vegetables: Final Report. Project Number: T002300/03. Unpublished study prepared by Syngenta Crop Protection, Inc. 302 p.

MRID: 47723501
Oakes, T. (2009) Emamectin Benzoate - Magnitude of the Residues in or on Almond and Pecan as Representative Commodities of Nut, Tree, Group 14: Final Report. Project Number: T002811/07, ML08/1427/SYN. Unpublished study prepared by Syngenta Crop Protection and Morse Laboratories, Inc. 311 p.

Guideline: 860.1380 Storage stability data

MRID: 46734701
Kvatermick, V. (1997) Storage Stability of Total Toxic Residues of MK-0244 on Various Fruiting Vegetables: Final Report. Project Number: 1462C/4, 1462C, 120294. Unpublished study prepared by Merck & Co., Inc. and Analytical Development Corp., Inc. 46 p.

MRID: 47296001
Kwiatkowski, A. (2007) Emamectin-Benzoate (MK244): Storage Stability in Cotton Seed and Gin Trash Stored Frozen for up to Nine Months: Final Report. Project Number: T001194/06/REG, T001194/06. Unpublished study prepared by Jealott's Hill Res. Station. 34 p.

Guideline: 860.1500 Crop field trials

MRID: 46587001
Ediger, K.; Oakes, T. (2005) Emamectin Benzoate - Magnitude of the Residues in or on Crop Group 4: Leafy Vegetables, Except Brassica: Final Report. Project Number: T002301/03. Unpublished study prepared by Syngenta Crop Protection, Inc. 187 p.

MRID: 46587002

Ediger, K.; Oakes, T. (2005) Emamectin Benzoate - Magnitude of the Residues in or on Crop Group 8: Fruiting Vegetables: Final Report. Project Number: T002300/03. Unpublished study prepared by Syngenta Crop Protection, Inc. 302 p.

MRID: 46783701
Ediger, K.; Cobin, J. (2006) Emamectin Benzoate (MK-0244) - Magnitude of the Residues in or on Crop Group 11: Pome Fruit: Final Report. Project Number: 37/00, 05/IR/001/00, NE/IR/802/00. Unpublished study prepared by Syngenta Crop Protection, Inc., Syngenta Crop Protection and Agricultural Chemicals Development Service. 347 p.

MRID: 47243301
Ediger, K. (2007) Emamectin Benzoate - Magnitude of the Residues in or on Almond and Pecan as Representative Commodities of Nut, Tree, Group 14: Final Report. Project Number: T007157/05, ML07/1339/SYN. Unpublished study prepared by Syngenta Crop Protection, Inc., Morse Laboratories, Inc. and Agricultural Systems Associates. 379 p.

MRID: 47723501
Oakes, T. (2009) Emamectin Benzoate - Magnitude of the Residues in or on Almond and Pecan as Representative Commodities of Nut, Tree, Group 14: Final Report. Project Number: T002811/07, ML08/1427/SYN. Unpublished study prepared by Syngenta Crop Protection and Morse Laboratories, Inc. 311 p.

Guideline: 860.1520 Processed food/feed

MRID: 46587002
Ediger, K.; Oakes, T. (2005) Emamectin Benzoate - Magnitude of the Residues in or on Crop Group 8: Fruiting Vegetables: Final Report. Project Number: T002300/03. Unpublished study prepared by Syngenta Crop Protection, Inc. 302 p.

MRID: 46783701
Ediger, K.; Cobin, J. (2006) Emamectin Benzoate (MK-0244) - Magnitude of the Residues in or on Crop Group 11: Pome Fruit: Final Report. Project Number: 37/00, 05/IR/001/00, NE/IR/802/00. Unpublished study prepared by Syngenta Crop Protection, Inc., Syngenta Crop Protection and Agricultural Chemicals Development Service. 347 p.

Guideline: 870.1100 Acute oral toxicity

MRID: 47002104
Durando, J. (2006) Emamectin Technical (MK244G): Acute Oral Toxicity Up and Down Procedure in Rats: Final Report. Project Number: 19852, T010796/05. Unpublished study prepared by Product Safety Laboratories. 17 p.

MRID: 47002105
Pooles, A. (2006) Emamectin: SYN545012: Acute Oral Toxicity in the Rat - Up and Down Procedure: Final Report. Project Number: 0006/0680, T011271/06. Unpublished study prepared by Safepharm Laboratories Ltd.. 20 p.

MRID: 47153906
Kuhn, J. (2006) Emamectin Benzoate RB (0.1) (A15276A): Acute Oral Toxicity Study in Rats: Final Report. Project Number: 9726/06, T001413/04. Unpublished study prepared by Stillmeadow, Inc. 14 p.

MRID: 47153907
Tisdel, M. (2006) Emamectin Benzoate RB (0.1) (A15276A): Summary of Acute Toxicology Studies with Emamectin Benzoate RB (0.1) (A15276A): Summary. Project Number: T008185/06. Unpublished study prepared by Syngenta Crop Protection. 10 p.

MRID: 47309303

Durando, J. (2007) Emamectin Benzoate ME (042.9) (A16297A)- Acute Oral Toxicity Up-and-Down Procedure in Rats: Final Report. Project Number: 23029, TOO7407/06. Unpublished study prepared by Product Safety Laboratories. 15 p.

Guideline: 870.1200 Acute dermal toxicity

MRID: 47002106
Durando, J. (2006) Emamectin Technical (MK244G): Acute Dermal Toxicity Study in Rats: Final Report. Project Number: 19853, T010797/05. Unpublished study prepared by Product Safety Laboratories. 20 p.

MRID: 47153907
Tisdel, M. (2006) Emamectin Benzoate RB (0.1) (A15276A): Summary of Acute Toxicology Studies with Emamectin Benzoate RB (0.1) (A15276A): Summary. Project Number: T008185/06. Unpublished study prepared by Syngenta Crop Protection. 10 p.

MRID: 47153908
Kuhn, J. (2006) Emamectin Benzoate RB (0.1) (A15276A): Acute Dermal Toxicity Study in Rats: Final Report Amendment. Project Number: 9727/06, T001410/04. Unpublished study prepared by Stillmeadow, Inc. 14 p.

MRID: 47309304
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MRID: 47002108
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MRID: 47002111

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MRID: 42743604
Citation: Gerson, R. (1993) MK-0244: Summary of Pertinent Toxicology: Lab Project Number: 618-244-TOXSUM. Unpublished study prepared by Merck & Co., Inc. Merck Research Labs. 22 p.

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MRID: 43415300
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Citation: Merck & Co., Inc. (1995) Submission of Product Chemistry and Toxicology Data in Support of the Experimental Use Permit for Proclaim 5 SG Insecticide (Emamectin Benzoate). Transmittal of 6 Studies.

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Citation: Merck & Co., Inc. (1995) Submission of Product Chemistry, Hazard to Wildlife and Aquatic Organisms, Residue, Environmental Fate and Exposure: Reentry Protection Data in Support of the Registration of Proclaim 0.16 EC and Proclaim 5 SG and Petition for Tolerance for Emamectin Benzoate on Cole Crops, Celery, and Lettuce. Transmittal of 26 Studies.

MRID: 43850101
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MRID: 43850120
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MRID: 43943300
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Citation: Neal, B. (1995) Mammalian Toxicology Summary for Emamectin Benzoate MK-244: Lab Project Number: 618-244-TOXSUM3. Unpublished study prepared by Jellinek, Schwartz & Connolly, Inc. 16 p.

MRID: 43943304

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Citation: Merck & Co., Inc. (1996) Submission of Product Chemistry, Toxicity, Hazard to Wildlife and Aquatic Organisms, and Environmental Fate and Residues Data in Support of the Application for Registration of PROCLAIM 0.16 EC, PROCLAIM 5 SG, and Emamectin Benzoate Technical Insecticides and Tolerance Petition for Emamectin Benzoate and Metabolites in/on Cole Crops, Celery, and Head Lettuce. Transmittal of 15 Studies.

