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Picloram

Human Health and Ecological Risk Assessment

Final Report

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

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Submitted by:
Patrick R. Durkin
Syracuse Environmental Research Associates, Inc.
8125 Solomon Seal
Manlius, New York 13104

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ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADD	attention-deficit disorder
ADHD	attention-deficit hyperactivity disorder
AEL	adverse-effect level
a.e.	acid equivalent
a.i.	active ingredient
APHIS	Animal and Plant Health Inspection Service
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
bw	body weight
CBI	confidential business information
cm	centimeter
CNS	central nervous system
DAA	days after application
DAT	days after treatment
DER	data evaluation record
d.f.	degrees of freedom
EC_x	concentration causing X% inhibition of a process
EC_{25}	concentration causing 25% inhibition of a process
EC_{50}	concentration causing 50% inhibition of a process
EFED	Environmental Fate and Effects Division (U.S. EPA/OPP)
ExToxNet	Extension Toxicology Network
F	female
FH	Forest Health
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FQPA	Food Quality Protection Act
g	gram
GLP	Good Laboratory Practices
ha	hectare
HED	Health Effects Division (U.S. EPA/OPP)
HQ	hazard quotient
IARC	International Agency for Research on Cancer
IC_{50}	concentration causing 50% inhibition
IRIS	Integrated Risk Information System
K	potassium (salt)
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
MCS	multiple chemical sensitivity
mg	milligram
mg/kg/day	milligrams of agent per kilogram of body weight per day
mL	milliliter
mM	millimole
MMAD	mass median aerodynamic diameter
mPa	millipascal, (0.001 Pa)
MOS	margin of safety
MRID	Master Record Identification Number
MSDS	material safety data sheet
MSMA	monosodium methanearsonate
MW	molecular weight
NAWQA	USGS National Water Quality Assessment
NCI	National Cancer Institute
NCOD	National Drinking Water Contaminant Occurrence Database
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOEL	no-observed-effect level
NOS	not otherwise specified
NRC	National Research Council
NTP	National Toxicology Program
OM	organic matter
OPP	Office of Pesticide Programs
OPPTS	Office of Pesticide Planning and Toxic Substances
OSHA	Occupational Safety and Health Administration
Pa	Pascal
PBPK	physiologically-based kinetic
POEA	polyoxyethyleneamine (surfactant)
ppm	parts per million
RBC	red blood cells
RED	re-registration eligibility decision
RfD	reference dose
S.A.	South American
SERA	Syracuse Environmental Research Associates
TEP	typical end-use product
T.G.I.A.	Technical grade active ingredient
TIPA	Triisopropanolamine
TRED	Tolerance Reassessment Eligibility Decision
TLm	Median tolerance limit (equivalent to LC_{50})
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

Picloram is a herbicide used in the control of a number of broadleaf weeds and undesirable brush. Picloram is used in Forest Service programs primarily for the control of noxious weeds. Tordon K and Tordon 22K are the formulations of picloram currently used by the Forest Service. Both formulations are produced by Dow AgroSciences as a liquid containing the potassium salt of picloram. Technical grade picloram also contains low concentrations of hexachlorobenzene. Hexachlorobenzene is classified as a carcinogen, and the carcinogenic risks associated with applications of picloram are considered quantitatively in this risk assessment.

Workers are not at substantial risk from exposures to either picloram or hexachlorobenzene—i.e., all of the upper bound HQs are less than 1 at the maximum anticipated application rate for picloram of 1 lb a.e./acre. Confidence in this assessment is relatively high. For workers, the risk characterization is based on exposure rates used in all Forest Service risk assessments, and these rates are derived from studies which include worker applications of picloram. Irritation and damage to the eyes can result from exposure to relatively high levels of picloram (i.e., placement of picloram directly onto the eye). In addition, repeated exposures to a Tordon formulation leads to skin sensitization in experimental mammals. From a practical perspective, eye irritation is likely to be the only overt toxic effect as a consequence of handling picloram. This effect can be minimized or avoided by prudent industrial hygiene practices during the handling of picloram formulations.

For members of the general public, the only exposure scenario that leads to an HQ above the level of concern (HQ=1) is the upper bound HQ for the longer-term consumption of contaminated vegetation (HQ=2) at the maximum anticipated application rate of 1 lb a.e./acre. This scenario would not lead to an exceedance in the level of concern at more typical application rates of 0.5 lb a.e./acre or less. While the HQ of 2 at the maximum application rate is a concern, the scenario for the longer-term consumption of contaminated vegetation may be unlikely in most instances because vegetation sprayed directly with picloram will evidence visible damage.

Like most effective herbicides, picloram poses the greatest risks to terrestrial plants. Even so, there are substantial differences in the sensitivity of various species of terrestrial plants to picloram. For sensitive species of terrestrial plants, particularly some species of dicots, HQs associated with direct spray, spray drift, and runoff are substantially above the level of concern. The exposure assessments on which these HQs are based involve conservative assumptions. Site-specific or region-specific refinements to the exposure assessments would probably lead to lower HQs. Nonetheless, it is apparent that picloram should be applied with care in order to prevent or minimize damage to nontarget, sensitive species of plants. Conversely, other species of plants, particularly some species of monocots, are much less sensitive to picloram. For these tolerant species, the HQs are below the level of concern, except in the event of a direct spray.

Risks to terrestrial animals are much less certain than risks to sensitive species of terrestrial plants. Exposures of terrestrial animals to contaminated water do not lead to apparent risks even in the case of an accidental spill. For contaminated vegetation or prey, none of the central estimates of exposure (i.e., the most likely events) result in HQs that exceed the level of concern (HQ=1). At the maximum anticipated application rate of 1 lb a.e./acre, upper bound HQs that

exceed the level of concern are associated with the consumption of contaminated grasses (i.e., food items which contain the highest concentrations of picloram) by a small mammal (HQ=3). This HQ would reach a level of concern at an application rate of about 0.33 lb a.e./acre. For longer-term scenarios, the consumption of contaminated grasses leads to upper bound HQs that exceed the level of concern for a small mammal (HQ=12), a 400 gram mammal (HQ=3), a large mammal (HQ=1.5), and a small bird (HQ=9). At the typical application rate of 0.25 lb a.e./acre, all of these upper bound HQs would be at or below the level of concern except for the small mammal and the small bird. Direct toxic effects on terrestrial invertebrates as well as terrestrial microorganisms cannot be ruled out but do not appear to be substantial. Because of effects on terrestrial vegetation, secondary effects on terrestrial animals may occur due to changes in habitat quality and/or food availability. These secondary effects could be beneficial to some species and detrimental to other species.

Based on expected concentrations of picloram in surface water, all central estimates of the HQs are below the level of concern for fish, aquatic invertebrates, and aquatic plants. No risk characterization for aquatic-phase amphibians can be developed because no directly useful data are available. Upper bound HQs exceed the level of concern for longer-term exposures in sensitive species of fish (HQ=3) and peak exposures in sensitive species of algae (HQ=8). It does not seem likely that either of these HQs would be associated with overt or readily observable effects in either fish or algal populations. In the event of an accidental spill, substantial mortality would be likely in both sensitive species of fish and sensitive species of algae.

1. INTRODUCTION

1.1. Chemical Specific Information

This document provides risk assessments for human health effects and ecological effects to support an assessment of the environmental consequences of using picloram in Forest Service vegetation management programs. This risk assessment is an update to previous USDA Forest Service risk assessments of picloram (SERA 1999, 2003).

In the preparation of this risk assessment, an updated literature search of picloram was conducted using TOXLINE. Additional sources of information were used including the U.S. EPA Reregistration Eligibility Decision document on picloram and related risk assessments (U.S. EPA/ODW 1987; U.S. EPA/OPP 1994a,b,c; 1995a,b; 1998a; 1999; 2009a; U.S. EPA/OWRS 1992) as well as a more recent ecological risk assessment on picloram by U.S. EPA/OPP (2009a). Other sources of relevant literature were identified through reviews and risk assessments in the open literature (Beyond Pesticides 2007; Bovey and Scifres 1971; Cal EPA 1997; Cox 1998; Dow AgroSciences 2002; Dow Chemical Company 2009; Environment Canada 1999; EXTOXNET 1996; FAO 2004; Health Canada 2007; IARC 1991; HSDB 2010; Kookana et al. 1998; Sassaman et al. 1984; Schulz et al. 1986; Trevathan 2002; U.S. DOE 2000; WSDOT 2006). Generally, these reviews are used only to identify published studies to ensure adequate coverage of the literature.

In the previous Forest Service risk assessment (SERA 2003), a large number of registrant submissions on picloram and picloram formulations were identified. Of these, 64 submissions – i.e., full copies of the studies submitted to the U.S. EPA – were kindly provided by the U.S. EPA Office of Pesticide Programs. The U.S. EPA/OPP no longer provides full copies of registrant studies for risk assessments conducted in support of activities outside of U.S. EPA/OPP. Consequently, summaries of some of the registrant submissions from SERA (2003) are included in the current Forest Service risk assessment. In the bibliography, these studies are specified as MRID03 at the end of the citation. Copies of all key registrant submitted studies cited in the 2003 risk assessment, however, were requested from and provided by Dow AgroSciences [n=41]. In the bibliography, these studies are specified as MRID03r at the end of the citation. In addition, newer registrant studies not cited in the previous Forest Service risk assessment were also requested from and provided by Dow AgroSciences [n=20]. In the bibliography, the new registrant studies not included in the previous risk assessment are specified as MRID11 at the end of the citation. Information from other registrant submitted studies taken from various U.S. EPA/OPP risk assessments are designated in the body of the current Forest Service risk assessment only by MRID number and the information is referenced to the U.S. EPA/OPP document from which the information is taken.

Also in the preparation of the current risk assessment, a FOIA was been submitted to the U.S. EPA/OPP for a current list of all registrant submitted studies of all registrant submitted studies (HQ-FOI-01717-11). This bibliography was kindly provided by U.S. EPA/OPP and is cited in the current risk assessment, as needed, to clarify whether or not specific studies have been submitted to the U.S. EPA/OPP.

The U.S. EPA/OPP is in the process of reviewing the registration of many pesticides (http://www.epa.gov/oppsrrd1/registration_review). The review of picloram, however, is not scheduled to begin until 2014 (U.S. EPA/OPP 2010, p. 13). Thus, while the registration review may impact the next Forest Service risk assessment on picloram, the EPA's review has no impact on the current Forest Service risk assessment.

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 discussed in Section 1.1, the current Forest Service risk assessment is an update to previous risk assessments on picloram (SERA 1999, 2003). At some point in the future, the Forest Service will update this risk assessment again and welcomes input from the general public and other interested parties on the selection of studies included in the risk assessment. This input is helpful, however, only if recommendations for including additional studies specify why and/or how the new or not previously included information would be likely to alter the conclusions reached in the risk assessments.

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

Some of the calculations, however, are cumbersome. For those calculations, EXCEL workbooks (sets of EXCEL worksheets) are included as attachments to this risk assessment. Attachment 1 is an EXCEL workbook covering terrestrial applications of picloram. This workbook includes all of the standard exposure scenarios typically used in Forest Service risk assessments of herbicides. Attachment 2 is a custom workbook for exposure scenarios associated with hexachlorobenzene as a contaminant of picloram. As discussed in Section 3.2, only a subset of chronic exposure scenarios is developed for hexachlorobenzene. The worksheets in Attachments

1 and 2 provide the detail for the estimates cited in the body of the document. Documentation for the use of these workbooks is presented in SERA (2010a, 2011a).

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. Program Description

2.1 Overview

Picloram is a herbicide used in the control of a number of broadleaf weeds and undesirable brush. Picloram is used in Forest Service programs primarily for the control of noxious weeds. Rights-of-way management is a minor use for picloram. Tordon K and Tordon 22K are the formulations of picloram currently used by the Forest Service. Both formulations are produced by Dow AgroSciences as a liquid containing the potassium salt of picloram (24.4% w/v). This is equivalent to a concentration of 2 lb a.e./gallon. The remaining 75.6% of the formulation consists of inerts, including a polyglycol polymer. Very little information is available on the polyglycol polymer. Technical grade picloram also contains low concentrations of hexachlorobenzene. Hexachlorobenzene is classified as a carcinogen and the carcinogenic risks associated with applications of picloram are considered quantitatively in the current risk assessment.

The most common application methods for Tordon involve backpack (selective foliar), boom spray (broadcast foliar), and aerial applications. Mist blower application of picloram is not permitted. The labeled application rates for picloram range from 0.125 to 1 lb a.e./acre. Typically, the Forest Service uses rates in the lower part of this range and, based on Forest Service use statistics, some applications may be below the lower bound of the labeled rates.

2.2. Chemical Description and Commercial Formulations

Picloram is a systemic herbicide that is registered for the post-emergent control of broadleaf weeds and woody plants. Picloram was developed in the early 1960s by Dow Chemical Company (Hamaker et al. 1963; Tomlin 2004).

Picloram is the common name for 4-amino-3,5,6-trichloropicolinic acid. As illustrated in Figure 1, picloram is a pyridine carboxylic acid, a class of herbicides including aminopyralid, clopyralid, fluroxypyr, and triclopyr. Structurally, picloram is most closely related to aminopyralid, differing only in the presence of a chlorine at the 5-carbon position on the picolinic acid ring of picloram which is absent in aminopyralid. As discussed further in Section 4.1.2.5 (hazard identification for terrestrial plants), the mechanism of action of picloram is like that of other auxin mimicking herbicides and involves mimicking the auxin plant growth hormone, indoleacetic acid (Retzinger and Mallory-Smith 1997). A summary of the chemical and physical properties of picloram is given in Table 1.

The formulations of picloram used most often by the Forest Service are Tordon K and Tordon 22K, both of which are produced by Dow AgroSciences. The current risk assessment is focused on these two formulations but it is intended to support of the use of other equivalent formulations. Both Tordon K and Tordon 22K are formulated as a liquid containing the potassium salt of picloram (24.4% w/v a.i. or ≈21.07% a.e.). Both of these formulations contain picloram at a concentration of 2 lb a.e./gallon.

The remaining 75.6% of the formulations consists of inerts. The identity of all inerts has been disclosed to the U.S. EPA as part of the registration process and this information has been reviewed in the preparation of this risk assessment (Lanman 1996a,b,c). This information is classified as CBI (confidential business information) under Section 7(d) and Section (10) of

FIFRA. Some inerts - i.e., those listed under SARA Title III, Section 313 - are specified on the product material safety data sheets and can be publicly disclosed. On the MSDS's for Tordon K and Tordon 22K, one inert is listed as a polymer of ethylene oxide, propylene oxide and di-sec-butyl-phenol (CAS No. 69029-39-6). As discussed further in Section 3.1.14 (Inerts and Adjuvants), very little specific information is available on this inert. This compound appears to be used as a surfactant. The U.S. EPA has recently exempted this compound from the requirement for tolerances when used in herbicide formulations at concentrations of no more than 30% (w/w) (CFR 2010) .

There is no indication that Tordon K and Tordon 22K differ substantially and the publically available information on the product labels and material safety data sheets (MSDSs) suggests that these two formulations may be identical. Specifically, the MSDSs indicate that these two formulations have identical physical and chemical properties including a specific gravity of 1.16 (at 20°C) and a vapor density of 1.14. As summarized in Table 1, the specific gravity of picloram is 0.895. Thus, the specific gravity given on the MSDSs appears to apply to the formulations and not the active ingredient. While it is possible that the two formulations could contain differing amounts of minor inerts, the identical chemical properties out to three significant digits suggest that the two formulations do not differ substantially.

Technical grade picloram contains hexachlorobenzene as a contaminant. The original registration standard for picloram required that the level of hexachlorobenzene in technical grade picloram was no more than 200 ppm and this requirement is maintained in Reregistration Eligibility Decision (RED) for picloram (U.S. EPA 1995a, p. 9-11). The picloram RED also indicates that the registrant had certified that the concentration of hexachlorobenzene in technical grade picloram is no greater than 100 ppm. As discussed further in Section 3.1.15.1 (Impurities), Dow AgroSciences currently indicates that the concentration of hexachlorobenzene in technical grade picloram is not greater than 3 ppm.

As discussed further in Section 3.1.15 (Impurities and Metabolites), all pesticides contain contaminants but the impact of contaminants is typically encompassed by the fact that most toxicity studies are conducted on technical grade material which includes both the active ingredient and impurities. For most endpoints associated with the human health risk assessment (Section 3.1) as well as for potential hazards to nontarget species in the ecological risk assessment (Section 4.1), this general approach is applicable for hexachlorobenzene as well as other contaminants in picloram. As discussed in Section 3.1.10 (Carcinogenicity and Mutagenicity), however, hexachlorobenzene is classified as a carcinogen while picloram itself is not. In addition and as summarized in Table 2, hexachlorobenzene is much more persistent than picloram. Because of the greater persistence of hexachlorobenzene relative to picloram, exposures to hexachlorobenzene associated with applications of picloram will not parallel exposures to picloram. Consequently, the current risk assessment develops a separate exposure assessment for the exposures of humans to picloram and quantitatively considers cancer risks associated with exposures to hexachlorobenzene following applications of picloram. This is similar to the approach used by the U.S. EPA/OPP (1998a,b) as well as the approach used in the previous Forest Service risk assessment on picloram (SERA 2003).

2.3. Application Methods

The most common methods of ground application for Tordon involve backpack (selective foliar) and boom spray (broadcast foliar) operations. In selective foliar applications, the herbicide sprayer or container is carried by backpack and the herbicide is applied to selected target vegetation. Application crews may treat up to shoulder high brush, which means that chemical contact with the arms, hands, or face is plausible. To reduce the likelihood of significant exposure, application crews are directed not to walk through treated vegetation. Usually, a worker treats approximately 0.5 acre/hour with a plausible range of 0.25–1.0 acre/hour.

Boom spray is used primarily in rights-of-way management. Spray equipment mounted on tractors or trucks is used to apply the herbicide on either side of the roadway. Usually, about 8 acres are treated in a 45-minute period (approximately 11 acres/hour). Some special truck mounted spray systems may be used to treat up to 12 acres in a 35-minute period with approximately 300 gallons of herbicide mixture (approximately 21 acres/hour and 510 gallons/hour) (USDA 1989, p. 2-9 to 2-10). The Tordon formulations may not be applied with a mist-blower.

Both Tordon formulations are labeled for aerial applications. Aerial applications may be made using helicopters. Tordon is applied under pressure through specially designed spray nozzles and booms. The nozzles are designed to minimize turbulence and maintain a large droplet size, both of which contribute to a reduction in spray drift. In aerial applications, approximately 40–100 acres may be treated per hour.

2.4. Mixing and Application Rates

The specific application rates used in a ground application vary according to local conditions and the nature of the target vegetation. Application rates may be expressed in various units such as gallons of formulation per acre (used in most product labels), lb a.i. per acre (designating the amount of the potassium salt of picloram), or lb a.e. per acre (designating the amount of the picloram acid equivalents). Unless otherwise specified, all application rates and other expressions of amounts are based on acid equivalents.

Application rates of ¼ to 2 quarts Tordon/acre are recommended on the product labels and no more than 2 quarts Tordon/acre may be applied in a single growing season. The application rates of ¼ to 2 quarts Tordon/acre are equivalent to 0.0625–0.5 gallons Tordon per acre. Given that there is 2 lbs picloram a.e./gallon in the Tordon formulations, these rates correspond to 0.125 to 1 lb picloram a.e./acre.

The use of picloram in Forest Service Programs for fiscal year 2004, the most recent year for which data are available, is summarized in Table 4. Picloram is used in Forest Service Programs primarily in noxious weed control (78.2% of total pounds used) and agricultural weed control (20.4% of total pounds used). No information is available on the specific uses that are classified in the Forest Service use report as *agricultural weed control*. The other minor use (totaling about 1.4% of total pounds used) includes rights-of-way management. Based on the total amount used and number of acres treated, the application rates are about 0.25 lb/acre for noxious weed control, 0.5 lb/acre for agricultural weed control, and 0.75 lb/acre for rights-of-way management.

The EXCEL workbooks that accompany this risk assessment are based on a unit application rate of 1 lb a.e./acre which is equivalent to the maximum application rate. The consequences of using lower application rates are discussed in the risk characterization for human health (Section 3.4) and ecological effects (Section 4.4).

For forestry applications, mixing volumes of 5 to 25 gallons of water per acre are recommended for aerial applications. Recommended mixing volumes for ground applications range from 10 to 100 gallons of water per acre. For this risk assessment, the extent to which a picloram formulation is diluted prior to application primarily influences dermal and direct spray scenarios, both of which are dependent on the 'field dilution' (i.e., the concentration of picloram in the applied spray). Exposure and subsequent risk increases as the concentration of picloram in the field solution increases. For this risk assessment, the lowest dilution will be taken at 5 gallons/acre, the minimum recommended for aerial applications. The highest dilution (i.e., that which results in the lowest risk) will be based on 100 gallons of water per acre, the highest application volume recommended for ground applications. The typical dilution rate will be taken as 30 gallons/acre, approximately the geometric mean of the range recommended for ground applications $[(10\times100)^{0.5}=31.6]$.

It should be noted that the selection of application rates and dilution volumes in this risk assessment is intended as a basis for discussion. Forest Service analysts may use different input variables such as application rates and dilution volumes in order to assess potential human health or ecological risks in specific projects that involve applications of picloram.

2.5. Use Statistics

Forest Service risk assessments attempt to characterize the use of an herbicide or other pesticide in Forest Service programs relative to the use of the herbicide or other pesticide in agricultural applications. Forest Service pesticide use reports up to the year 2004 are available on the Forest Service web site (http://www.fs.fed.us/ foresthealth/pesticide/reports.shtml). Information on agricultural use is compiled by the U.S. Geological Survey (http://water.usgs.gov/nawqa/pnsp/usage/maps/). In addition, detailed pesticide use statistics compiled by the state of California (http://www.calepa.ca.gov/).

The USDA Forest Service tracks and reports pesticide use by geographical areas referred to as "*Regions*". The Forest Service classification divides the U.S. into nine regions designated from Region 1 (Northern) to Region 10 (Alaska). [Note: There is no *Region 7* in the Forest Service system.] The use of picloram in Forest Service regions for the year 2004 (the most recent year for which statistics are available) is illustrated in Figure 2 and detailed further in Table 3.

Virtually all picloram use by the Forest Service (96.7% in terms of total pounds) occurs in three contiguous Forest Service regions: Regions 1 (Northern, 40.2%), Region 2 (Rocky Mountain, 38.5%), and Region 4 (Intermountain, 18%). Relatively low uses of picloram are reported in Region 6 (Pacific Northwest, 2.8%) and Region 8 (Southern, 0.5%). No uses of picloram in Forest Service programs are reported for 2004 by other Forest Service regions. The total amount of picloram reported for 2004 by all Forest Service regions is about 18,700 pounds.

Much greater amounts of picloram are used in agriculture. The USGS provides national agricultural use statistics for 2002 and reports a total agricultural use of about 1,900,000 lbs. As

illustrated in Figure 3, about 1,700,000 lbs of picloram were applied to pastureland is 2002. Much less picloram is applied to other commodities – i.e., about 170,000 lbs to hay, 10,000 lbs to cropland in summer fallow, about 9000 lbs to wheat, 650 lbs to barley, and 80 lbs to other grains. As noted in Table 3, the total annual use of picloram by the Forest Service for 2004 was about 18,700 lbs, which is somewhat less than 1 percent of the agricultural use [≈18,700 lbs ÷ ≈1,900,00 lbs = 0.0098 or 0.98%]. The states associated with the greatest agricultural uses of picloram do not parallel the geographic distribution of use by the Forest Service. The greatest concentration of picloram uses in agricultural appear to occur in the south central states comprising parts of Forest Service Region 8 (i.e., Texas and Oklahoma) and Region 9 (i.e., Missouri).

California provides very detailed annual use reports for pesticides (http://www.cdpr.ca.gov/docs/pur/) and many Forest Service risk assessments will use the more recent California use statistics to elaborate on forestry versus agricultural uses of pesticides. This approach, however, is not applicable for picloram because very little picloram is used in California. Based on the most recent report for 2009 (CDPR 2010, p. 482), the annual use of picloram in California was only 1.50 lbs and the nature of the use is specified only as *Regulatory Pest Control* (1.48 lbs) and *Rangeland* (0.02 lb). This minor use in California may reflect a misapplication in that picloram no longer appears to be registered in California (Rutz 1997; www.greenbook.net).

As indicated in Section 2.2 and discussed further in Section 3.1.15.1, technical grade picloram contains hexachlorobenzene as a contaminant at a concentration no greater than 3 ppm – i.e., three parts per million or a proportion of 0.000003. As discussed above, the most recent use statistics from the Forest Service indicate that about 18,700 pounds of picloram were used by the Forest Service in 2004. Taking this quantity of technical grade picloram as an approximation of annual Forest Service use, the amount of hexachlorobenzene released with picloram would be about 0.2 lb [66,000 lb picloram x 0.000003 lb HCB/lb picloram = 0.198 lb HCB]. Based on the most recent release statistics from ATSDR (2002), a total of 13,818 lbs of hexachlorobenzene were released to the environment in 1998. This amount is greater than the 0.2 lb that may be associated with the use of picloram by the Forest Service by a factor of about 69,000 [13,818 lbs ÷ 0.2 lb = 69,090]. Relative to the total release of hexachlorobenzene from all uses, the release of hexachlorobenzene during the course of picloram applications in Forest Service programs is extremely small.

3. HUMAN HEALTH

3.1. HAZARD IDENTIFICATION

3.1.1. Overview

The toxicity of picloram is characterized relatively well in a series of standard toxicity studies conducted with rats, mice, dogs, rabbits, and guinea pigs. These studies are summarized in the U.S. EPA Reregistration Eligibility Decision (RED) document (U.S. EPA/OPP 1995a) as well as a science chapter prepared by the Health Effects Division of U.S. EPA/OPP (1994a) in support of the RED. The current Forest Service risk assessment was conducted using full copies of several of the key studies or cleared reviews of these studies.

The U.S. EPA/OPP standard classification system for pesticides indicates that picloram and its potassium salt are not very toxic according to acute oral and acute dermal exposures (Category III/IV). Picloram and the potassium salt of picloram are classified as relatively toxic in acute inhalation studies (Category I/II); however, this is an artifact of the inhalation studies available on picloram and the potassium salt of picloram. For the most part, the acute effects of picloram, the potassium salt of picloram, as well as the Tordon K and Tordon 22K formulations covered in the current risk assessment do not differ substantially. One notable exception involves skin sensitization. There is no indication that either picloram or its potassium salt is a skin sensitizer, with the exception of a standard assay in guinea pigs in which exposure to Tordon 22K resulted in skin sensitization.

Longer-term toxicity studies with picloram most often note effects on the liver and kidneys, with effects on the liver generally occurring at lower doses than effects on the kidneys. *In vivo* studies offer no indication that picloram causes specific developmental or reproductive effects. In addition, *in vivo* studies do not suggest that picloram causes effects on the immune system, the nervous system, or endocrine function. A recent *in vitro* study found that picloram can damage cultures of neuroblastoma cells. The concentration at which this effect has been demonstrated (about 1200 mg/L) is much higher than the concentration of picloram in blood likely to occur following *in vivo* exposures.

Picloram itself is not carcinogenic. Technical grade picloram, however, contains hexachlorobenzene, which is classified as a potential human carcinogen. Because carcinogenicity is generally considered to be a nonthreshold effect (i.e., some risk may exist even at low levels of exposure), carcinogenicity is an endpoint of concern in the current risk assessment. Dow AgroSciences indicated that the concentration of hexachlorobenzene in technical grade picloram is no more than 3 ppm and that this concentration is reduced in the Tordon 22 and Tordon 22K formulations. The extent of the reductions, however, is not clear due to proprietary restrictions on the release of information on the Tordon formulations. Thus, the assumption is made that an application rate for picloram formulations of 1 lb a.e./acre is functionally equivalent to an application rate of 0.000003 lb hexachlorobenzene/acre [1 lb/acre x 0.000003 hexachlorobenzene/picloram]. This estimate is used in the exposure assessment (Section 3.2) to develop quantitative estimates of exposures to hexachlorobenzene. These exposure estimates as well as the estimate of the cancer potency of hexachlorobenzene (Section 3.3.5) are used to characterize cancer risks associated with hexachlorobenzene as a contaminant of picloram.