MRID: 44010000
Citation: Merck & Co., Inc. (1996) Submission of Environmental Fate Data in Support of Registration of PROCLAIM 0.16 EC Insecticide and PROCLAIM 5 SG Insecticide and Petition for Tolerances of Emamectin Benzoate (MK-0244) on Cole Crops and Leafy Vegetables. Transmittal of 1 Study.

MRID: 44030600
Citation: Merck Research Laboratories (1996) Submission of Metabolism and Residue Data in Support of the Applications for Registration of Proclaim 0.16 EC Insecticide, Proclaim 5 SG Insecticide, and Emamectin Benzoate Technical and Petition for Tolerances for Emamectin Benzoate in/on Cole Crops, Celery, and Head Lettuce. Transmittal of 2 Studies.

MRID: 44257400
Citation: Merck & Co., Inc. (1997) Submission of Exposure/Risk Data in Support of the Applications for Registration for Emamectin Benzoate Technical, Proclaim 0.16 EC and Proclaim 5% SG Insecticide and Tolerance Petition for Emamectin Benzoate in/on Certain Cole Crops and Leafy Vegetables. Transmittal of 1 Study.

MRID: 44257401
Citation: Kidwell, J.; Petersen, B. (1997) Dietary Exposure and Risk Assessment for Emaamectin (sic) Benzoate on Broccoli, Cabbage, Cauliflower, Brussels Sprouts, Celery, and Head Lettuce: Lab Project Number: 618-244-FQPA1. Unpublished study prepared by Novigen Sciences, Inc. 41 p.

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Citation: Merck & Co., Inc. (1997) Submission of Toxicity, Residue, Risk Assessment and Exposure Data in Support of the Petition for Tolerance for Emamectin Benzoate on Cole Crops and Leafy Vegetables and the Applications for Registration of Emamectin Benzoate Technical, Proclaim 0.16 EC, and Proclaim 5% SG Insecticides. Transmittal of 1 Study.

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MRID: 44300100
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MRID: 44300104
Citation: Kidwell, J.; Petersen, B. (1997) Dietary Exposure and Risk Assessment for Emamectin Benzoate on Broccoli, Cabbage, Cauliflower, Brussels Sprouts, Celery, Head Lettuce, and Fruiting Vegetables: Lab Project Number: 618-244-FQPA2. Unpublished study prepared by Novigen Sciences, Inc. 50 p.

MRID: 44300105
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MRID: 44563801
Citation: Kidwell, J.; Petersen, B. (1997) Dietary Exposure and Risk Assessment for Emaamectin (sic) Benzoate on Broccoli, Cabbage, Cauliflower, Brussels Sprouts, Celery and Head Lettuce: Lab Project Number: 618-244-FQPA1. Unpublished study prepared by Novigen Sciences, Inc. 41 p.

MRID: 44585000
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MRID: 44585001
Citation: Stevens, J. (1998) Emamectin Benzoate: P-Glycoprotein Deficiency in Polymorphic CF-1 Mice and Neonatal Rats and its Relevance to Human Risk Assessment: Lab Project Number: 524-98. Unpublished study prepared by Novartis Crop Protection, Inc. 651 p.

MRID: 44596300
Citation: Novartis Crop Protection, Inc. (1998) Submission of Residue Data in Support of the Application for Registration of Proclaim 0.16 EC Insecticide, Proclaim 5 SG Insecticide and Emamectin Benzoate Technical and the Petition for Tolerance of Emamectin Benzoate in/on Cole Crops, Celery and Head Lettuce. Transmittal of 1 Study.

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MRID: 44795000
Citation: Novartis Crop Protection, Inc. (1999) Submission of Product Chemistry Data in Support of the Petition for Tolerance of Emamectin Benozoate in/on Fruiting Vegetables and Cottonseed and the Applications for Registration of Emamectin Benzoate Technical, Proclaim 0.16 EC Insecticide and Proclaim 5 SG Insecticide. Transmittal of 1 Study.

MRID: 44883700
Citation: Novartis Crop Protection, Inc. (1999) Submission of Product Chemistry and Residue Chemistry Data in Support of the Petition for Tolerances of Emamectin Benzoate in/on Fruiting Vegetables, Leafy Brassica Vegetables, Cotton, and Leafy Vegetables, and the Registration of Emamectin Benzoate, Proclaim, and Denim. Transmittal of 16 Studies.

MRID: 44883706
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Citation: Bray, L.; Dunbar, D.; Koenig, J.; et al. (1999) Reduced-Risk Pesticide Rationale for Proclaim and Denim: Lab Project Number: 1098-99. Unpublished study prepared by Novartis Crop Protection, Inc. 174 p.

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MRID: 45509900
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MRID: 45899800
Citation: Syngenta Crop Protection, Inc. (2003) Submission of Residue Data in Support of the Amended Registrations of Proclaim Insecticide and Emamectin Benzoate Technical and the Petition for Tolerance of Emamectin Benzoate in or on Pome Fruit. Transmittal of 1 Study.

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MRID: 46587000
Citation: Syngenta Crop Protection, Inc. (2005) Submission of Residue Data in Support of the Amended Registration of Proclaim Insecticide. Transmittal of 2 Studies.

MRID: 46734700
Citation: Syngenta Crop Protection, Inc. (2006) Submission of Residue Data in Support of the Registration of Proclaim Insecticide. Transmittal of 1 Study.

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Citation: Chukwudebe, A. (2006) Substantial Similarity of Emamectin Benzoate Technical, MK 244 to Emamectin Benzoate Technical II: Assessment. Project Number: T010782/06. Unpublished study prepared by Syngenta Crop Protection. 39 p.

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Citation: Syngenta Crop Protection, Inc. (2007) Submission of Product Chemistry and Toxicity Data in Support of the Application for Registration of TreeAge. Transmittal of 8 Studies.

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Citation: J.J. Mauget Co. (2008) Submission of Efficacy Data in Support of the Registration of Dutrex. Transmittal of 15 Studies.

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Citation: Syngenta Crop Protection, Inc. (2008) Submission of Exposure and Risk Data in Support of the Application for Registration of Treeage. Transmittal of 1 Study.

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Citation: Joseph, T. (2008) Occupational Exposure and Risk Assessment for Tree Injection Application of Emamectin Benzoate 4% Insecticide: Assessment. Project Number: T001352/08, AH204/M, AH501/M/2. Unpublished study prepared by Syngenta Crop Protection. 18 p.

MRID: 47465500
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MRID: 47691000
Citation: Syngenta Crop Protection, Inc. (2009) Submission of Efficacy Data in Support of the Application for Registration of Treeage. Transmittal of 1 Study.

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Citation: Syngenta Crop Protection, Inc. (2009) Submission of Exposure and Risk Data in Support of the Application for Registration of Tree-Age. Transmittal of 1 Study.

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Citation: Overmyer, J.; Cox, D. (2009) Hazard Assessment of Emamectin Benzoate (Tree-Age) Tree Injection to Pollinators. Project Number: T001986/09. Unpublished study prepared by Syngenta Crop Protection, Inc. 15 p.

MRID: 47878900
Citation: Syngenta Crop Protection, Inc. (2009) Submission of Efficacy Data in Support of the Amended Registration of TreeAge. Transmittal of 1 Study.

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Appendix 2: Toxicity to Mammals

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Note on Nomenclature: Both MK-0243 and MK-0244 appear to be 0.16 lb./gal. EC Formulations of Emamectin benzoate. This is equivalent to Denim formulation, which is not specifically covered in the current Forest Service risk assessment.