3.1.2. Mechanism of Action

As noted in Section 2.2 and discussed further in Section 4.1.2.5, the mechanism of action of picloram in plants involves mimicking the auxin plant growth hormone, indoleacetic acid (Retzinger and Mallory-Smith 1997). This mechanism of action, however, is not relevant to mammals; moreover, a specific mechanism of action for the effects of picloram on mammals has not been clearly identified.

The effects most often noted in mammals following longer-term exposures to picloram involve the liver and kidney (Section 3.1.5); furthermore, the chronic RfD for picloram is based on effects in the liver (Section 3.3). Picloram is a weak acid, and, at physiologic pH, picloram will be predominantly in the anion (acid) form. The liver has a non-specific anion active transport system (Hagenbuch 2010; Burckhardt and Burckhardt 2011). It seems unlikely, however, that this system has a substantial impact on the sensitivity of the liver to picloram since other organs, particularly the kidney, also have extremely efficient anion active transport systems (You 2004). The liver also has a major involvement in the metabolism of many chemicals, both naturally occurring and synthetic. Picloram, however, is not metabolized substantially by the liver or other organs (Section 3.1.3); thus, there is no basis for asserting that metabolic activation could account for the apparent sensitivity of the liver to picloram.

As discussed further in Section 3.1.6, a study by Reddy et al. (2011) indicates that picloram can cause damage in mice neuroblastoma cell cultures. Nonetheless, this *in vitro* effect occurred at concentrations of 5 mM or about 1,200 mg/L [5 mMoles/L x 241.5 mg/mMole = 1,207.5 mg/L]. As discussed further in the following subsections (Pharmacokinetics), concentrations of 1200 mg/L are far above those that will occur following plausible *in vivo* exposures to picloram.

3.1.3. Pharmacokinetics and Metabolism

3.1.3.1. General Considerations

As noted in Section 2.2 and illustrated in Figure 1, picloram is structurally similar to several other auxin mimicking herbicides, like aminopyralid (SERA 2007c), clopyralid (SERA 2004), fluroxypyr (SERA 2009), and triclopyr (SERA 2003b). All of these compounds as well as other auxin herbicides, like 2,4-D (SERA 2006), are weak acids. This class of compounds is typically well absorbed after oral exposure, rapidly concentrated in the kidney, and excreted via a well-characterized active transport mechanism. As discussed in the 2,4-D risk assessment (SERA 2006a), this mechanism of active transport involves active secretion of the acid by the proximal tubules of the kidney in a manner similar to the excretion of paraminohippuric acid (PAH). Since this active transport mechanism can become saturated, the pharmacokinetics of weak acids tend to exhibit dose-dependent patterns in which the acid concentrations in blood and/or tissues increase disproportionately as the dose increases beyond the point at which excretion is saturated.

The U.S. EPA/OPP requires standard metabolism studies in rats including both intravenous (i.v.) and oral administration. Nolan et al. (1980) and Reitz et al. (1989) are two such registrant-submitted studies. As discussed in U.S. EPA/OPP (1994a, p. 9), these studies adequately characterize the pharmacokinetics and metabolism of picloram in rats. The study by Nolan et al.

(1980) used ^{14}C-ring-labeled picloram administered to male rats at i.v. doses of 14 and 160 mg/kg bw and oral doses of 9.6 and 1634 mg/kg bw. In the oral dosing studies, peak plasma concentrations were about 300 mg/L plasma at the dose of 1634 mg/kg bw and 6 mg/L at the dose of 9.6 mg/kg bw. The study by Reitz et al. (1989) used ^{14}C-ring-labeled picloram administered to female rats at 10 mg/kg bw (both i.v. and oral) as well as a single oral dose of 1000 mg/kg bw. Both studies demonstrate that picloram is rapidly absorbed following oral administration and rapidly excreted following i.v. or oral administration with most of the dose recovered as unmetabolized picloram in the urine (≈70 to 85%) and feces (≈5 to 25%). In the study by Reitz et al. (1989), somewhat more picloram was recovered in the high dose group, compared with the low dose group, which suggests that a possible saturation of kidney excretion might have occurred in the high dose group. In both studies, the excretion of picloram followed a two-compartment model with an initial rapid excretion followed by a slower rate of excretion.

In addition to the pharmacokinetic studies in rats, Nolan et al. (1984) conducted a pharmacokinetic study in humans. In this study, volunteers (six male Caucasians) were administered oral doses of 0.5 and 5.0 mg/kg in grape juice as well as dermal doses of 2 mg/kg. The dermal phase of the study is discussed in the following subsection. As with the studies in rats, the excretion of picloram following oral exposures was characterized by a two-compartment model with half-lives of about 1 and 19 hours. Picloram was rapidly absorbed with an average oral first order absorption rate constant of about 2 hours^{-1}. More than 75% of the administered picloram was eliminated after 6 hours, and more than 90% of the administered dose was eliminated after 72 hours, primarily in the urine. Although Nolan et al. (1984) does not provide a tabular summary of concentrations of picloram in blood, it appears from Figure 1 in the study that the peak blood concentrations were about 0.35 mg/L at the low dose (0.5 mg/kg bw) and 3.5 mg/L at the high dose (5.0 mg/kg bw). Thus, the plasma concentrations are proportional to the doses, and there is no indication of possible saturation of kidney excretion.

As discussed further in Section 3.2 (exposure assessment), most exposures to picloram will be far less than 5 mg/kg bw. Thus, the maximum concentrations of picloram in whole blood will be substantially less than 3.5 mg/L—i.e., the maximum concentration in blood noted in the high dose group from Nolan et al. (1983). This detail is significant in terms of interpreting the recent study by Reddy et al. (2011) which noted damage to mice neuroblastoma cell cultures at a picloram concentration of about 1200 mg/L, which is more than 340 times greater than the blood concentration associated with a dose of 5 mg/kg bw[1200 mg/L ÷ 3.5 mg/L ≈ 342.86].

3.1.3.2. Dermal Absorption

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

Two types of dermal exposure scenarios are considered: immersion and accidental spills. In the scenarios involving immersion, the concentration of the chemical in contact with the surface of the skin is assumed to remain constant or at least nearly so. As detailed in SERA (2007), the calculation of absorbed dose for dermal exposure scenarios involving immersion requires an

estimate of the dermal permeability coefficient (K_p) expressed in cm/hour, and the rate of absorption is assumed to be essentially constant. In exposure scenarios involving direct sprays or accidental spills where the compound is deposited directly on the skin, the concentration or amount of the chemical on the surface of the skin is assumed to be the limiting factor in dermal absorption. For these scenarios first-order dermal absorption rate constants (k_a), expressed as a proportion of the deposited dose absorbed per unit time—e.g., $hour^{-1}$—are used in the exposure assessment.

3.1.3.2.1. First-Order Dermal Absorption

As noted in Section 3.1.3.1, the dermal absorption of picloram in humans was studied by Nolan et al. (1984). Nolan et al. (1984) report a first-order dermal absorption rate constant of 0.056 $hour^{-1}$ with a range of 0.031 to 0.075 $hour^{-1}$ (Nolan et al. 1984, Table 1, column 6). As detailed in Appendix 9, however, this estimate is not consistent with the urinary excretion given by Nolan et al. (1984). A reanalysis of the urinary excretion data from this study, also detailed in Appendix 9, indicates that the data in the study by Nolan et al. (1984) is consistent with a first-order dermal absorption rate constant of 5.0 (3.0 to 7.1) x 10^{-5} $hour^{-1}$.

In the absence of experimental data, Forest Service risk assessments generally estimate first-order dermal absorption rates based on quantitative structure activity relationships (QSAR), as documented in SERA (2007a). The algorithm on which these estimates are based is developed from the analysis of dermal absorption rates for compounds with K_{ow} values ranging from 0.0015 to 3,000,000 and molecular weights ranging from 60 to 400 g/mole. As indicated in Table 1, the reported K_{ow} values for picloram range from 0.89 (USDA/ARS 1995) to 79.4 (Tomlin 2004). The higher K_{ow} from Tomlin (2004) is for the protonated form of picloram, which is applicable only to highly acidic solutions. The lower K_{ow} of 0.89 from USDA/ARS (1995) is specifically associated with pH values in the range of 5 to 9. While this pH range is rather broad, the average is a pH of 7 (i.e., a neutral solution), which seems most relevant to dermal exposures. Using the QSAR method from SERA (2007a) with the molecular weight of 241.5 g/mole and K_{ow} of 0.89, the estimated first-order dermal absorption rate constants are approximately 1.3 x10^{-3} (5.1x10^{-4} to 3.5x10^{-3}) $hour^{-1}$. The calculation of these rates is detailed in Worksheet B03b of Attachment 1 (the EXCEL workbook for picloram). The central estimate of 1.3 x10^{-3} is about a factor of 26 above the central estimate of 5 x 10^{-5} $hour^{-1}$ estimated from the study by Nolan et al. (1984). Given the human data from Nolan et al. (1984), the estimates based on quantitative structure activity relationships are not used.

For this risk assessment, the estimated dermal absorption rate of 5.0 (3.0 to 7.1) x 10^{-5} $hour^{-1}$ is used based on the analysis in Appendix 9 of the urinary excretion data from Nolan et al. (1984). The Nolan et al. (1984) study is well documented, and there is no basis for using the higher estimated dermal absorption rates from Worksheet B03b nor the higher rate constants reported by Nolan et al. (1984).

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 contact with a constant concentration of the pesticide. As discussed further in Section 3.2, this type of exposure scenario is assumed for workers wearing grossly contaminated gloves as well as members of the general public swimming in water

contaminated with picloram. This type of exposure scenario requires an estimate of dermal permeability (K_p) in units of cm/hour.

No experimental data are available on the dermal permeability rate of picloram. In the absence of experimental data, Forest Service risk assessments generally use a QSAR algorithm developed by the EPA (U.S. EPA/ORD 1992, 2007). This approach is discussed in further detail in SERA (2007a). As with the algorithm for estimating the first-order dermal absorption rate constant (Section 3.1.3.2.1), the algorithm developed by the U.S. EPA/ORD (1992, 2007) is based on molecular weight and K_{ow}. The algorithms for estimating the K_p are identical to those used in the estimate of the first-order dermal absorption rate constants (i.e., a molecular weight of 241.5 g/mole and K_{ow} of 0.89).

The algorithm developed by the U.S. EPA/ORD (1992, 2007) is derived from an analysis of 95 organic compounds with K_{ow} values ranging from about 0.0056 to 309,000 and molecular weights ranging from approximately 30 to 770. This ranges of values for K_{ow} and molecular weight encompass the estimates of the corresponding values for picloram.

Details of the implementation of the algorithms are given in Worksheet B03a in the EXCEL workbooks for picloram (Attachment 1). The algorithm developed by the U.S. EPA/ORD (1992, 2007) results in an estimated dermal permeability (K_p) of about 5.6×10^{-5} (2.8×10^{-5} to 1.1×10^{-4}) cm/hour.

As discussed in Section 3.1.3.2.1, the QSAR algorithms used to estimate the first-order dermal absorption rate for picloram yield somewhat higher estimates than those based on urinary excretion from the study by Nolan et al. (1984). It is possible that the QSAR methods developed by U.S. EPA/ORD (1992, 2007) might overestimate the K_p for picloram. In the absence of any experimental data, however, the QSAR estimates of the K_p for picloram are used without modification.

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, p. 320 ff). Under the assumption of first-order elimination, the first-order elimination rate constant (***k***) is inversely related to the half-life ($\boldsymbol{T_{50}}$) [$\boldsymbol{k} = \ln(2) \div \boldsymbol{T_{50}}$]. If a chemical with a first-order elimination rate constant of ***k*** is administered at fixed time interval (***t****) between doses, the body burden after the $\boldsymbol{N^{th}}$ dose ($\boldsymbol{X_{N\ Dose}}$)relative to the body burden immediately following the first dose ($\boldsymbol{X_{1\ Dose}}$) is:

Equation 1

$$\frac{X_{N\ Dose}}{X_{1\,Dose}} = \frac{(1 - (e^{-kt*})^N)}{1 - e^{-kt*}}$$

As the number of doses (***N***) increases, the numerator in the above equation approaches a value of 1. Over an infinite period of time, the plateau or steady-state body burden ($\boldsymbol{X_{Inf}}$) can be calculated as:

Equation 2

$$\frac{X_{Inf}}{X_1} = \frac{1}{1 - e^{-kt^*}} \cdot$$

In applying the plateau principal to compounds such as picloram which display a biphasic elimination pattern, terminal half-lives should be used. In general, whole-body half-lives are most appropriate for estimating steady-state body burdens. Because picloram is eliminated very rapidly in the urine, however, the terminal blood half-lives of 18.6 (4.3 to 40.8) hours reported by Nolan et al. (1984) can serve as a reasonable basis for approximating the steady state body burden. Converting the terminal blood half-lives to days [18.6 (4.3 to 40.8) hours ÷ 24 hours/day = 0.775 (0.179 to 1.7) days], the terminal excretion rates are about 0.89 (0.41 to 3.87) $days^{-1}$ [k_e = ln(2) ÷ 0.775 (0.179 to 1.7) $days^{-1}$]. Assuming daily doses (t* = 1 day) and substituting the excretion rates into the above equation for the plateau principal, the estimated plateau in the body burden after daily doses over a prolonged period of time would be about 1.7 (1.02 to 3) [1 ÷ (1 – $e^{-0.775\ (0.179\ to\ 1.7)}$)]. In other words, over very prolonged periods of exposure, the maximum increase in the body burden of picloram in humans should be no more than a factor of 3.