A2 Table 1: Acute Oral/Gavage Toxicity, Technical

Species	Exposure	Response	Reference[1]
Rat	Oral	Males LD_{50}: 88 mg a.i./kg bw Females LD_{50}: 76 mg a.i./kg bw	MRID 42743612
Mouse	Oral	Males LD_{50}: 22 mg a.i./kg bw Females LD_{50}: 31 mg a.i./kg bw Signs of toxicity: tremors, ataxia, bradypnea (slow breathing) and loss of righting reflex.	MRID 42743612
Rat	Oral, MK-0243 technical (96.9% a.i.). Single dose of 0, 0.5, 2.5, 5.0, 10.0, or 25.0 mg/kg. `Working note: DER specifies a purity of 94.2%.`	LD_{50}: >25 mg a.i./kg bw NOAEL: 5 mg/kg bw LOAEL: 10 mg/kg bw, tremors. FEL: 25 mg/kg bw based on neurotoxicity and neuronal lesions.	Manson 1992e MRID 42743619
Rat	0.16 EC (1.94% a.i.)	LD_{50}: >38.8 mg a.i./kg bw	MRID 42743605
Rats	Emamectin benzoate Technical, **L-656,748-038**	LD_{50}: 53 mg/kg bw	MRID 42851519[2]
Rats	Emamectin benzoate Technical II[2], **L-656,748-038**	LD_{50}: 53 mg/kg bw	MRID 47002104[2]
Rats	MK-0243 Single oral doses of 27.4, 54.8 or 82.2 mg/kg.	From U.S. EPA/OPP 2008a *Toxic signs of neurotoxicity as well as histological lesions in the brain, spinal cord and sciatic nerve occurred at all doses tested.* Signs of toxicity: salivation, tremors, ataxia, bradypnea (slow breathing), loss of righting reflex, and decreased activity. NOAEL: not established. Adverse effects observed at lowest dose tested. Male LD_{50}: 67 (54-84) mg/kg bw Female LD_{50}: 70 (55-104) mg/kg bw	Manson 1992d MRID 42743618

[1] Studies designated with only MRID numbers are taken from U.S. EPA/OPP 2009, Table D4, p. 75 unless otherwise specified.
[2] Taken from U.S. EPA/OPP 2008a

A2 Table 2: Acute Studies, Other than Oral			
Species	**Exposure**	**Response**	**Reference[1]**
Rabbits, male	Dermal: Vehicle in 0.16 EC, 500, 1000, and 2000 mg vehicle/kg bw. Note: This probably corresponds to Denim.	Slight to severe skin irritation	Bagdon 1992 MRID 42743611
Rabbits, male	Dermal: 0.16 EC, 500, 1000, and 2000 mg formulation/kg bw	Slight to severe skin irritation. Irritation attributed to vehicle/carrier in the formulation. See above.	Bagdon 1992 MRID 42743611
Rabbits	Dermal, Technical	LD_{50}: > 2,000 mg/kg bw, Category III	MRID 43850111
Rabbits	Dermal, Technical II[2]	LD_{50}: > 2,000 mg/kg bw, Category III	MRID 47002106
Rats	Inhalation, Technical	LC_{50}: 0.1 mg/L, Category IV	MRID 43868101
Rats	Inhalation, Technical II[2]	LC_{50}: 0.1 mg/L, Category II	MRID 47002107
Rabbits	Eye Irritation, Technical	Severe eye irritation, Category I	MRID 42743615
Rabbits	Eye Irritation, Technical II[2]	Severe eye irritation, Category III Working Note:	MRID 47002108
Rabbits	Dermal Irritation, Technical	No irritation, Category IV	MRID 42743616
Rabbits	Dermal Irritation, Technical II[2]	No irritation, Category IV	MRID 47002109
Guinea pigs	Skin sensitization, Technical	Not a dermal sensitizer	MRID 42743617
Guinea pigs	Skin sensitization, Technical II[2]	Not a dermal sensitizer	MRID 47002110

[1]Studies designated with only MRID numbers are taken from U.S. EPA/OPP 2008a.
[2]See Section 2.2 for a discussion of emamectin benzoate *Technical II*.

A2 Table 3: Reproductive and Developmental Studies			
Species	**Exposure**	**Response**	**Reference[1]**
Reproduction			
Rats	Oral, Two-generation, MK-0244 Doses: 0, 0.1, 0.6, or 3.6/1.8 mg/kg/day. High dose reduced from 3.6 mg/kg bw/day to 1.8 mg/kg bw/day due to decreased bw gain.	From U.S. EPA/OPP 2008a *Systemic Toxicity* *NOAEL=0.6 mg/kg/day* *LOAEL=1.8 mg/kg/day based on decreased body weight gain and histopathological changes (neuronal degeneration in the brain and spinal cord) in both sexes and generations.* *Reproductive Toxicity* *NOAEL=0.6 mg/kg/day* *LOAEL=1.8 mg/kg/day based on decreased fecundity and fertility indices and clinical signs (tremors and hind limb extension) in offspring of both generations.* Note from U.S. EPA/OPP 2009: Dietary NOAEC/LOAEC = 12/35 mg a.i./kg diet. Working Notes: The DER indicates that this was actually two studies, dietary and gavage. Gavage NOAEL: 0.6 mg/kg bw/day Gavage LOAEL: 5 mg/kg bw/day based on decreased bw. Dietary NOAEL: 0.6 mg/kg bw/day Dietary LOAEL: 4.6 mg/kg bw/day based on decreased bw., tremors and histopathology in brain and spinal cord.	Lankas 1992c MRID 42851511
Developmental			
Rabbits	Oral, MK-0243 (benzoate salt) Gavage: 0, 1.5, 3, or 6 mg/kg/day on Days 6-18 of gestation.	From U.S. EPA/OPP 2008a *Maternal Toxicity* *NOAEL=3 mg/kg/day* *LOAEL=6 mg/kg/day based on a significant trend towards decreased body weight gain during dosing period and increased clinical signs (mydriasis and decreased pupillary reaction).* *Developmental Toxicity* *NOAEL=6 mg/kg/day,* *LOAEL= Not Determined.*	Manson 1992b. MRIDs 42743636 (full study), 42743635 (range finding study)
Rats	Oral, MK-0243 (benzoate salt) Gavage doses: 0, 2, 4, or 8 mg/kg/day on days 6-18 of gestation.	From U.S. EPA/OPP 2008a *Maternal Toxicity* *NOAEL=2 mg/kg/day* *LOAEL=4 mg/kg/day based on a significant trend towards decreased body weight gain during the dosing period.* 8 mg/kg bw/day: tremors in 15/25 dams *Developmental Toxicity* *NOAEL=4 mg/kg/day* *LOAEL=8 mg/kg/day based on altered growth and an increased incidence of supernumerary rib.*	Manson 1992c MRIDs 42743632 (full study), 42743631 (range finding study)

A2 Table 3: Reproductive and Developmental Studies

Species	Exposure	Response	Reference[1]
Rats	Oral, Developmental neurotoxicity. Doses: 0, 0.1, 0.6, or 3.6/2.5 mg/day from Day 6 to 20 of gestation.	From U.S. EPA/OPP 2008a *Maternal Toxicity* *NOAEL=3.6/2.5 mg/kg/day (highest dose tested)* *Developmental Neurotoxicity* *NOAEL=0.10 mg/kg/day (lowest dose tested). The LOAEL is 0.60 mg/kg/day based on the dose-related decrease in open field motor activity in females at postnatal day 17. This study was the basis of the FQPA Committee's conclusion that emamectin demonstrated increased susceptibility* [i.e., offspring were more sensitive than dams].	Wise 1993a MRID 42851508
Rats, Sprague-Dawley	MK-0244 (emamectin benzoate), gavage at doses of 0.1, 0.6, and 3.5 mg/kg bw from Days 6 to 20. From Days 17 to 20, the high dose reduced to 2.5 mg/kg bw.	Maternal Effects Significant increase in body weights at the two highest doses. No effects on any reproductive parameters. Offspring High Dose: Signs of neurotoxicity (tremors and hind limb splay) in all litters. Decrease in pup weights (14% F, 11% M) on PND 11. Decreased weights progressed (40-42% below controls) through to PND 21. Decreased activity in open field assay and startle response. Delayed develop (time to vaginal canalization and preputial separation). Slight decrease in absolute brain weights. Mid Dose: Significant but not substantial time-related decrease in female offspring body weights. Decreased field behavior activity in females. Tremors and hindlimb splay in some offspring. Low Dose: No adverse effects. NOAEL	Wise et al. 1997 Note: This open literature paper appears to be identical to MRID 42851508 above.