3.1.4. Acute Oral Toxicity

The standard acute oral toxicity studies are typically used to determine LD_{50} values—i.e., the treatment dose estimated to be lethal to 50% of the animals. LD_{50} values are not used directly to derive toxicity values as part of the dose-response assessment in Forest Service risk assessments. Even so, comparing the LD_{50} values for the active ingredient to the LD_{50} values for the formulations may be useful in assessing the potential impact of inerts in pesticide formulations.

For picloram, acute oral LD_{50} values are available for picloram acid (Jeffrey 1987a), the potassium salt of picloram (Hayes et al. 1986; Jeffrey et al. 1987b), and Tordon 22K (Jeffrey et al. 1987c). These studies are summarized in Appendix 1, Table 1. With the exception of the study by Hayes et al. (1986) which is published in the open literature, these acute oral toxicity studies were conducted by the registrant and submitted to the U.S. EPA in support of the registration for picloram. Full copies of the registrant studies were used in the preparation of this risk assessment.

The acute oral LD_{50} for the Tordon 22K formulation is given as an indefinite LD_{50} of >5000 mg formulation/kg bw in male and female rats (Jeffrey et al. 1987c). The Tordon 22K formulation is specified as containing 20.36% picloram a.e. Thus, the formulation LD_{50} is equivalent to an indefinite LD_{50} of about >1153 mg a.e./kg bw. As discussed in Section 2.2, the Tordon formulations considered explicitly in the current Forest Service risk assessment both contain picloram at a nominal concentration of about ≈21.07% a.e. The difference between the 20.36% used by Jeffrey et al. (1987c) and the nominal concentration of 21.07% in Tordon K and Tordon 22K is insubstantial and may reflect minor variability in different batches of the formulations. In this formulation study, no adverse effects were noted in any of the five male or five female rats.

The bioassay of technical grade picloram acid yielded an LD_{50} of >5000 mg a.e./kg bw in male rats and >4012 mg a.e./kg bw in female rats (Jeffrey et al. 1987a). While this study only involved a single dose of 5000 mg a.e./kg bw in male rats, doses of 500 and 2500 mg a.e./kg bw

were assayed in female rats and no effects in female rats were noted at these lower doses. Thus, this study on technical grade picloram is consistent with the formulation study (Jeffrey et al. 1987c), in which no adverse effects were noted in male or female rats at a dose equivalent to 1153 mg a.e./kg bw.

The LD_{50} studies on potassium salt of picloram are somewhat more difficult to interpret. In the bioassay by Jeffrey et al. (1987b), the test material is specified as a 38.8% solution of potassium picloram and referenced as a *Tordon K^+ salt liquor*, an intermediate in the production of Tordon, with a dark brown color. Jeffrey et al. (1987b) report an LD_{50} in male rats of >5000 mg test material/kg bw, which is equivalent to >1676 mg a.e./kg bw. For female rats, a definitive LD_{50} is reported as 3536 mg test material/kg, equivalent to about 1185 mg a.e./kg bw.

In the open literature study by Hayes et al. (1986), the test material is characterized as a 37.3% solution of potassium picloram, also with a dark brown color. Hayes et al. (1986) also note that the test material was highly alkaline, with a pH of 11.3. As detailed in Appendix 1 (Table 1), these investigators report LD_{50} values of 823 mg a.e./kg bw in male rats and 592 mg a.e./kg bw in females. These LD_{50} values are substantially below the corresponding values reported by Jeffrey et al. (1987b).

The reasons for the discrepancy between Hayes et al. (1986) and Jeffrey et al. (1987b) are not entirely clear. The review of picloram by U.S. EPA/OW (1992) concludes that the relatively low LD_{50} values obtained by Hayes et al. (1986) compared to the results of other investigators "*is probably due in part to the extreme alkalinity of the dosing solution*" (U.S. EPA/OW 1992, page V-3). This supposition may have merit; however, Jeffrey et al. (1987b) tested what appears to be a similar material, although the pH of the solution tested is not specified. In addition, the MSDS of both Tordon K and Tordon 22K indicate that the formulations are also alkaline, with a pH of 9-11.2. In terms of pathology, Jeffrey et al. (1987b) note focal hyperemia (excess blood) of the stomach. Hayes et al. (1986), however, report no damage in the stomachs of treated rats.

One pattern in the acute oral LD_{50} studies is that females appear to be somewhat more sensitive than males. This is evident in the studies with picloram acid (Jeffrey 1987a) as well as the potassium picloram solutions (Hayes et al. 1986; Jeffrey et al. 1987b). The magnitude of the difference, however, does not appear to be substantial. Hayes et al. (1986) is the only study that provides definitive LD_{50} values for both male and female rats, and, based on this study, females are more sensitive than males by about a factor of about 1.4 [954 mg a.i./kg ÷ 686 a.i. mg/kg ≈ 1.3907]. Based on the confidence intervals provided by Hayes et al. (1986), this difference is not statistically significant. Similarly, under the assumption that males and females are equally sensitive (i.e., probability equal to 0.5 for females evidencing a lower LD_{50} than males) the likelihood of three bioassays indicating that females are more sensitive is about 12.5% [0.5^3 = 0.125], which would not generally be viewed as statistically significant using the convention of p=0.05.

Data on the acute oral toxicity of picloram to species other than rats is sketchy, and no details of the studies in other species are available. Nonetheless, several reviews (HSDB 2011; Sassman et al. 1984; U.S. EPA/OW 1992) report oral LD_{50} values in rabbits, guinea pigs, mice, sheep, and cows, as well as rats. As summarized in Appendix 1, Table 1, the available definitive oral LD_{50}

values do not report any systematic differences in the relationship of the magnitude of the definitive LD_{50} values to body weight.

For acute oral toxicity studies, U.S. EPA/OPP (2010c) uses a ranking system for response ranging from Category I (most severe response) to Category IV (least severe response). Based on the available data, U.S. EPA/OPP (1994a, p. 3) classifies both picloram acid and potassium picloram as Category IV for male rats and Category III for female rats.

3.1.5. Subchronic or Chronic Systemic Toxic Effects

As discussed in SERA (2007a, Section 3.1.5), *subchronic* and c*hronic* are somewhat general terms which refer to studies involving repeated dosing. Some studies are designed to detect toxic endpoints, like reproductive and neurological effects. Except for some comments in this subsection on general signs of toxicity, these more specialized studies are discussed in subsequent subsections of this hazard identification. The focus of this subsection is toxicity studies designed to detect more general signs of systemic toxicity and to quantify no-observable-effect levels (NOAELs) for the identified endpoints as well as levels associated with adverse effects—i.e., lowest-observed-effect-levels (LOAELS).

The subchronic and chronic toxicity studies on picloram are summarized in Appendix 1 (Table A1-2), and an overview of these studies is given in Table 5. Although some subchronic dermal toxicity studies have been conducted on picloram (Section 3.1.11), most of the subchronic and chronic toxicity studies on picloram involve oral exposures. Most of these studies were submitted to the U.S. EPA in support of the registration of picloram and are summarized in EPA risk assessment documents on picloram (e.g., U.S. EPA 1994a, 1995a; U.S. EPA/ORD 1992). With the exception of the 1-year feeding study in dogs (MRID 40834301), discussed further below, cleared reviews or full copies of the subchronic and chronic studies were available for the conduct of the current risk assessment.

The most commonly reported effects associated with subchronic and chronic exposures to picloram involve the liver and the kidney. Except for the chronic study in mice (Stott et al. 1992), effects on the liver appear to be the most sensitive endpoint (i.e., Gorzinski et al. 1982; Landry et al. 1986). As indicated in Table 5 and discussed further in Section 3.3, the rat NOAEL of 20 mg/kg bw (Landry et al. 1986) is the basis for the U.S. EPA chronic RfD on picloram. In the chronic study by Landry et al. (1986), groups of 50 rats/sex/dose were fed picloram in the diet over a period of 2 years with interim sacrifices (10 rats/sex/dose) made at 6 months and 1 year. At the end of the 2-year exposure, the only statistically significant observations included an increase in liver size and an alteration in the staining properties of centrilobular hepatocytes in the 60 and 200 mg/kg/day dose groups. Both of these effects were more pronounced in males than in females. Increased liver weights as well as slight increases in the size and pallor of centrilobular hepatocytes were also seen in the 6- and 12-month interim sacrifices. While the U.S. EPA has classified 60 mg/kg/day as the LOAEL for this study (U.S. EPA 1992b, 1999), the U.S. EPA/OPP RfD workgroup (U.S. EPA/OPPTS 1994) "...felt that the LOAEL might have been higher". In other words, while effects were seen at 60 mg/kg/day, the magnitude and severity of these effects were not regarded with substantial concern by the workgroup. The lack of severe pathology either in the liver or the kidneys is common in the longer-term studies on picloram. As summarized in Table 5, the primary effects noted involve increases in organ weight, an acceleration of normal renal and hepatic lesions.

The 180-day subchronic study in dogs does report an increase in liver weight but no evidence of liver pathology at a dose of 35 mg/kg bw/day with a NOAEL of 7 mg/kg bw/day (Barna-Lloyd et al. 1982). This NOAEL in dogs is somewhat lower than the 20 mg/kg bw/day chronic NOAEL in rats from the study by Landry et al. (1986). As discussed by U.S. EPA/OPPTS (1994), the 7 mg/kg bw/day NOAEL in dogs was used as the basis of an earlier RfD on picloram. The decision to use the somewhat higher rat NOAEL appears to reflect the assessment by the U.S. EPA that the effects seen in dogs were not toxicologically substantial. In addition and as also summarized in Table 5, the 1-year feeding study in dogs yields a NOAEL of 35 mg/kg bw/day.

3.1.6. Effects on Nervous System

In severely poisoned animals, virtually any chemical may cause gross signs of toxicity which might be attributed to neurotoxicity—e.g., incoordination, tremors, or convulsions. A direct neurotoxicant, however, is defined as a chemical that interferes with the function of nerves, either by interacting with nerves directly or by interacting with supporting cells in the nervous system. This definition of a direct neurotoxicant distinguishes agents that act directly on the nervous system (direct neurotoxicants) from those agents that might produce neurological effects secondary to other forms of toxicity (indirect neurotoxicants). U.S. EPA has developed a battery of assays to test for neurotoxicity (U.S. EPA/OCSPP 2010), and U.S. EPA/OPP requires neurotoxicity studies for pesticides when standard toxicity studies or other considerations such as chemical structure suggest that concerns for effects on the nervous system are credible. The EPA has not required specialized neurotoxicity studies on picloram (U.S. EPA/OPP 1995a, 2009a).

In most standard subchronic and chronic rodent bioassays used and accepted by U.S. EPA for pesticide registration, brain morphology is assessed. The spinal cord and peripheral nerves (e.g., sciatic nerve) are usually evaluated only if there are other indications of neurotoxicity. As discussed in Sections 3.1.4, 3.1.5 and 3.1.9, the toxicology of picloram has been investigated in acute, subchronic, chronic, developmental, and reproductions studies in mammals. Relatively high doses of picloram may produce signs of toxicity which might be associated with neurotoxicity——e.g., convulsions in rats following acute lethal doses of picloram, as detailed in Section 3.1.4. Subchronic and chronic toxicity studies of picloram, however, do not report effects that might be associated with neurotoxicity (Section 3.1.5). As discussed in Section 3.1.9, excessive salivation has been noted at very high doses of potassium picloram (1000 mg a.i./kg bw or about 864 mg a.e./L) in one developmental study (Schroeder 1990). The toxicological significance of this observation is unclear, since this effect was not observed in the longer-term developmental study at the high dose of 1000 mg/kg bw/day (Breslin et al. 1991).

One *in vitro* study has been conducted to assess the potential neurotoxicity of picloram (Reddy et al. 2011). In this study, neuroblastoma cell cultures were exposed to picloram at a concentration of 5 mM or about 1200 mg/L for 48 hours. Signs of cytotoxicity were evidenced as decreased neuronal branching and neuron degeneration. While these results indicate that picloram will damage nerve cells *in vitro* at a concentration of about 1200 mg/L, the relevance of this observation to potential neurotoxicity in humans is questionable. As discussed in Section 3.1.3.1, the concentration of 1200 mg/L used in the study by Reddy et al. (2011) is several hundred times greater than the concentrations of picloram likely to be seen in humans. In

addition and as also discussed in Section 3.1.3.1, the metabolism study in rats by Nolan et al. (1984) notes a maximum concentration of picloram in plasma of 300 mg/L plasma at the dose of 1634 mg/kg bw. While peak concentrations of picloram in the plasma of rats might reach a concentration of 1200 mg/L following very high doses of picloram, it is not likely that concentrations of 1200 mg/L would be seen in nerve tissue. Combined with the lack the neurotoxicity from *in vivo* exposures of mammals to very high doses of picloram, the likelihood of observing damage to nerve tissue in humans or experimental mammals following exposures to picloram appears to be remote.

3.1.7. Effects on Immune System

There is very little direct information on which to assess the immunotoxic potential of picloram. The only studies specifically related to the effects of picloram on immune function are skin sensitization studies (Section 3.1.11). While these studies provide support for asserting that picloram may cause skin sensitization, they provide no information useful for directly assessing the immune suppressive potential of picloram.

Typical subchronic or chronic animal bioassays conduct morphological assessments of the major lymphoid tissues, including bone marrow, major lymph nodes, spleen and thymus (organ weights are sometimes measured as well), and blood leukocyte counts. These assessments can detect signs of inflammation or injury indicative of a direct toxic effect of the chemical on the lymphoid tissue. Changes in morphology/cellularity of lymphoid tissue and blood, indicative of a possible immune system stimulation or suppression, can also be detected. As discussed in Section 3.1.5, however, the subchronic and chronic toxicity studies on picloram failed to note any adverse effects in blood or other organs/tissues associated with immune function.

A commercial formulation of picloram and 2,4-D, Tordon 202C, has been shown to inhibit immune function in mice (Blakley 1997). The design of this study does not permit the determination of which agent caused the immune response or whether the immune response was attributable to a toxicological interaction of the two herbicides. This formulation is not used in Forest Service programs. In addition and as discussed in the Forest Service risk assessment on 2,4-D (SERA 2006), 2,4-D appears to be toxic to the immune system, and the observations by Blakley (1997) of the effect of Tordon 202C on immune function may be attributable to 2,4-D rather than picloram.