[1]Studies designated with only MRID numbers are taken from U.S. EPA/OPP 2008a.

A2 Table 4: Subchronic Toxicity			
Species	**Exposure**	**Response**	**Refer-ence[1]**
Dogs	3 and 14 week dietary, MK-0243 [L-656,748] 0, 0.5, 1.0, or 1.5 mg/kg/day for 2 weeks. Doses reduced to 0, 0.25, 0.5, 1.0 mg/kg/day for rest of study due to excessive toxicity.	From U.S. EPA/OPP 2008a *NOAEL=0.25 mg/kg* *LOAEL=0.50 mg/kg based on microscopic pathological signs of neurotoxicity consisting of skeletal muscle atrophy and white matter multifocal degeneration in the brains of both sexes and white matter multifocal degeneration in the spinal cords of males.* 1 mg/kg/day: ataxia, tremors, mydriasis, and recumbency occurred in both sexes. Optic nerve degeneration in 2/4 males and 3/4 females. Prior to the reduction in dosing, decrease food consumption. Thymus atrophy also seen in the high dose group in 1/4 males and 2/4 females.	Mason 1992a MRIDs 42743623 (14 wks), 42743622 (3 wks)
Mice	Dietary, 2 weeks, MK-0243. Doses: 0, 0.2, 0.6, 1.2, and 2 mg/kg/day.	*Neurotoxicity NOAEL=2.0 mg/kg/day (highest dose tested). No characteristic neuronal lesions in the brain, spinal cord or sciatic nerve in mice of high dose group (2.0 mg/kg/day).* No signs of toxicity at any dose. Increased weight gain at 0.6 and 1.2 mg/kg/day in males but not females considered treatment related.	Lankas 1992a MRID 42743629
Mice	Dietary, 15 days, MK-244	*Neurotoxicity NOAEL=0.075 mg/kg/day* *LOAEL=0.10 mg/kg/day based on tremors observed beginning on day 3, decreases in body weight and food consumption as well as degeneration of the sciatic nerve.* **Working/Reviewer Note: The above entry is taken from Table A.2., p. 45, in U.S. EPA/OPP 2008a. This entry designated the test material as MK-244. Based on the DER for this MRID (detailed further in Table 5 of this appendix), the study title (from Appendix 1), as well as the discussion of this study in U.S. EPA/OPP (2008a, p. 14), the test material was L-660,599, a plant metabolite of emamectin benzoate. This distinction is important because this study is the basis of the acute and chronic RfDs.**	MRID 42851503 See more detailed entry in Table 6 of this appendix.
Mice	Dietary, 16 days, MK-0243 (EC formulation). 0, 0.05, 0.1, 0.3, and 0.9 mg/kg	NOAEL: 0.1 mg/kg LOAEL: 0.3 mg/kg based on a broad spectrum of neurotoxicity including a moribund condition in 4 mice.	Gerson 1992e, MRID 42743630 Not cited in U.S. EPA/OPP 2008a

Appendix 2: Toxicity to Mammals *(continued)*

A2 Table 4: Subchronic Toxicity

Species	Exposure	Response	Reference[1]
Mice	Dietary, 13 weeks, MK-0243 [deoxyavermectin], 0, 0.5, 4.5, or 15 mg/kg bw/day. Another group had TWA dose of 5.4 mg/kg bw/day [1.5 mg/kg bw/day for 7 weeks and 10 mg/kg bw/day for 6 weeks]	NOAEL: 5.4 mg/kg bw/day. LOAEL: 15 mg/kg bw/day based on decreased bw and body weight gain.	Gerson 1992a, MRID 42743621 Not cited in U.S. EPA/OPP 2008a
Rats	3 and 14 week dietary, MK-0243 Dietary concentrations of 0, 5, 25, or 125 ppm corresponding to doses of 0, 0.5, 2.5, and 12.5 mg/kg bw/day.	From U.S. EPA/OPP 2008a *NOAEL=2.5 mg/kg/day* *LOAEL=5 mg/kg/day based on tremors, hindlimb splaying, urogenital staining, histological changes in brain and spinal cord, sciatic and optic nerves and skeletal muscles in males, emaciation, reduced body weight and reduced food consumption in both sexes.* Working Notes: Because of reduced body weight and food consumption observed at the highest dose level, the high dose was decreased from 12.5 to 8 mg/kg/day in week 3, and from 8 to 5 mg/kg/day in week 9. The time-weighted average high-dose levels were 6.7, 7.1, and 7.5 mg/kg/day for males, females, and sexes combined, respectively.	Lankas 1992d MRIDs 42794201 (14 wks), 42743620 (3 wks)
Rats	Dietary, 14 weeks, MK-0243. 0, 0.25, 1.0, and 5.0 mg/kg/day Note: The study title refers to the test material as MK-0244.	*Neurotoxicity NOAEL=1.0 mg/kg/day* *LOAEL=5.0 mg/kg/day (highest dose tested) based on mild tremors, posture, rearing, excessive salivation, fur appearance, gait, strength, mobility and righting reflex.* Based on food consumption, the actual NOAEL is 0.85 mg/kg bw/day. Decreased body weight at high dose of 25.3%. Decrease in bw corresponds to decrease in food consumption. DER summary: *Neuronal vacuolation in the brain and spinal cord and degeneration of nerve fibers in the spinal cord and sciatic nerve of both sexes of rats. Male rats were more affected than female rats. Skeletal muscle atrophy was also seen in some high-dose male rats.*	Gerson 1992c MRID 42743628

[1]Studies designated with only MRID numbers are taken from U.S. EPA/OPP 2008a. Some study details are inferred from the information in Appendix I. If the study is designated by author(s) and date as well as an MRID, the summary section in italics is from U.S. EPA/OPP 2008a but other information not in italics is taken from the DER/cleared review.

A2 Table 5: Chronic Toxicity			
Species	**Exposure**	**Response**	**Refer-ence[1]**
Dogs	53 weeks, MK-0244 Gavage in water at 0, 0.25, 0.5, 0.75, and 1.0 mg/kg/day. Dose of 0.75 mg/kg bw/day initiated after other doses because of extreme toxicity at 1 mg/kg bw/day.	From U.S. EPA/OPP 2008a *Systemic Toxicity* *NOAEL= 0.25 mg/kg/day* *LOAEL=0.5 mg/kg/day based on axonal degeneration in the pons medulla and peripheral nerves (sciatic, sural, and tibial) in both sexes, clinical signs of neurotoxicity (whole body tremors, stiffness of the hind legs), spinal cord axonal degeneration, and muscle fiber degeneration in females.* Damage to optic nerve at 0.75 and 1 mg/kg bw/day. 0.75 mg/kg bw/day: Sacrificed at 7 weeks due to extreme neurotoxicity and decreased bw. 1.0 mg/kg bw/day: Sacrificed at 3 weeks because of severe neurotoxicity. No indication of effects to the thymus.	Gillet 1992a MRID 42763624 [or 42743624] [2]
Mice	78 weeks, MK-0244	*Systemic Toxicity* *NOAEL=2.5 mg/kg/day* *LOAEL=5.0 mg/kg/day for males and 7.5 mg/kg/day for females based on increased mortality, decreased weight gain, neurological signs, and increased incidence of severity of infections. There were no signs of carcinogenicity in this study.*	MRID 4386805 [43868105] [2]
Rats	53 weeks, MK-0244 (deoxy avemectin: 95.9% pure) Doses of 0, 0.1, 1.0, 2.5 mg/kg bw for males. For females, the TWA high dose is 3.3 mg/kg bw/day. High dose lowered to 2.5 mg/kg bw/day at week 18 due to toxicity.	*Systemic Toxicity* *NOAEL=1.0 mg/kg/day* *LOAEL=2.5 mg/kg/day, based on increased incidence of neuronal degeneration in the brain and spinal cord, decreased rearing, and an increased incidence of animals with low arousal.* At 3.3 mg/kg bw/day, females had a number of signs of neurotoxicity including tremors. No damage to optic nerve.	Gerson 1992b MRID 42868902

Appendix 2: Toxicity to Mammals *(continued)*

Rats	105 weeks, Emamectin	Systemic Toxicity NOAEL=1.0 mg/kg/day LOAEL=2.5/5.0 mg/kg/day based on marked neural degeneration in the brain and spinal cord of both sexes, brain white matter degeneration in males, and on decreased body weight, body weight gain, and food efficiency in males. There were no signs of carcinogenicity in this study. Note on LOAEL Dose: *The initial dose of the high dose group was 5.0 mg/kg/day. Due to unacceptable weight loss and/or tremors occurring at this dose in another concurrent study (TT#91-006-0) during week 9 in males and week 11 in females, the dose was lowered to 2.5 mg/kg/day starting at week 6 in males and week 10 in females.*	MRID 43868104

[1] Studies designated with only MRID numbers are taken from U.S. EPA/OPP 2008a. Some study details are inferred from the information in Appendix I. If the study is designated by author(s) and date as well as an MRID, the summary section in italics is from U.S. EPA/OPP 2008a but other information not in italics is taken from the DER/cleared review.

[2] The MRID number given in U.S. EPA/OPP 2008a appears to be a typo. The correct MRID (based on Appendix 1) is given in brackets.

A2 Table 6: Toxicity of Metabolites and Derivatives			
Species	**Exposure**	**Response**	**Reference**
L-657,831; 4''-epi-(N-formyl)-amino-4'' –deoxyavermectin B1 (Formyl amino derivative of MK-0244)			
Mice, CF-1	15 day dietary Target dose: 0, 0.050, 0.075, 0.100, and 0.300 mg/kg/day. Actual Doses: Males: 0. 0.04, 0.06, 0.07, 0.23 mg/kg bw/day Females: 0, 0.04, 0.05, 0.08, 0.24 mg/kg bw/day	NOAEL: 0.07 mg/kg/day [actual dose to males in targeted 0.1 mg/kg bw/day dose group] LOAEL: 0.23 mg/kg/day based on decreased weight gain. No clinical signs of toxicity or neuropathology at highest dose tested. [Actual dose to males in targeted 0.3 mg/kg bw/day dose group]	Gerson 1992d, MRID 42868901
L-695,638: (8,9-Z-isomer); 4"-deoxy-4"-epimethylamino-avermectin B1a-Delta-8,9-isomer (Photoproduct of MK-0244)			
Mice, CF-1	14 day dietary 0, 0.05, 0.075, 0.10, and 0.30 mg/kg/day.	NOAEL: 0.3 mg/kg bw/day LOAEL: not established	Gerson 1992h, MRID 42851504
L-660,599: 4"-epi-(N-formyl-N-methyl)-amino-4"-deoxyavermectin B1 (an MK-0244 plant metabolite)			
Mice, CF-1 10 animals per sex per dose	14 day dietary except for high dose which was only 7 days. Target doses: 0, 0.05, 0.075, 0.10, and 0.30 mg/kg bw/day. Actual Doses: Males: 0.05, 0.07, 0.09, and 0.43 mg/kg bw/day Females: 0.05, 0.07, 0.09, and 0.37 mg/kg bw/day	NOAEL: 0.075 mg/kg bw/day. LOAEL: 0.1 mg/kg bw/day based on mortality, decreased food consumption and body weight, and degeneration of sciatic nerve. Working Note: The above NOAEL and LOAELs are given as targeted doses. These are the doses used in the U.S. EPA/OPP risk assessments. The differences between targeted and actual doses are insubstantial but this should be noted in the dose-response assessment.	Gerson 1992g, MRID 42851503 **This study is the basis of the acute and chronic RfDs. See Section 3.3.**
Mice, CF-1	14 day dietary 0, 0.1, 0.3, and 0.9 mg/kg bw/day	NOAEL: not determined. LOAEL: 0.1 mg/kg bw/day based on tremors and piloerection in one animal on Day 14. Working note: This appears to have been the initial study. Above study probably done to establish an NOAEL.	Gerson 1992i, MRID 42851506
L-930,905: Complex mixture of polar MK-0244 photodegradates which co-elute upon HPLC (Polar photodegradates of MK-0244)			
Mice, CF-1	14 day gavage 0,3, 6, 12, or 18 mg/kg/day	NOAEL: 18 mg/kg bw/day LOAEL: not determined.	Gerson 1992j, MRID 42851507
Concurrent tests of MK-0243 (L656,748), L-682,901, L-653,648, L-653,649, L-655,372 **Note: This is a group of concurrent tests done on two male and two female dogs for each compound. The compounds were not tested as a mixture. Each agent was tested at a single dose of 1.5 mg/kg bw/day by gavage for 13 to 14 days.**			
Dogs	MK-0243 [emamectin benzoate]	Tremors in 2/4 dogs. Very slight to slight neuronal degeneration in all dogs.	Lankas 1992b

Appendix 2: Toxicity to Mammals *(continued)*

A2 Table 6: Toxicity of Metabolites and Derivatives			
Species	**Exposure**	**Response**	**Reference**
	L-682,901 [4'' epi-methylamino ivermectin]	No neural lesions.	Lankas 1992b
	L-653,648 [4'' epi-acetyl avermectin]	Dilation of pupils (mydriasis) in 4/4 dogs. No neural lesions.	Lankas 1992b
	L-653,649 [4'' epi-amino avermectin]	Dilation of pupils (mydriasis) in 3/4 dogs and tremors in 2/4 dogs. One dog was drooling and laterally recumbent prior to necropsy. Very slight to slight neuronal degeneration in all dogs.	Lankas 1992b **This appears to be the mammalian metabolite.**
	L-655,372 [4'' epi-dimethylamino avermectin]	Tremors in 3/4 dogs. Very slight to slight neuronal degeneration in all dogs.	Lankas 1992b

Appendix 3: Toxicity to Birds

A3 Table 1: Acute Oral/Gavage Toxicity to Birds 176
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A3 Table 3: Reproductive Toxicity to Birds..... 178

A3 Table 1: Acute Oral/Gavage Toxicity to Birds

Species	Exposure	Response	Reference[1]
Mallard duck (*Anas platyrhynchos*)	95.9% a.i.	LD_{50}: 46 (30-69) mg/kg bw Slope: 3.5 (1.9-5.2) NOAEL: <12 mg/kg bw based on reduced body weight and signs of toxicity at all doses.	MRID 42743601 U.S. EPA/OPP 2008a, Table 12, p. 15. U.S. EPA/OPP 2009a, Table 4.1, p. 19
Mallard duck (*Anas platyrhynchos*), 19 weeks old, 1.007-1.196 kg, 5 per sex per dose group	≈96% a.i. in corn oil at doses of 0, 25, 50, 100, 200, 400, and 800 mg/kg bw. 14 day observation period.	LD_{50}: 76 (56-102) mg/kg bw No mortality and no substantial impact on BW at 25 mg/kg bw. Complete mortality at doses of 200 mg/kg bw and higher Signs of toxicity: lethargy, ruffled appearance, and loss of righting reflex. **Working note: Based on a 2.5% decrease in BW in females at 25 mg/kg bw, the authors suggest that the NOEL is not defined – i.e., <25 mg/kg bw.**	Chukwudebe et al. 1998
Northern bobwhite quail (*Colinus virginianus*)	95.9% a.i.	LD_{50}: 264 (201-329) mg/kg bw Slope: 7.15 (2.8-11)	MRID 42868905
Northern bobwhite quail (*Colinus virginianus*) 26 weeks old, 187-202 g (av=194.5 g)	≈96% a.i. in corn oil at doses of 0, 12.5, 25, 50, 100, 200, and 400 mg/kg body weight. 21 day observation period.	LD_{50}: 264 (201-348) mg/kg bw Slope: 7 No mortality at 100 mg/kg bw and lower. 95% mortality at 400 mg/kg bw. Signs of toxicity: lethargy, ruffled appearance, and loss of righting reflex. NOEC: 25 mg/kg bw LOEC: 50 mg/kg bw, 2% bw decrease in females at 0 to 3 days after treatment.	Chukwudebe et al. 1998

[1] Studies specified with only an MRID number are taken from U.S. EPA/OPP 2008b or U.S. EPA/OPP 2009.