3.1.8. Effects on Endocrine System

Assessments of the direct effects of chemicals on endocrine function are most often based on mechanistic studies on estrogen, androgen, or thyroid hormone systems (i.e., assessments on hormone synthesis, hormone receptor binding, or post-receptor processing). 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). Picloram has been selected as one of the pesticides for which the screening assays are being required (U.S. EPA/OPP 2009b, p. 6). Results from the screening assays as well as the rationale for selecting picloram for the screening assays have not been located.

A 2-generation reproduction study of picloram (K salt) in CD rats reported no endocrine effects at doses as high as 1000 mg/kg/day (Breslin et al. 1991, as reviewed by U.S. EPA 1995b). Endocrine effect endpoints examined in this study included reproductive outcomes and

histopathological examination of tissues. In this study, renal effects and increased body weight gain were observed at 1000 mg/kg/day (i.e., the maximum tolerated dose that was tested). None of the other studies reviewed in this risk assessment provides evidence that exposure to picloram causes direct effects on the endocrine system.

While the Registration Eligibility Decision document for picloram (U.S. EPA/OPP 1995a) does not specifically address effects on endocrine function, U.S. EPA/OPP (1998d) provides the following assessment of the potential impact of picloram on endocrine function:

> *An evaluation of the potential effects on the endocrine systems of mammals has not been determined; however, no evidence of such effects was reported in the chronic or reproductive toxicology studies described above. There was no observed pathology of the endocrine organs in these studies. There is no evidence at this time that picloram causes endocrine effects.*
>
> U.S. EPA/OPP 1998a, p. 64492

As discussed above, this assessment provided in U.S. EPA/OPP (1998d) is consistent with the evaluation of picloram in the current risk assessment.

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 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 by the EPA 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.

In an oral gavage study with the potassium salt of picloram, doses of 0, 34, 172, or 344 mg a.e./kg/day were administered to New Zealand rabbits from days 6 to 18 of gestation (John et al. 1984). No effects were noted on offspring at the highest dose tested. The only effect of treatment observed in the adults was decreased body weight, which occurred at 172 mg a.e./kg/day with a NOAEL of 34 mg a.e./kg/day. Another gavage teratology study on the potassium salt of picloram was conducted in rats at doses of 0, 30, 150, or 298 mg a.e./kg/day on days 6-15 of gestation (Schroeder 1990). The only effect seen in this study was excessive salivation in dams at 298 mg a.e./kg/day with a corresponding NOAEL of 150 mg a.e./kg/day. No adverse reproductive effects were noted. Other teratology studies summarized in various EPA reviews (U.S. EPA 1992b, 1995b; 1999) involve salts or esters of picloram, which are not used in Forest Service programs.

As with potential effects on the immune system (Section 3.1.7), there may be greater concern for mixtures of picloram and 2,4-D. Exposure to Tordon 202c, a commercial formulation of picloram and 2,4-D, has been associated with adverse reproductive effects in mice (Blakley et al.

1989a,b,c). More recently, Oakes et al. (2002b) reported a statistically significant reduction in absolute and relative testicular weight (17and 26%, respectively) in male Sprague Dawley rats exposed to Tordon 75D (75 g a.e./L picloram and 300 g a.e./L 2,4-D) by gavage 5 days/week for 9 weeks. The reduction in testicular weight occurred in the absence of adverse reproductive effects (Oakes et al. 2002a). The dose of Tordon 75D associated with a statistically significant reduction in testicular weight was 37.5 mg/kg, the NOAEL was 18.7 mg/kg (Oakes et al. 2002b). Exposure to Tordon 75D did not result in male-mediated birth defects (Oakes et al. 2002a). Again, this formulation of 2,4-D and picloram is not used in Forest Service programs.

3.1.9.2. Reproduction Studies

Multi-generation reproduction studies typically involve dietary exposures of a group of rats or mice referred to as the *parental generation* or P_1. Male and female animals are selected from this group and mated. Exposure of the female continues through gestation and after delivery. Offspring from the parental generation, typically referred to as F_1, are then continued on dietary exposure through sexual maturity. The F_1 offspring are mated (and then referred to as the P_2 generation) producing an F_2 generation. This is the basic design of a "2-generation" study, although variations on this design are sometimes used, and occasionally the study is carried over to a third generation. Multi-generation reproduction studies typically focus on effects on reproductive capacity—i.e., the number of young produced and their survival. Teratogenicity studies, which are designed to assess the potential for producing birth defects, typically involve daily gavage exposure of the pregnant female (most often rats or rabbits) during sensitive periods of fetal development.

A 2-generation reproduction study was conducted on picloram acid. In this study, male and female rats were administered picloram in the diet at levels corresponding to doses at 0, 20, 200, or 1000 mg a.e./kg/day. Histopathological effects on the kidney as well as other signs of kidney damage were noted at 1000 mg a.e./kg/day. There were, however, no effects on reproductive performance (Breslin et al. 1991).

3.1.10. Carcinogenicity and Mutagenicity

3.1.10.1. Picloram

As summarized in Appendix 1 (Table 2), picloram has been assayed for carcinogenicity in life-time studies in both rats (Landry et al. 1986) and mice (Stott et al. 1992), and no increase in tumors was observed. Based on these studies, the Reregistration Eligibility Decision for picloram notes that the …*Agency has classified picloram as a Group E carcinogen (evidence of noncarcinogenicity for humans* (U.S. EPA/OPP 1995a, p. v). This position is repeated in other EPA reviews of picloram (U.S. EPA/OPP 1999).

Picloram has been tested for mutagenicity in a number of different test systems, and there is minimal evidence for mutagenicity in mammals. A review and detailed evaluation of the mutagenicity assays on picloram by U.S. EPA/OW (1992) concluded that:

> *No compelling evidence of a mutagenic effect in relevant biological systems was uncovered. Although picloram at a single reported dose was mutagenic in S. coelicolor, the weight of evidence from well-conducted microbial (Ames test),*

> *mammalian cell, and Drosophila mutagenicity studies tends to support the conclusion that picloram does not possess mutagenic activity*.
>
> U.S. EPA/OW 1992, pp. V19 to V20

Some additional studies report mutagenic activity in assays using higher plants. Mohammed and Ma (1999) observed a dose-dependent increase in *Tradescantia* (spiderwort) micronucleus formation. Tomkins and Grant (1976) observed that picloram treatment produced a statistically significant increase in the frequency of chromosome aberration in *Pastinaca sativa* (parsnips) growing in normal field conditions. While these studies may have some relevance in assessing potential effects in plants, they do not suggest a mutagenic risk in mammals.

Some commercial preparations of picloram are formulated as the isooctyl ester of picloram. The compound used to produce this ester (ethylhexyl phthalate) is a potential carcinogen (U.S. EPA/OPPTS 1994). Formulations of picloram as the ethylhexyl ester are not used by the Forest Service.

3.1.10.2. Hexachlorobenzene

As discussed further in Section 3.1.15.1, technical grade picloram as well as the Tordon K and Tordon 22K formulations of picloram are contaminated with hexachlorobenzene. While there is no basis for asserting that picloram itself poses a carcinogenic risk, hexachlorobenzene is classified as a potential human carcinogen.

For most impurities as well as endpoints associated with impurities, it is generally reasonable to assert that any hazards associated with the impurities are encompassed by the toxicity studies that are available on the technical grade active ingredient. This supposition can be made because toxicity studies are typically conducted on the technical grade pesticide or pesticide formulations (i.e., materials that contain both the active ingredient as well as impurities). For hexachlorobenzene as a contaminant in picloram, however, this assumption is not reasonable. As noted in the previous subsection, technical grade picloram does not appear to be carcinogenic. Nonetheless, technical grade picloram does contain hexachlorobenzene. While a detailed review of hexachlorobenzene is beyond the scope of this risk assessment, adequate information is available on hexachlorobenzene to classify this compound as a carcinogen (ATSDR 2002), and the U.S. EPA classifies hexachlorobenzene as a probable human carcinogen for which the data are adequate to consider risk quantitatively (U.S. EPA 1997). That technical grade picloram does not appear to be carcinogenic seems to reflect the low concentrations of hexachlorobenzene in picloram. Nonetheless, because carcinogenicity is frequently considered to be a nonthreshold effect (i.e., some risk may exist even at low levels of exposure), carcinogenicity associated with exposure to hexachlorobenzene is an endpoint of concern in the current risk assessment.

Details of the concentrations of hexachlorobenzene in picloram and picloram formulations are discussed in Section 3.1.15.1. This information is used in the exposure assessment (Section 3.2) to develop quantitative estimates of exposures. These exposures as well as the estimate of the cancer potency of hexachlorobenzene (Section 3.3.5) are used to characterize cancer risks associated with hexachlorobenzene as a contaminant of picloram. Conceptually, this approach is identical to that taken in U.S. EPA/OPP (1995a, p. v), the *Reregistration* Eligibility Decision document on picloram.

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 (U.S. EPA/OCSPP 2010). These studies are summarized in Appendix 1: Table A1-6 for skin irritation, Table A1-7 for skin sensitization, and Table A2-8 for eye irritation. For each endpoint, assays are available on both technical grade picloram and potassium picloram formulations. As with acute oral toxicity, the U.S. EPA/OPP uses a ranking system for responses ranging from Category I (most severe response) to Category IV (least severe response) for all three groups of endpoints discussed in this subsection (U.S. EPA/OPP 2010c).

3.1.11.1. Skin Irritation

Neither technical grade picloram (Jeffrey 1987c) nor Tordon K+ salt liquor (Jeffrey 1987f) caused dermal irritation in standard bioassays in rabbits. U.S. EPA/OPP (1994a, p. 3) classifies both of these compounds as Category IV (i.e., essentially non-irritating to the skin).

3.1.11.2. Skin Sensitization

As with skin irritation, technical grade picloram did not evidence skin sensitization in a standard assay using guinea pigs (Jeffrey 1987b). The Tordon 22K formulation, however, did cause delayed contact hypersensitivity (Haut and Bell 1997). Based on these studies, U.S. EPA/OPP (1994a, p. 3) classifies Tordon 22K (but not technical grade picloram) as a skin sensitizer.

The Tordon 22K formulation tested by Haut and Bell (1997) contained picloram acid at a concentration of 20.6%. This concentration is modestly different from the nominal concentration of picloram acid in Tordon K and Tordon 22K formulations (i.e., ≈21.07% a.e., as discussed in Section 2.2). This difference is insubstantial and probably reflects modest batch-to-batch variability typical in many pesticide formulations.

3.1.11.3. Ocular Effects

In standard eye irritation studies in rabbits, essentially identical effects on the eye (i.e., conjunctival irritation) are reported for technical grade picloram acid (Jeffrey 1987d), Tordon K+ salt liquor (Jeffrey 1987e), and Tordon 22K (Teeters 1973). Transient corneal involvement was observed in one of six rabbits in the assays with technical grade picloram and Tordon K+ salt liquor. Based on these assays, U.S. EPA/OPP (1994a) classifies both picloram and potassium picloram as a Category III eye irritant.

3.1.12. Systemic Toxic Effects from Dermal Exposure

As summarized in Appendix 1 (Table A1-4), standard single dermal dose toxicity studies in rabbits have been conducted on technical grade picloram (Jeffrey et al. 1987e), Tordon K+ salt liquor (Jeffrey et al. 1987d), as well as Tordon 22K (Gilbert 1996c; Jeffrey et al. 1987a). No mortality or signs of systemic toxicity were noted in any of the rabbits at doses of up to 5000 mg/kg bw. Based on these studies, U.S. EPA/OPP (1994a) classifies picloram and the picloram formulations as Category III. While this is not the least toxic category for acute oral toxicity, it should be noted that the Category III classification simply reflects the highest doses tested in the studies on picloram. For acute dermal toxicity, Category IV is used only if the acute dermal LD_{50} is >20,000 mg/kg bw (U.S. EPA/OPP 2010c, Table 1, p. 7-2).

As also summarized in Appendix 1 (Table A1-4), one subchronic toxicity study in rabbits is available on an aqueous solution of potassium picloram at doses of up to 650 mg a.e./kg/day given as 15 doses, 5 days/week for 3 weeks. No mortality or signs of systemic toxicity were noted. This conclusion is consistent with the subchronic oral toxicity of picloram in rats (Section 3.1.5) and the limited dermal absorption of picloram (Section 3.1.3.2).

3.1.13. Inhalation Exposure

As summarized in Appendix 1, Table A1-6, standard 4-hour inhalation studies in rats are available on picloram acid (Streeter et al. 1987a), Tordon K salt liquor (Streeter et al. 1987b), and Tordon 22K (McGuirk and Cieszlak 1996; Streeter et al. 1988). With the exception of the nose-only exposure study by McGuirk and Cieszlak (1996), the inhalation studies involved whole body exposures. The study using picloram acid (Streeter et al. 1987a) involved aerosol dust exposures. All of the other studies involved liquids (i.e., exposures to aerosol mists). Each study involved exposures to only a single concentration—i.e., 0.0351 mg/L for picloram (Streeter et al. 1987a), 1.63 mg/L for the salt liquor (Streeter et al. 1987b), 8.11 mg/L for Tordon 22K in the nose-only exposure study by McGuirk and Cieszlak (1996), and 0.65 mg/L in the study by Streeter et al. (1988). With the exception of the nose-only exposure study by McGuirk and Cieszlak (1996), all of the studies indicate that the test concentrations were the highest concentrations that could be achieved.