A3 Table 2: Acute Dietary Toxicity to Birds

Species	Exposure	Response	Reference[1]
Mallard duck (*Anas platyrhynchos*)	95.9% a.i. , MK-244, 5-day dietary with 3 day post-exposure period	LC_{50}: 570 (391 - 915) mg a.i./kg diet[2] Slope: 2.8 (1.5-4.2)	MRID 42851528
Mallard duck (*Anas platyrhynchos*) , 10 day old, 152-172 g, 5 per dose.	≈96% a.i. Nominal dietary concentrations of 10, 20, 40, 80, 163, 327, 654, and 1,308 mg/kg diet. 5 days of dietary exposure with a 7 day post-exposure observation period. **Working note: Based on an approximate Day 0 bw 0.162 g and a Day 5 bw of 0.318 kg, the average bw was ≈0.24 kg. The reported food consumption at 20 ppm was 0.081 kg/day. Thus, the fractional food consumption was ≈0.33 and the 20 ppm concentration corresponds to a dose of ≈6.6 mg/kg bw.]**	LC_{50}: 570 (391 - 915) mg a.i./kg diet Slope: 3 No mortality at 80 ppm and below. Signs of toxicity: lethargy, ruffled appearance, and loss of righting reflex. Decreases in food consumption and body weight at 327 ppm and higher. NOEC: 20 ppm LOEC: 40 ppm based on reduced food consumption.	Chukwudebe et al. 1998
Northern bobwhite quail (*Colinus virginianus*)	95.9% a.i. , MK-244, 5-day dietary with 3 day post-exposure period	LC_{50}: 1318 (1008-1729) mg a.i./kg diet [2] Slope: 7.2 (2.9-11)	MRID 42851527
Northern bobwhite quail (*Colinus virginianus*), 10 days old, 17-19g	≈96% a.i. Nominal dietary concentrations of 125, 250, 500, 1,000, 2,000, and 4,000 mg/kg diet. 5 days of dietary exposure with a 7 day post-exposure observation period. **Working note: 125 ppm group, Day 0 bw 0.018 kg and a Day 5 bw of 0.028 kg for an average of ≈0.023 kg. The reported food consumption at 125 ppm was 0.007 kg. Thus, the fractional food consumption was 0.30 and the 125 ppm concentration corresponds to a dose of 37.5 mg/kg bw.]**	LC_{50}: 1318 (1008-1729) mg a.i./kg diet Slope: 7 No mortality at 500 ppm and lower. Signs of toxicity: lethargy, ruffled appearance, and loss of righting reflex. Dose-related decrease in body weight gain with weight losses at 1000 ppm and higher. NOEC: 125 ppm LOEC: 250 PPM, signs of toxicity	Chukwudebe et al. 1998

[1] Studies specified with only an MRID number are taken from U.S. EPA/OPP 2008b or U.S. EPA/OPP 2009.

[2] The footnote in U.S. EPA/OPP 2009, Table D2, p. 74 indicate that the confidence limits are given in units of mg a.i./kg bw. This appears to be typographical error. The confidence intervals are consistent with units of mg a.i./kg diet for these dietary studies.

A3 Table 3: Reproductive Toxicity to Birds

Species	Exposure	Response	Reference[1]
Mallard duck (*Anas platyrhynchos*)	MK-0244, 94.6% a.i.	NOAEC 40 mg a.i./kg diet LOAEC: not defined	MRID 44007910
Northern bobwhite quail (*Colinus virginianus*)	MK-0244, 94.6% a.i.	NOAEC 125 mg a.i./kg diet LOAEC: not defined	MRID 44007911
Mallard duck (*Anas platyrhynchos*), 22 weeks old	0, 4, 8, 20, and 40 ppm in diet. **Working Note: Using a food consumption factor of 0.07 kg food/kg bw, 40 ppm corresponds to an NOAEL of 2.8 mg/kg bw. See Section 4.1.2.2 for details.**	No mortality attributable to treatment or overt signs of toxicity. No effect on food consumption (details not given in publication). No significant impact on any reproductive parameters. No neuropathology.	O'Grodnick et al. 1998a[2]
Northern bobwhite quail (*Colinus virginianus*), 19 weeks old	0, 4, 13, 40, and 125 ppm in diet. **Working Note: Using a food consumption factor of 0.07 kg food/kg bw, 125 ppm corresponds to an NOAEL of 8.75 mg/kg bw. See Section 4.1.2.2 for details.**	No mortality attributable to treatment or overt signs of toxicity. No effect on food consumption (details not given in publication). No significant impact on any reproductive parameters. No neuropathology.	O'Grodnick et al. 1998a[2]

[1] Studies specified with only an MRID number are taken from U.S. EPA/OPP 2008b or U.S. EPA/OPP 2009.

[2] The two MRID submissions in the above table and the O'Grodnick et al. (1998a) paper cover the same studies. Separate entries are given to differentiate between the EPA and published summaries. The paper looks OK. The EPA clearly went over the data.

Appendix 4: Toxicity to Terrestrial Invertebrates

A4 Table 1: Acute Toxicity 179
A4 Table 2: Field or Field Simulation Studies 183

A4 Table 1: Acute Toxicity
Note: This table is sorted by group (Honey bee; Lepidoptera; Other Insects; Other Invertebrates. Studies within in each group are sorted by author.

Species	Exposure	Response	Reference
Honey bee			
Honey bee (*Apis mellifera*)	0.16 EC formulation plus Leaf Act 80A surfactant , 0.0168 hg a.i./ha to alfalfa, foliar contact	High initial mortality (≈95-100%%) with diminishing mortality by 6 hours (≈40-50%) and very little mortality by 24 hours (≈0-15%%).	Chukwudebe et al. 1997b
Honey bee (*Apis mellifera*)	95.9% a.i. Contact assay	LD_{50} 3.5 (0.6-17) ng/bee Slope: 2.6 (0.3-4.8) Working Note: U.S. EPA/OPP 2009a uses the 3.5 ng/bee toxicity value for risk characterization of insects.	U.S. EPA/OPP 2009, Table D6, MRID 42851530
Lepidoptera			
Spotted bollworm (*Earias vittella*), 2nd instars. Organisms collected from cotton fields yearly over a six year period to assay for resistance.	Proclaim (Syngenta), 19 g/L EC. Leaf dip bioassays. Mortality assessed at 48 hours.	Year / LC_{50} (mg/L) / RF[a] 1999 / 0.22 / 1 2000 / 0.28 / 1.3 2003 / 0.49 / 2.2 2004 / 0.22 / 1 2005 / 0.96 / 4.4 2006 / 1.11 / 5 [a] Resistance factor: LC_{50} for 1999 divided by LC_{50} for specified year.	Ahmad and Arif 2009
Obliquebanded leafroller (*Choristoneura Rosaceana*), two populations collected from areas of low and heavy pesticide use, second instar.	Proclaim (Syngenta), 50 g/kg SG. Artificial liquid diet. Dietary: Concentrations appear to be reported as concentration in diet. Mortality assessed at 48 hours.	Sensitive strain: LC_{50}: 0.096 mg/L Tolerant strain: LC_{50}: 0.15 mg/L	Ahmad et al. 2002
Leaf worm (*Spodoptera litura*), second instar larvae.	Proclaim (Syngenta), 19 EC. Leaf dip bioassays. Mortality assessed at 48 hours.	LC_{50}: 1.39 mg/L Slope: 1.74 Working note: Shallow slope	Ahmad et al. 2006

A4 Table 1: Acute Toxicity

Note: This table is sorted by group (Honey bee; Lepidoptera; Other Insects; Other Invertebrates. Studies within in each group are sorted by author.

Species	Exposure	Response	Reference
Five species of lepidopteran pest species (specified in Column 3)	Proclaim 0.16 EC, >90% B1a and 10% < B1b). **Dietary:** Artificial diet assays for 6 days. Concentrations refer to 50 µL aliquots pipette to diet (volume not specified). Dietary concentrations cannot be estimated.	Species / LC_{50} (µg/L): Beet armyworm: 2.7 Tobacco budworm: 5.5 Diamondback moth: 1.4 Cabbage looper: 4.1 Fall armyworm: 2.2 Note Units: µg/L.	Argentine et al. 2002
Two species of lepidopteran pest species (Column 4)	Proclaim 0.16 EC, >90% B1a and 10% < B1b). **Dietary/Contact:** Foliar spray with 6 day exposure period. Exposure appears to be mixed contact/dietary.	Species / LC_{50} (µg/L): Beet armyworm: 5.0 Tobacco budworm: 5.7	Argentine et al. 2002
Codling moth (*Cydia pomonella*), neonate larvae	Affirm (Syngenta), 9.5 g/L EC formulation with wetting adjuvant, apple leaves . Foliar Contact, 2 hour exposures	Time after treatment (h) / LC_{50} (mg/L): 0: 0.59 24: 0.28 48: 2.77 Working note: This shows a higher residual activity than in Chukwudebe et al. 1997b.	Ioriatti et al. 2009
Codling moth (*Cydia pomonella*), neonate larvae	Affirm (Syngenta), 9.5 g/L EC formulation with wetting adjuvant. Oral x 2 weeks: dip assay using apples sprayed at various concentrations. No data on concentrations in apples.	LC_{50}: 0.026 (0.008-0.05) mg/L Slope: 0.89 (±0.10) Working Note: Shallow slope. Not clear if common or natural log was used.	Ioriatti et al. 2009
Tortricid moth (*Cydia molesta*), neonate larvae.	Affirm (Syngenta), 9.5 g/L EC formulation with wetting adjuvant Oral x 2 weeks: dip assay using apples sprayed at various concentrations. No data on concentrations in apples.	LC_{50}: 0.046 (0.023-0.079) mg/L Slope: 1.12 (±0.06) Working Note: Shallow slope. Not clear if common or natural log was used.	Ioriatti et al. 2009
Beet armyworm (*Spodoptera exigua*), neonate larvae.	0.16 EC (Merck), 3 bioassays (2 contact and oral), responses assayed at 96 hours. Diet preparation involved 50µL of test concentration mixed with 500 µL of diet.	Bioassay / LC_{50} (mg/L): Tower: 0.006 Airbrush: 0.005 Diet: 0.001 Note: This is the lowest dietary LC_{50}. Comparable values reported for this species by Argentine et al. (2002).	Jansson et al. 1997

A4 Table 1: Acute Toxicity

Note: This table is sorted by group (Honey bee; Lepidoptera; Other Insects; Other Invertebrates. Studies within in each group are sorted by author.

Species	Exposure	Response	Reference
Tobacco budworm, (*Heliothis virescens*), neonate larvae.	0.16 EC (Merck), 3 bioassays (2 contact and oral), responses assayed at 96 hours. Diet preparation involved 50µL of test concentration mixed with 500 µL of diet.	Bioassay / LC_{50} (mg/L): Tower: 0.004 Airbrush: 0.004 Diet: 0.004 Cannot determine doses in mg/kg bw.	Jansson et al. 1997
Corn earworm (*Helicoverpa zea*) adult males, feral.	Dietary, emamectin benzoate (MK-0244 5% SG), serial dilutions from 0.0125 to 200 mg/L. These appear to be dietary concentrations. Feeding Period: 30 minutes.	Duration after Exposure / LC_{50} (mg/L): 24-hours: 0.718 48-hours: 0.525 96-hours: 0.182	Lopez et al. 2010
Corn earworm (*Helicoverpa zea*) adult males, feral.	Dietary, emamectin benzoate (MK-0244 5% SG), Test 1: 0.0125 to 0.1 mg/L Test 2: 0.05 to 1 mg/L Feeding Period: ≤30 minutes.	Test 1: No dose-related decrease in fecundity. Test 2: Significant reduction in larval hatching at concentrations as low as 0.0125 mg/L.	Lopez et al. 2010
Beet armyworm (*Spodoptera exigua*), larvae	Proclaim 5SG, 5% w/w, liquid diet to field collected populations and one commercial population (ECOGEN). Exposure Period: 120 hours (5 days). Working Note: 0.1 mL of pesticide a various reported concentrations added to 3 mL of artificial diet. Thus, dilution factor of ≈0.033 for estimating the concentration of emamectin benzoate in the diet relative to reported LC_{50}s	As reported: Laboratory Population LC_{50}: 2.4 mg/L Wild Populations LC_{50}: 0.2 to 0.6 mg/L As Dietary Concentration: Laboratory Population LC_{50}: ≈0.08 mg/L Wild Populations LC_{50}: ≈0.007 to 0.02 mg/L Working note: Not clear why the field strains were more sensitive. This pattern was not apparent for other insecticides tested.	Mascarenhas et al. 1998
Obliquebanded Leafroller (*Choristoneura rosaceana*)	Proclaim 5 soluble granules. Two colonies to assess development of resistance. Leaf Dip Bioassays: Leaves of *Vicia faba* soaked at different concentrations for 5 seconds and then dried.	Sensitive strain LC_{50}: 0.03 (0.03-0.06) mg/L Tolerant strain LC_{50}: 0.09 (0.05-0.3) mg/L Resistance factor: 2.3 (1.2-5)	Waldstein and Reissig 2000

A4 Table 1: Acute Toxicity

Note: This table is sorted by group (Honey bee; Lepidoptera; Other Insects; Other Invertebrates. Studies within in each group are sorted by author.

Species	Exposure	Response	Reference
Other insects			
Geocoris punctipes, adults Beneficial heteropteran insect predators	Proclaim 0.16 EC, Foliar (mixed contact and oral) exposure up to 72 hours at a residue rate equivalent to 0.008 kg/ha on soybean foliage	Mortality (%) Duration (hrs): 24 / 48 / 72 No surfactant: 11.7% / 0% / 5%	Boyd and Beothel 1998
Nabis roseipennis, adults Beneficial heteropteran insect predators	Proclaim 0.16 EC, Foliar (mixed contact and oral) exposure up to 72 hours at a residue rate equivalent to 0.008 kg/ha on soybean foliage with and without a surfactant, Dyne-Amic.	Mortality (%) Surfactant: None / With 4 hrs: 3.3% / 6.7% 48 hrs: 16.7% / 6.7% 72 hrs: 0.0% / 13.3%	Boyd and Beothel 1998
Podisus maculiventris, adults Beneficial heteropteran insect predators	Proclaim 0.16 EC, Foliar (mixed contact and oral) exposure up to 72 hours at a residue rate equivalent to 0.008 kg/ha on soybean foliage with and without a surfactant, Dyne-Amic.	Mortality (%) Surfactant: None / With 4 hrs: 10.0% / 10.0% 48 hrs: 0.0% / 0.0% 72 hrs: 5.0% / 5.0%	Boyd and Beothel 1998
Podisus maculiventris, nymphs Beneficial heteropteran insect predators	Proclaim 0.16 EC, Foliar (mixed contact and oral) exposure up to 72 hours at a residue rate equivalent to 0.008 kg/ha on soybean foliage with and without a surfactant, Dyne-Amic.	Mortality (%) Surfactant: None / With 4 hrs: 5.0% / 10.0% 48 hrs: 0.0% / 5.0% 72 hrs: 6.0% / 5.0%	Boyd and Beothel 1998
Diglyphus isaea (Leafminer parasitoid) Hymenoptera.	0.16 EC formulation plus Leaf Act 80A surfactant , 0.0168 hg a.i./ha to alfalfa, foliar contact	High initial mortality (≈90%) with diminishing mortality by 24 hours (≈25%) and very little mortality by 72 hours (≈0%).	Chukwudebe et al. 1997b
Other Invertebrates			
Pine wood nematode (*Bursaphelenchus xylophilus*) Nematoda**.**	Injection of pine trees with emamectin benzoate in a Japanese formulation (Shot Wan Liquid Formulation) intended to prevent pine wilt disease	IC_{50}: 0.017 µg/g tree tissue IC_{90}: 0.031 µg/g tree tissue Working Note: This paper is discussed in some detailed in Sections 3.2.3.4. and 3.2.3.6.	Takai et al. 2004