No treatment related deaths were observed in any of the studies. Other than transient losses in body weight, there were no treatment-related signs of toxicity. The highest concentrations used in each of the studies may be viewed as an indefinite LC_{50}—e.g., the study by Streeter et al. (1987a) on picloram acid may be viewed as indicating an LC_{50} of >0.0351 mg/L. The interpretation of the LC_{50} values is important in terms of classifying the inhalation toxicity of picloram. As with other acute endpoints, the EPA uses a ranking system to classify pesticides from Category I (most toxic) to Category IV (least toxic), as discussed in U.S. EPA/OPP (2010c, Table 1, p. 7-2),. For acute inhalation toxicity, Category I is defined as compounds with an acute inhalation toxicity of up to 0.05 mg/L and Category II is defined as compounds with an acute inhalation toxicity of >0.05 mg/L up to 0.5 mg/L. Thus, U.S. EPA/OPP (1995a, p. 12) classifies picloram as Category I and the salt liquor as Category II. As with the classification of picloram for dermal toxicity (Section 3.1.12), these classifications may be viewed as artifacts of the maximum concentrations that could be tested rather than an inherently high inhalation toxicity for either picloram or the salt liquor. U.S. EPA/OPP (1995a) does not provide a toxicity category for Tordon 22K. Based on the LC_{50} of >8.11 mg/L in the nose-only exposure study by McGuirk and Cieszlak (1996), Tordon 22K would be classified as Category IV, the least toxic category. Based on the LC_{50} of >0.65 mg/L in the whole-body exposure study by Streeter et al. (1988), Tordon 22K would be classified as Category III.

3.1.14. Adjuvants and Other Ingredients

U.S. EPA is responsible for regulating both the active ingredients (a.i.) in pesticide formulations as well as any other chemicals that may be added to the formulation. As implemented, these regulations affect only pesticide labeling and testing requirements. The term *inert* was used to designate compounds that are not classified as active ingredient on the product label. While the term *inert* is codified in FIFRA, some inerts can be toxic, and the U.S. EPA now uses the term *Other Ingredients* rather than *inerts* (http://www.epa.gov/opprd001/inerts/). For brevity, the

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

As indicated in Section 2, the commercial formulation of picloram used by the Forest Service is in the form of the potassium salt of picloram. Both of the Tordon formulations also contain the surfactant, Polyglycol 26-2 (CAS No. 069029-39-6). Surfactants are surface active agents that can disrupt cellular membranes and lead to a number of adverse effects (e.g., Warisnoicharoen et al. 2003). In an *in vitro* study on oxidative phosphorylation in submitochondrial particles derived from a marine algae, Oakes and Pollak (1999) noted that a commercial preparation of 2,4-D and picloram that contained Polyglycol 26-2 as well as Polyglycol 26-2 both inhibited oxidative function in the submitochondrial preparations at a concentration of about 0.01%. While this study clearly indicates that Polyglycol 26-2 will impact mitochondrial function *in vitro*, the implications for potential effects in humans at plausible levels of exposure are not apparent.

Other inerts used in Tordon K and Tordon 22K have been publicly disclosed by Northwest Coalition for Alternatives to Pesticides. These include emulsified silicone oil (CAS No. 63148-62-9), ethoxylated cetyl ether (CAS No. 9004-95-9), and potassium hydroxide (CAS No. 1310-58-3). All of these compounds are classified in U.S. EPA (2004) as List 4B, inerts of minimal concern. Potassium hydroxide is a GRAS (generally recognized as safe) compound and is approved as an indirect food additive (Clydesdale 1997). Both formulations also contain water as an inert.

The limited toxicity data on picloram formulations do not suggest substantial differences between the toxicity of the formulations (when dose is expressed in units of acid equivalents) and the toxicity of picloram (when dose is expressed in units of acid equivalents). Dow Chemical Co. (1970) specifically compared the acute oral toxicity of picloram (98.5% a.e.) to a Tordon formulation (22% a.e.). The acute oral LD_{50} in rats for the formulation was 8.2 mg a.e./kg and the corresponding LD_{50} for the formulation is given as approximately 10 mg a.e./kg (Dow Chemical Co. 1970).

The only qualitative difference in the activity of picloram and formulations of picloram involves skin sensitization. As discussed in Section 3.1.11.2, Tordon 22K but not picloram is a skin sensitizer according to standard assays for skin sensitization in guinea pigs.

3.1.15. Impurities and Metabolites

3.1.15.1. Impurities

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

As discussed in Section 3.1.10.2, an exception to this general rule involves carcinogens, most of which are presumed to act by non-threshold mechanisms. Because of the non-threshold

assumption, any amount of a carcinogen in an otherwise non-carcinogenic mixture may pose a carcinogenic risk. This is the situation with picloram.

As also discussed in Section 3.1.10.2, technical grade picloram contains hexachlorobenzene. As discussed in the Reregistration Eligibility Document for picloram, the maximum concentration of hexachlorobenzene in technical grade picloram is 200 ppm, and, as of 1995, the registrant (Dow AgroSciences) certified to the U.S. EPA/OPP that the actual concentration of hexachlorobenzene in technical grade picloram is less than 100 ppm (U.S. EPA/OPP 1995a, p. 11).

More recently, the Proposed Re-Evaluation Decision for Picloram by Health Canada (2007, p. 7) summarizes the results of assays of hexachlorobenzene in 204 batches of technical grade picloram. The average concentration of hexachlorobenzene in the samples was 3 ppm with a range of from 1 to 30 ppm. While the document from Health Canada (2007) does not specifically state the source of the samples, the only registered picloram products cited in the document are from Dow AgroSciences Canada Inc.

As part of the current Forest Service risk assessment, Dow AgroSciences was contacted and information on the current concentrations of hexachlorobenzene in technical grade picloram was requested. In response to this query, Dr. John Jachetta (Regulatory Sciences and Government Affairs Leader, Dow AgroSciences LLC) provided the following information:

> *The Picloram Technical (EPA Reg. No. 62719-187) Confidential Statement of formula states a nominal concentration of HCB of 7.4 ppm, but under current production practices in practices* [sic]*, this material does not exceed 3 ppm. … the manufacturing process for the K-salt end-use products of picloram* [i.e., Tordon K and Tordon 22K] *removes any trace HCB that may have carried through from the technical source to non-detectable levels.*
>
> John Jachetta, email to P. Durkin dated March 28, 2011

In response to a follow-up query concerning the limit of detection of hexachlorobenzene in picloram formulation, Dr. Jachetta indicated that the precise limit of detection is proprietary but that the limit of detection is …*substantially less than 1 ppm*. As discussed in Section 2.2, the nominal concentration of technical grade picloram in Tordon K and Tordon 22K is 21.07%. Thus, taking the maximum concentration of 3 ppm of hexachlorobenzene in technical grade picloram and assuming only dilution in the formulation, the maximum expected concentration of hexachlorobenzene in the Tordon formulations would about 0.6 ppm [3 ppm x 0.2107 = 0.6321 ppm]. Thus, the statement that the concentration of hexachlorobenzene in picloram formulations is <1 ppm is consistent with the statement that hexachlorobenzene in technical grade picloram is 3 ppm.

As discussed further in Section 3.2.3.4.3.2 (Exposure Assessment for hexachlorobenzene), the current risk assessment assumes that technical grade picloram contains hexachlorobenzene at a concentration of 3 ppm, based on the personal communication from John Jachetta. Thus, the assumption is made that an application rate for picloram of 1 lb a.e./acre is functionally equivalent to an application rate of 0.000003 lb hexachlorobenzene/acre (i.e., 0.000003 is equivalent to 3 ppm. Based on the communication from Dr. Jachetta, additional

hexachlorobenzene may be removed from picloram formulations; nonetheless, the available information does not allow for an estimation of how much hexachlorobenzene is removed.

3.1.15.2. Metabolites

As with contaminants, the potential effect of metabolites on a risk assessment is often encompassed by the available *in vivo* toxicity studies under the assumption that the toxicological consequences of metabolism in the species on which toxicity studies are available will be similar to those in the species of concern (i.e., humans). Uncertainties in this assumption are encompassed by using an uncertainty factor in deriving the RfD (Section 3.3) and may sometimes influence the selection of the study used to derive the RfD.

As discussed in Section 3.1.3.1 and reviewed in U.S. EPA/OW (1992), the metabolism of picloram has been studied in several mammalian species and there is no indication that picloram is extensively metabolized *in vivo* by mammals. In the environment, however, picloram may undergo decarboxylation by microorganisms, photolysis, or pyrolysis, which may impact the assessment of the toxicity to some nontarget species (Section 4.1.2.5). There are no studies, however, on the toxicity of environmental metabolites of picloram to mammals.

3.1.16. Toxicological Interactions

As discussed in Section 3.1.7 (Effects on Immune System), a study is available indicating that Tordon 202C, a mixture of picloram and 2,4-D, may impact immune function in rats. This study, however, does not permit an evaluation of any potential interaction between picloram and 2,4-D. In addition, the available information on 2,4-D indicates that any impact on immune function could be attributed to 2,4-D.

In terms of the mechanism of action, it is likely that picloram would influence and be influenced by other weak acids excreted by the kidney. These influences, however, would be significant only at relatively high doses that saturated the active transport processes involved in kidney excretion.

3.2. EXPOSURE ASSESSMENT

3.2.1. Overview

An overview of the exposure assessments for picloram and hexachlorobenzene is presented in Table 6. The estimated exposures assessments for workers are summarized in Worksheet E01 of the EXCEL workbooks that accompany this risk assessment: Attachment 1 for picloram and Attachment 2 for exposures to hexachlorobenzene which may be associated with picloram applications. Summaries of the corresponding exposure assessments for members of the general public are summarized in Worksheet E03. The summary worksheets reference other worksheets in the workbooks which provide the details of and computations for each exposure scenario. Documentation for these worksheets is presented in SERA (2010a, 2011a). The exposure assessments given in the following subsections provide a plain language description of the worksheets and discuss the specific data used in the worksheets.

For picloram (Attachment 1), all exposure assessments for workers as well as those for members of the general public and ecological receptors, are based on a unit application rate of 1lb a.e./acre, which is also the maximum anticipated application rate for picloram. For most exposure scenarios, exposure and consequent risk will scale linearly with the application rate, and the consequences of using lower application rates are considered as necessary in the risk characterization (Section 3.4). A full set of standard exposure scenarios involving both acute and longer-term exposures is developed for picloram. A general overview of these standard exposure scenarios is given in SERA (2007a).

For hexachlorobenzene (Attachment 2), a somewhat different approach is taken. As discussed in Section 3.1.15.1 (Impurities), the current risk assessment assumes that an application rate for picloram of 1 lb a.e./acre is functionally equivalent to an application rate of 0.000003 lb hexachlorobenzene/acre (i.e., three one-millionths of a pound per acre). Thus, in Attachment 2, the functional application rate for hexachlorobenzene associated with an application of picloram at 1 lb a.e./acre is taken as 0.000003 lb hexachlorobenzene/acre. In addition and as discussed in Section 3.1.15.1, carcinogenicity is the only endpoint of concern for hexachlorobenzene. Consequently, for both workers and members of the general public, exposure scenarios for hexachlorobenzene are developed only for longer-term exposure scenarios.

3.2.2. Workers

As summarized in Table 6, two types of worker exposure assessments are considered for picloram: general and accidental/incidental. The term *general exposure* is used to designate exposures involving absorbed dose estimates based on handling a specified amount of chemical during specific types of applications. The accidental/incidental exposure scenarios involve specific events that may occur during any type of application. Because concern for hexachlorobenzene apart from picloram is limited to carcinogenicity, only general exposure scenarios (i.e., those associated with the longer-term durations) are developed for hexachlorobenzene.

3.2.2.1. General Exposures

As described in SERA (2007a) and summarized in Table 7 of the current risk assessment, worker exposure rates are expressed in units of mg of absorbed dose per kilogram of body weight per pound of chemical handled. These rates are based on analyses of several different pesticides

using a variety of application methods, as detailed in SERA (1998). Based on these studies, default exposure rates are estimated for three different types of applications: directed foliar (backpack), boom spray (hydraulic ground spray), and aerial. As summarized in Table 7, the ranges of estimated occupational exposure rates vary substantially among individuals and groups, (i.e., by factors of up to 100). The studies used to develop these exposure rates provide information on estimates for individual workers of both absorbed dose (typically from monitoring urinary excretion) as well as the amount of pesticide that each worker applied (SERA 1998). In addition to the application rate and absorbed dose rate, the other factor affecting worker exposure is the number of acres per day that a worker will treat. Estimates of the number of acres per day that a worker might treat are also given in Table 7. These values are based on treatment rates used in several Forest Service Environmental Impact Statements (USDA/Forest Service 1989a,b,c).

Two studies (Lavy et al. 1987; Libich et al. 1984) have been conducted on workers handling picloram which permit an estimate of worker exposure rates in terms of absorbed dose (mg/kg body weight per lb a.e. handled) and both of these studies were used to develop the exposure estimates given in SERA (1998). By far the most detailed study on worker exposure to picloram is that conducted by Lavy et al. (1987). In this study, the uptake of 2,4-D, picloram, and dichlorprop was assayed in four groups of forestry workers using four different application methods: backpack, injection bar, hypohatchet, and hack-and-squirt. In addition, for each method, uptake was studied under standard work practices (referred to as T1 in this publication) and work practices involving special precautions (referred to as T2 in this publication). The special precautions involved the use of new gloves for mixing and application, improved personal hygiene, and exposure avoidance. Absorption of the herbicides was assayed using 5-day complete urine collections. In another study, Libich et al. (1984) studied the exposure of herbicide applicators involved in electric power transmission rights-of-way maintenance to 2,4-D, dichlorprop, and picloram. Absorbed dose was estimated from daily urine sampling rather than total urine collection. Two application methods were examined: spray guns mounted on vehicles and mist blowers connected to a back pack. The spray guns were mounted either on trucks—for roadside spraying—or all terrain vehicles (ATV's)—for spraying less accessible areas. The herbicides used were Tordon 101, a formulated 4:1 mixture of 2,4-D and picloram (463 g/L) and a 1:1 mixture of 2,4-D and dichlorprop (480 g/L). For spray gun applications, the commercial product was diluted with 100 parts water. For the backpack application, the product was diluted with 16 parts water. A limitation in the comparison of this study with the study by Lavy et al. (1987) is that Libich et al. (1984) do not specify the amount of product handled. The ranges of estimated occupational exposure rates vary substantially among individuals and groups, (i.e., by a factor of 50 for backpack applicators and a factor of 100 for mechanical ground sprayers). It seems that much of the variability can be attributed to the hygienic measures taken by individual workers (i.e., how careful the workers are to avoid unnecessary exposure).

3.2.2.2. Accidental Exposures

The skin surface and eyes of workers are most likely to be affected by accidental spills or splashes of pesticide solutions. Quantitative exposure scenarios for eye exposures are not developed in this or other Forest Service risk assessments. As discussed in Section 3.1.11.3 (Ocular Effects), picloram and potassium picloram are classified by the U.S. EPA/OPP as only

moderate eye irritants (Category III), and the product labels for Tordon K and Tordon 22K do not require or recommend the use of protective eyewear.

Generally, dermal exposure is the predominant route of exposure for pesticide applicators (Ecobichon 1998; van Hemmen 1992), and accidental dermal exposures are considered quantitatively in all Forest Service risk assessments. The two types of dermal exposures modeled in the risk assessments include direct contact with a pesticide solution and accidental spills of the pesticide onto the surface of the skin. In addition, two exposure scenarios are developed for each of the two types of dermal exposure, and the estimated absorbed dose for each scenario is expressed in units of mg chemical/kg body weight. Both sets of exposure scenarios are summarized in Worksheet E01 of the EXCEL workbooks that accompany this risk assessment. Additionally, Worksheet E01 references other worksheets in which the calculations of each exposure assessment are detailed.

Exposure scenarios involving direct contact with solutions of picloram 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's body will be immersed in a chemical solution for a prolonged period of time may seem unreasonable; however, it is possible that the gloves or other articles of clothing worn by a worker may become contaminated with a pesticide. For these exposure scenarios, the key assumption is that wearing gloves grossly contaminated with a chemical solution is equivalent to immersing the hands in the solution. In both cases, the chemical concentration in contact with the skin and the resulting dermal absorption rate are essentially constant.

For both scenarios (hand immersion and contaminated gloves), the assumption of zero-order absorption kinetics is appropriate. For these types of exposures, the rate of absorption is estimated based on a zero-order dermal absorption rate (K_p). Details regarding the derivation of the K_p value for picloram are provided in Section 3.1.3.2.2.

The amount of the pesticide absorbed per unit time depends directly on the concentration of the chemical in solution. For terrestrial applications, the current risk assessment uses an application volume of 30 gallons/acre with a range of 5 to 100 gallons per acre, which encompasses the potential range of applications to be used in ground and aerial treatments (Section 2.4). At an application rate of 1 lb a.e./acre, the estimated concentration in a field solution is taken as 4.0 mg/mL with a range of 1.2 to 24 mg a.e./mL (Worksheet A01 in Attachment 1).

The details of the accidental dermal exposure scenarios for workers consist of spilling a chemical solution on to the lower legs as well as spilling a chemical solution on to the hands with at least some of chemical adhering to the skin. The absorbed dose is then calculated as the product of the amount of chemical on the skin surface (i.e., the amount of liquid per unit surface area multiplied by the surface area of the skin over which the spill occurs and the chemical concentration in the liquid), the first-order absorption rate, and the duration of exposure. As with the zero-order dermal absorption rate, the first-order absorption rate constant (k_a) is derived in Section 3.1.3.2.2.

As discussed in Section 3.1.3.2.2, the estimated first-order dermal absorption rate constant is based on the study by Nolan et al. (1984), in which the dermal loading was about 0.16 mg/cm^2. As detailed in Worksheet C03a, the anticipated dermal loading in accidental exposure scenarios for workers is about 0.032 (0.0096 to 0.192) mg/cm^2. The upper bound loading of about 0.19 mg/cm^2 is only modestly above the dermal loading from the study by Nolan et al. (1984). As discussed by Kissel (2010), a substantial discrepancy in dermal loadings between studies on which dermal absorption rate constants are based and dermal loadings in anticipated exposures is a concern, because excessive dermal loadings can lead to saturation (i.e., zero-order absorption rather than first-order absorption). Because of the similarities in upper bound anticipated dermal loadings and the dermal loadings used in the study by Nolan et al. (1984), the estimated first-order dermal absorption rate from Nolan et al. (1984) is well-matched to the exposure scenarios for workers in the current risk assessment.

Numerous other 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, the surface area of the affected skin, and the duration of exposure. As discussed further in the risk characterization (Section 3.4.2), however, the accidental scenarios lead to exposure levels far below the level of concern and reasonable variations in these exposure scenarios would not affect the assessment of potential risks to workers.

3.2.3. General Public

3.2.3.1. General Considerations

3.2.3.1.1. Likelihood and Magnitude of Exposure

The chances that members of the general public will be exposed to picloram in Forest Service applications are highly variable. In some Forest Service applications, picloram could be applied in recreational areas, including campgrounds, picnic areas, and trails. Because of the conservative exposure assumptions used in the current risk assessment, neither the probability of exposure nor the number of individuals who might be exposed has a substantial impact on the risk characterization presented in Section 3.4. As noted in Section 1 (Introduction) and detailed in SERA (2007a, Section 1.2.2.2), the exposure assessments developed in this risk assessment are based on *Extreme Values* rather than a single value. Extreme value exposure assessments, as the name implies, bracket the most plausible estimate of exposure (referred to statistically as the central or maximum likelihood estimate) with lower and upper bounds of credible exposure levels.

This Extreme Value approach is essentially an elaboration on the concept of the *Most Exposed Individual* (MEI), sometime referred to as the M*aximum Exposed Individual*. As this name implies, exposure assessments that use the MEI approach attempt to characterize the extreme but still plausible upper limit on exposure. This common approach to exposure assessment is used by U. S. EPA, other government agencies, and the International Commission on Radiological Protection (e.g., ATSDR 2002; ICRP 2005; Payne-Sturges et al. 2004). In the current risk assessment, all upper bounds on exposure are intended to encompass exposures to the MEI.

In addition to this upper bound MEI value, the Extreme Value approach used in this risk assessment provides a central estimate of exposure as well as a lower bound on exposure.

Although not germane to assessing the upper bound risk, using the central estimate and especially the lower bound estimate is not intended to lessen concern. To the contrary, the central and lower estimates of exposure are used to assess the prospect of mitigation—e.g., protective measures to limit exposure. If lower bound exposure estimates exceed a level of concern (which is not the case in the current risk assessment), there is strong indication that the pesticide cannot be used in a manner that will lead to acceptable risk.

In addition to concern for the most exposed individual, there is concern for individuals who may be more sensitive than most members of the general population to picloram exposure. This concern is considered in the dose-response assessment (Section 3.3) which bases exposures on the most sensitive endpoint in the most sensitive species and uses an uncertainty factor for sensitive individuals. Atypical sensitivities—i.e., special conditions that might increase an individual's sensitivity to a particular agent—are also considered separately in the risk characterization (Section 3.4.4).

3.2.3.1.2. Summary of Assessments

For picloram, the exposure scenarios developed for the general public are summarized in Worksheet E03 of Attachment 1, the EXCEL workbook for picloram that accompanies this risk assessment. As with the worker exposure scenarios, details about the assumptions and calculations used in these assessments are given in the detailed calculation worksheets in the EXCEL workbook (Worksheets D01–D11). As summarized Table 6 as well as in Worksheet E03 of Attachment 1, the kinds of exposure scenarios developed for the general public include acute accidental, acute non-accidental, and longer-term or chronic exposures. The accidental exposure scenarios assume that an individual is exposed to the compound of concern either during or shortly after its application. The nature of the accidental exposures is intentionally extreme. Non-accidental exposures involve dermal contact with contaminated vegetation as well as the consumption of contaminated fruit, vegetation, water, or fish. The longer-term or chronic exposure scenarios parallel the acute exposure scenarios for the consumption of contaminated fruit, water, or fish. Like the exposure scenarios for workers, all of the exposure scenarios for members of the general public are based on levels of exposure to be expected in the routine uses of picloram at a unit application rate of 1 lb a.e./acre, which is also the maximum anticipated application rate for picloram (Section 2.4). The upper bounds of the exposure estimates for the non-accidental scenarios involve conservative assumptions intended to reflect exposure for the MEI (*Most Exposed Individual*). The impact of lower application rates on the risk characterization is discussed in Section 3.4.

For hexachlorobenzene, only a subset of the typical exposure scenarios, specifically those scenarios associated with longer-term exposures, are developed (Table 6). In addition, the longer-term exposure scenarios for hexachlorobenzene are used only to assess carcinogenic risk. As discussed in Section 3.1.15.1, this approach is taken because the available data on technical grade picloram encompass concerns for the systemic toxicity of hexachlorobenzene in technical grade picloram but do not encompass concerns for the potential carcinogenic risks associated with longer-term exposures to hexachlorobenzene as a result of picloram applications.

3.2.3.2. Direct Spray

Direct sprays involving ground applications are modeled similarly to accidental spills for workers (Section 3.2.2.2). In other words, the scenarios assume that an individual is sprayed

with a chemical solution, some of which remains on the skin and is absorbed by first-order kinetics. Two direct spray scenarios are included in this risk assessment: one for a young child (D01a) and the other for a young woman (D01b).

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

The exposure scenario involving the young woman (Worksheet D01b) is somewhat less extreme, but more credible. In this scenario, it is assumed that the woman is accidentally sprayed over the feet and lower legs. The preference for using a young woman rather than an adult male in many of the exposure assessments relates to concerns for both the *Most Exposed Individual* (MEI) as well as the most sensitive individual. Based on general allometric considerations, the smaller the individual, the greater will be the chemical doses per unit body weight (e.g., Boxenbaum and D'Souza. 1990). In general, the body size of a female is smaller than that of males. Thus, in direct spray exposure scenarios, females are subject to somewhat higher doses than males. More significantly, reproductive effects are a major concern in all Forest Service risk assessments. Consequently, exposure levels for a young woman of reproductive age are used in order to better assess the potential for adverse effects in the population at risk from potential reproductive effects—i.e., the most exposed and the most sensitive individual.

For this exposure scenario, assumptions are made regarding the surface area of the skin and the body weight of the individual, as detailed in Worksheet A03. The rationale for and sources of the specific values used in these and other exposure scenarios is given in the documentation for the worksheets (SERA 2010a, 2011a) as well as the documentation for the preparation of Forest Service risk assessments (SERA 2007a). The first-order absorption dermal absorption rates are identical to those used in the similar worker exposure scenarios (Section 3.2.2.2).

3.2.3.3. Dermal Exposure from Contaminated Vegetation

In this exposure scenario, it is assumed that the herbicide is sprayed at a given application rate and that an individual comes in contact with sprayed vegetation or other contaminated surfaces at some period after the spray operation. For these exposure scenarios, some estimates of dislodgeable residue and the rate of transfer from the contaminated vegetation to the surface of the skin must be available. No such data are available on dermal transfer rates for picloram; hence, the estimation methods of Durkin et al. (1995) are used as defined in Worksheet D02. The exposure scenario assumes a contact period of 1 hour and assumes that the chemical is not effectively removed by washing for 24 hours. Other estimates used in this exposure scenario involve estimates of body weight, skin surface area, and first-order dermal absorption rates, as discussed in the previous section.

3.2.3.4. Contaminated Water

3.2.3.4.1. Accidental Spill

The accidental spill scenario assumes that a young child consumes contaminated water shortly after an accidental spill of a field solution into a small pond. The specifics of this scenario are

given in Worksheet B04b. Because this scenario is based on the assumption that exposure occurs shortly after the spill, no dissipation or degradation is considered. Since this exposure scenario is based on assumptions that are somewhat arbitrary and highly variable, it may overestimate exposure. The actual chemical concentrations in the water will vary according to the amount of compound spilled, the size of the water body into which the chemical is spilled, the time at which water consumption occurs relative to the time of the spill, and the amount of contaminated water consumption. To reflect the variability inherent in this exposure scenario, a spill volume of 100 gallons (range of 20-200 gallons) is used to reflect plausible spill events. The concentrations of picloram in the field solution are also varied to reflect the plausible range of concentrations in field solutions—i.e., the material that might be spilled—using the same values as in the accidental exposure scenarios for workers (Section 3.2.2.2). The calculations of the concentrations in field solutions are detailed in Worksheet A01. Based on these assumptions, the estimated concentration of picloram in a small pond ranges from about 0.09 mg a.e./L to about 18 mg a.e./L, with a central estimate of about 1.5 mg a.e./L (Worksheet B04b).

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

Scenarios involving direct spray or drift are less severe but more plausible than the accidental spill scenario described in the previous subsection. The concentrations of picloram in a small pond (Worksheet B04c) and a small stream (Worksheet B04d) are based on standard estimates of drift adapted from AgDrift for four application methods: aerial, high boom ground broadcast, low boom ground broadcast and backpack applications. As discussed in SERA (2010a), AgDRIFT permits very detailed modeling of drift based on the chemical and physical properties of the applied product, the configuration of the aircraft, wind speed, and temperature for aerial applications. The generic estimates used in the current risk assessment are intended to be conservative, and more refined estimates of drift would be appropriate in any site-specific application.

If a 1-meter deep pond is directly sprayed with picloram at a unit application rate of 1.0 lb a.e./acre, the peak concentration in the pond would be about 0.11 mg/L, equivalent to 110 µg/L or 110 ppb (Worksheet B04c). This concentration is a factor of about 164 below 18 mg a.e./L, the upper bound of the central estimate of the concentration in pond water after an accidental spill (Section 3.2.3.4.1). Based on the Tier 1 estimates of drift, picloram concentrations in a small pond contaminated by drift would range from about 0.000035 mg/L (35 part per trillion) to 0.025 mg/L (25 part per billion), depending on the application method and the distance of the pond from the treated site.

For the stream scenario, the resulting water concentrations depend on the surface area of the stream and the rate of water flow in the stream. The stream modeled using Gleams-Driver (Section 3.2.3.4.3) is about 6 feet wide (1.82 meters), and it is assumed that the pesticide is applied along a 1038 foot (316.38 meters) length of the stream with a flow rate of 710,000 L/day. Using these values, the concentration in stream water after a direct spray is estimated at about 0.09 mg/L (90 parts per billion). Much lower concentrations, ranging from about 0.00003 mg/L (30 part per trillion) to 0.02 mg/L (20 parts per billion) are estimated based on drift at distances from 25 to 900 feet (Worksheet B04d).