A4 Table 2: Field or Field Simulation Studies

Species	Exposure	Response	Reference
Fall army worm (*Spodoptera frugiperda*)	Leaf residue: Proclaim 5SG, cotton leave or white flowers treated with Proclaim SG at a rate equivalent to 0.01 kg a.i./ha. Larvae exposed two hours after the plant material was treated.	Mortality rates of 54.3% to 92% after 24 to 48 hours	Adamczyk et al. 1999
Tobacco budworms (*Heliothis virescens*)	MK-2445 SG, field application to cotton in Louisiana (rates in column 3).	Application Rate (lb a.i./ac) / % Mortality: 0 / 12%; 0.005 / 48%; 0.0075 / 54%; 0.01 / 92%; 0.015 / 96%; 0.02 / 96%. Working note: Could do BMD.	Gore et al. 1998
Trichogramma brassicae, egg parasitoid	Direct Spray: Proclaim, 50 g/L (NOS), direct spray at a concentration of 1.5 g/100 L (15 mg/L).	100% mortality in 1 hours. Cannot estimate exposure in mass per unit area.	Hewa-Kauge et al. 2003
Trichogramma brassicae, egg parasitoid	Leaf Residue Contact: Tomato plants sprayed to runoff at 15 mg/L. Insects exposed on Days 1, 1, 4, and 7 after spraying. 24 hour observation period	Mortality rates of about 20% to 30% on DATs 0, to 7. See Figure 2 of publication.	Hewa-Kauge et al. 2003
Trichogramma brassicae, egg parasitoid	Field application to tomato beds. The application rate appears to be at 110 L/ha of 1.5 g/100L = 1.65 g/ha but this is not clear 0.0016 lb a.i.ac. Not clear.	Significant but not substantial reduction in survival (≈4% relative to water control). See Figure 4 in publication.	Hewa-Kauge et al. 2003
Insidious Flower Bug (*Orius insidiosus*), beneficial predator	Field applications to cotton at rates of 0.005 and 0.01 kg a.i./ha (formulation not specified). Monitored survival of males, females, and nymphs for 0, 1, 2, 3, and 7 DAT. See Tables 2-7 in paper.	Year / Rate Kg/ha / NOEC Days*: M 2000 0.005 7; 0.01 7; F 2000 0.005 3; 0.01 7; N 2000 0.005 7; 0.01 7; M 2001 0.005 7; 0.01 >7; F 2001 0.005 7; 0.01 7; N 2001 0.005 7; 0.01 7. M=Males; F=Females; N=Nymphs *Days to NOEC based on significant differences in mortality from controls.	Studebaker and Kring 2003a

Appendix 5: Toxicity to Fish.

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A5 Table 1: Acute Toxicity (Aqueous)

Species	Exposure	Response	Reference[1]
Rainbow trout (*Oncorhynchus mykiss*)	MK-244, 95.9% a.i., 96 hours, flow-through	LC_{50}: 174 (146-207) µg a.i./L Slope: 7.0 (3.6-10.3)	MRID 42851529
Bluegill sunfish (*Lepomis macrochirus*)	MK-244, 95.9% a.i., 96 hours, flow-through	LC_{50}: 180 (140-240) µg a.i./L Slope: N/A	MRID 42743602
Fathead minnow (*Pimephales promelas*)	MK-244, 94.6% a.i., 96 hours, flow-through	LC_{50}: 194 (157-257) µg a.i./L Slope: N/A	MRID 43850106
Sheepshead minnow (*Cyprinodon variegatus*)	MK-244, 95.9%, 96 hours, flow-through	LC_{50}: 1,430 (1250-1670) µg a.i./L Slope: 7.9 (4.6-11)	MIRDs 43393003 and 44007914

[1] Studies specified with only an MRID number are taken from U.S. EPA/OPP 2008b or U.S. EPA/OPP 2009a.

A5 Table 2: Acute Toxicity (Oral)

Species	Exposure	Response	Reference[1]
Atlantic salmon (*Salmo salar*)	50 µg/kg bw/day (in feed) for 7 days. Note: The precision of the estimated dose is not clear.	No signs of toxicity reported. No apparent adverse effects based on comparisons to the control groups for mortality rates and body weights.	Armstrong et al. 2000

[1] This studies were conducted to assess efficacy in the control of sea lice (e.g., *Lepeophtheirus salmonis*), parasitic marine copepods that impact farmed Atlantic salmon populations.

A5 Table 3: Chronic toxicity

Species	Exposure	Response	Reference[1]
Fathead minnow (*Pimephales promelas*)	MK-244, 94.6%, Early life-stage, flow-through	NOEC: 6.5 µg a.i./L LOEC: 12 µg a.i./L based on reductions in larval survival (74%), total length (9%), wet weight (27%), dry weight (26%), and biomass (21%).	MRID 43850107

[1] Taken from U.S. EPA/OPP 2008b.

Appendix 6: Toxicity to Aquatic Invertebrates.

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A6 Table 1: Acute toxicity

Species	Exposure	Response	Reference[1]
Daphnia magna	MK-244, 95.9%, 48 hours, flow-through	EC_{50}: 1 (0.84-1.19) µg a.i./L Slope: 4.7 (3.2-6.2)	MRID 42743603
Eastern oyster (*Crassostrea virginica*)	MK-244, 95.9%, 96 hours, flow-through	EC_{50}: 490 (410-590) µg a.i./L Slope: 4.9 based on shell deposition.	MRID 43393002
Mysid shrimp (*Americamysis bahia*)	MK-244, 95.9%, 96 hours, flow-through	EC_{50}: 0.04 (0.035-0.046) µg a.i./L Slope: 8.1 (4.9-11.2) Working Note: Unlike the case with fish, estuarine arthropods are more sensitive than freshwater arthropods.	MRID 43393001

[1] Studies specified with only an MRID number are taken from U.S. EPA/OPP 2008b or U.S. EPA/OPP 2009a.

A6 Table 2: Chronic toxicity

Species	Exposure	Response	Reference[1]
Daphnia magna	MK-244, 95.9%, flow-through, 21-days, life-cycle	NOEC: 0.088 µg a.i./L LOEC: 0.16 µg a.il./L based on egg production, survival of young, and growth of young.	MRID 43393004

[1] Studies specified with only an MRID number are taken from U.S. EPA/OPP 2008b and U.S. EPA/OPP 2009a.

A6 Table 3: Field Studies

Species	Exposure	Response	Reference
Mixed sea zooplankton	Three applications of about 315 g of emamectin benzoate at three times over a 10 month period after an initial application of cypermethrin (78 g). Estimated concentration of emamectin benzoate in the water column of 0.01 ng/L	Normal seasonable variations in invertebrate abundance. No apparent adverse effects. Working note: Given the very low concentrations estimated in the water column, the lack of adverse effects would be expected. Marginal use in hazard identification.	Willis et al. 2005