3.2.3.4.3. GLEAMS Modeling

The Forest Service developed a program, Gleams-Driver, to estimate expected peak and longer-term pesticide concentrations in surface water. Gleams-Driver serves as a preprocessor and postprocessor for GLEAMS (Knisel and Davis 2000). GLEAMS (Groundwater Loading Effects of Agricultural Management Systems) is a field scale model developed by the USDA/ARS and has been used for many years in Forest Service and other USDA risk assessments. Gleams-Driver offers the option of conducting general exposure assessments using site-specific weather files from Cligen, a climate generator program developed and maintained by the USDA Agricultural Research Service (http://horizon.nserl.purdue .edu/Cligen). Details concerning the use of Gleams-Driver are given in SERA (2007b). Gleams-Driver is used in the current risk assessment to model concentrations of picloram and hexachlorobenzene in a small stream and small pond.

3.2.3.4.3.1. Inputs to Gleams-Driver

The generic site parameters used in the Gleams-Driver runs are summarized in Table 8, and additional details are available in the documentation for Gleams-Driver (SERA 2007b). For each site modeled, simulations were conducted using clay (high runoff, low leaching potential), loam (moderate runoff and leaching potential), and sand (low runoff, high leaching potential) soil textures.

The locations of the generic sites selected for modeling include a total of nine sites, as summarized in Table 9. As discussed in SERA (2007b), these locations are standard sites for the application of Gleams-Driver in Forest Service risk assessments and are intended to represent combinations of precipitation (dry, average, and wet) and temperature (hot, temperate, and cool). For each site, Gleams-Driver was used to simulate 100 applications and each of the simulations was followed for a period of about 1½ years after application.

For picloram, all applications were modeled at a unit application rate of 1 lb a.e./acre. This is a standard practice in applications of Gleams-Driver in Forest Service risk assessments because the outputs from GLEAMS will typically scale linearly with the application rate. As discussed further in Section 3.2.3.4.3.2, the results from Gleams-Driver are expressed as Water Contamination Rates (WCRs), concentrations of the chemical in water for an application rate of 1 lb/acre. In the EXCEL workbooks that accompany this risk assessment, the WCRs are multiplied by the application rate to yield the expected concentration of the chemical in water.

An exception to linear scaling, however, may occur if soil pore water is saturated. As summarized in Table 1, this is not a concern with picloram because picloram is extremely soluble in water – i.e., ≈200,000 mg/L for the potassium salt. As summarized in Table 2, however, hexachlorobenzene is much less soluble in water – i.e., about 0.0035 to 0.006 mg/L. Exploratory GLEAMS runs with hexachlorobenzene indicated that an application rate of 1lb/acre could lead to concentrations of hexachlorobenzene in soil pore water that would approach the solubility of hexachlorobenzene in water. Consequently, all Gleams-Driver simulations of hexachlorobenzene were conducted at an application rate of 0.1 lb hexachlorobenzene/acre. As discussed further in Section 3.2.3.4.3.1, the outputs from Gleams-Driver are multiplied by a factor of 10 to estimate concentrations that would be associated with an application of 1 lb/acre – i.e., the Water Contamination Rate (WCR) in units of mg/L per lb/acre.

As indicated in Section 2.2 and discussed further in Section 3.1.15.1, technical grade picloram contains hexachlorobenzene as a contaminant at a concentration no greater than 3 ppm – i.e., three parts per million or a proportion of 0.000003. Thus, in the EXCEL workbook for hexachlorobenzene, the function application rate for hexachlorobenzene is entered as 0.000003 lb a.i./acre and the WCR is multiplied by 0.000003 lb a.i./acre to calculate the expected concentrations of hexachlorobenzene in surface water.

The chemical-specific values used in the Gleams-Driver simulations are summarized in Table 10 for picloram and Table 11 for hexachlorobenzene. The notes to these tables provide specific references for the parameters that were selected. The input values for picloram are based on recommended values from the documentation for GLEAMS (Knisel and Davis 2000), other standard reference sources (USDA/ARS 1995; U.S. EPA/OPP 1994b), as well as studies from the open literature (Close et al. 1999; Havens et al. 2001; Newton et al. 1990; Scifres et al. 1989; Zhao et al. 2011). For parameters with substantial variability, ranges and central estimates with ranges are given. In the Gleams-Driver simulations, these parameters are modeled with uniform and triangular distributions, respectively.

The input parameters for hexachlorobenzene are, for the most part, taken from the review of hexachlorobenzene by ATSDR (2002) with additional parameters from Beall (1976), Knisel and Davis (2000) and U.S. EPA/OPP (1998a). The predominant factors in the environmental fate of hexachlorobenzene are persistence and volatility. As discussed in both ATSDR (2002) and U.S. EPA/OPP (1998a), hexachlorobenzene is highly persistent in soil with metabolic half-lives of about 3 to 6 years. Conversely, hexachlorobenzene is relatively volatile and is expected to dissipate rapidly from soil surfaces. Specifically, the vapor pressure of hexachlorobenzene is about 1 to 2 x 10^{-5} mg Hg (Table 2), which is higher than the vapor pressure of picloram by several orders of magnitude (Table 1).

Neither ATSDR (2002) nor U.S. EPA/OPP (1998a) gives quantitative estimates of the evaporation rates for hexachlorobenzene from soil surfaces. Approximate rates, however, can be estimated from the study by Beall (1976). In this study, hexachlorobenzene was applied to short grass (i.e., *Zoysia japonica*, 5.4 cm or ≈2 inches in height) growing on sandy loam soil. The initial concentration of picloram in the top 2 cm (≈0.8 inches) of soil is reported as 5.5992 ppm (mg HCB/kg soil dry weight). Over a 1-year period after application, the concentration of hexachlorobenzene in soil is reported as 0.2654 ppm, about 4.74% of the concentration on the day of application [0.2654 ppm ÷ 5.5992 ppm ≈ 0.0473996]. Figure 4 of the current risk assessment illustrates the time-course of hexachlorobenzene dissipation in the 2 cm of soil using data taken from the publication by Beall (1976, Table1, p. 396). As illustrated in Figure 4, the dissipation pattern is clearly biphasic (i.e., two-compartment) processes. The line included in Figure 4 is based on an eye-fit with the standard two-compartment model with an initial half-life of about 14 days and a terminal half-life of about 170 days. As discussed by Knisel and Davis (2000), GLEAMS Version 3 does include a feature to incorporate a two-compartment model for degradation in soil. This feature, however, is not commonly used and is not incorporated into Gleams-Driver. Exploratory runs with Gleams-Driver indicated that the use of a 14-day half-life resulted in unrealistically low concentrations of hexachlorobenzene in the upper soil horizons, relative to results from the study by Beall (1976). As an alternative, the proportion remaining after 1 year (i.e., 0.0473996, as discussed above) is used to estimate the simple first-order

dissipation rate for hexachlorobenzene in the top one inch of soil at 0.0084 day^{-1} [ln(0.0473996) ÷ 365 day ≈ 0.0083538 day^{-1}], which corresponds to a half-life of about 80 days [ln(2) ÷ 0.0084 day^{-1} ≈ 82.52 days]. As indicated in Table 11, the half-life of 80 days is used in all Gleams-Driver simulations for the top 1 inch of soil. Exploratory Gleams-Driver simulations (discussed further below) indicated the concentrations of hexachlorobenzene estimated in the upper 1 inch of soil are consistent with the study by Beall (1976). For all deeper soil layers, the soil half-life was simulated with a uniform distribution ranging from 1095 to 2190 days—i.e., 3 to 6 years, based on estimates from the reviews by ATSDR (2002) and U.S. EPA/OPP (1998a).

As with the surface of soil, hexachlorobenzene will rapidly volatilize from plant surfaces; however, no published estimates of half-lives on vegetation were found in the literature. The study by Beall (1976) measured residues of hexachlorobenzene in grass as well as soil over a 1-year period after application. As illustrated in Figure 5 of the current risk assessment, residues on grass also followed a bi-exponential pattern of dissipation with apparent half-lives of about 3 and 77 days. As discussed by Beall (1976), the initial rapid dissipation of hexachlorobenzene is clearly attributable to volatilization. The terminal phase of dissipation, however, is somewhat more complex but appears to reflect a close correlation between the concentration of hexachlorobenzene in soil and the concentration of hexachlorobenzene in the grass. Over the period from Day 50 to Day 365, the residues in soil and grass evidence a correlation coefficient of about 0.91 (p<0.005). As discussed further in Section 3.2.3.6.2, a separate exposure scenario is developed for the uptake of hexachlorobenzene from soil to vegetation. For the Gleams-Driver modeling, the half-life of hexachlorobenzene on vegetation is taken as 3 days, reflecting only the rapid volatilization of hexachlorobenzene, because the slower dissipation of hexachlorobenzene from soil is considered in the longer soil half-life of 80 days, as discussed above.

3.2.3.4.3.2. Output from Gleams-Driver

3.2.3.4.3.2.1. Picloram

The results for the Gleams-Driver simulation are summarized in Table 12, along with a summary of other modeling efforts and monitoring data, both of which are discussed further in the following subsections. Details of the results from the Gleams-Driver simulations are provided in Appendix 7 (Tables A7-5 to A7-8). All results from the Gleams-Driver runs are expressed as the median value with approximate 95% empirical limits. In other words, the two extreme lower and upper values from the 100 simulations at each site are dropped, and the lowest and highest remaining values are used for the lower and upper bound estimates. As noted in Section 3.2.3.4.3.1, all simulations for picloram involve an application rate of 1 lb a.e./acre. Thus, all of the concentrations discussed below are identical to Water Contamination Rates (WCRs)—i.e., concentrations in surface water expected at the unit application rate of 1 lb a.e./acre.

The central and upper bound estimates for peak and longer-term concentrations in surface water from the Gleams-Driver simulations are not remarkably different for streams and ponds. The central estimates of peak concentrations are about 10 µg/L (i.e., 8.8 µg/L for ponds and 14 µg/L for streams) and the upper bounds of the estimated peak concentrations are about 150 µg/L (i.e., 134 µg/L for ponds and 178 µg/L for streams). The central estimates of the longer-term concentrations are about 0.8 µg/L (i.e., 1.1 µg/L for ponds and 0.6 µg/L for streams) and the

upper bounds of the estimated peak concentrations are about 10 µg/L (i.e., 13 µg/L for ponds and 7 µg/L for streams).

Note that the upper bounds of the expected peak concentrations from the Gleams-Driver simulations are somewhat higher than the estimated peak concentrations from the direct spray of a small pond (112 µg/L) and a small stream (91 µg/L). While not intuitive, this situation is not unusual. The upper bound concentrations from Gleams-Driver are associated with severe rainfall events shortly following applications to a 10-acre field under the assumption that all of the runoff and percolate losses go directly to a small pond or stream. In this event, Gleams-Driver simulations often yield concentrations in surface water that exceed the concentrations in the direct spray scenarios.

For both ponds and streams, the lower bounds of the expected concentrations of picloram in surface water are zero (i.e., no contamination of surface water is expected). Again, this is a common finding in Gleams-Driver modeling of pesticides. GLEAMS tracks the movement of pesticides in a field due to precipitation and subsequent transport of the pesticide in sediment, runoff, and percolation, all of which are a function of water flow. If there is no water flow, GLEAMS will not predict offsite losses of the pesticide. As detailed in Appendix 7 (Tables A7-5 to A7-8), the contamination of surface water following applications of picloram is expected to be minimal in relatively arid areas and even areas with normal rainfall, particularly in locations with predominantly loam or sandy soils.

3.2.3.4.3.2.2. Hexachlorobenzene

The results of the Gleams-Driver simulations for hexachlorobenzene are summarized in Table 13 and additional details of these simulations are included in Appendix 8 (Tables A8-5 to A8-6). While Table 13 and Appendix 8 include information on expected peak concentrations, these results are not used in the current risk assessment. As discussed in Section 3.1.15.1 (Impurities), the acute and longer-term systemic toxicity of hexachlorobenzene as a contaminant in technical grade picloram are encompassed by the available acute and longer-term systemic toxicity studies on technical grade picloram. The only potential adverse effect of hexachlorobenzene not encompassed by these data is carcinogenicity. For carcinogenicity, only chronic exposures are considered quantitatively.

As discussed in Section 3.2.3.4.3.1, the Gleams-Driver simulations for hexachlorobenzene were conducted at an application rate of 0.1 lb/acre rather than 1 lb/acre. Table 13 provides a summary of the simulations from Gleams-Driver at 0.1 lb/acre followed by a normalization of the estimated concentrations of hexachlorobenzene in surface water at an application of 1 lb/acre (i.e., Water Contamination Rates or WCRs). The normalization simply involves multiplying the results of the 0.1 lb/acre simulations by a factor of 10. This approach is taken because WorksheetMaker requires WCRs to be expressed in units of mg/L per lb/acre (SERA 2011a).

The longer-term WCRs for hexachlorobenzene are somewhat less than those for picloram—i.e., 0.32 (0 to 4) µg/L per lb/acre for ponds and 0.46 (0 to 5) µg/L per lb/acre for streams. As indicated in Appendix 8 (Table 4), the maximum penetration of hexachlorobenzene into the soil column is estimated at about 12 inches. All of the Gleams-Driver simulations were conducted with a 36 inch root zone. Thus, unlike the case with picloram, all of the surface water

contamination with hexachlorobenzene is associated with runoff and sediment loss (i.e., no contamination of surface water is associated with percolation below the root zone).

As summarized in Table 11, the half-lives for hexachlorobenzene in surface water are taken as about 2.7 to 5.7 years. These are metabolic half-lives taken from ATSDR (2002). This is an extremely and perhaps unreasonably conservative approach. As discussed in Section 3.2.3.4.3.1, hexachlorobenzene is extremely volatile. U.S. EPA/OPPTS (2011) estimates volatilization half-times for hexachlorobenzene of about 0.1 day in a model river and 7 days for a model pond. As discussed further in Section 3.4 (Risk Characterization), the use of the longer metabolic half-lives for hexachlorobenzene leads to estimates of risks for carcinogenicity that are below the level of concern. Thus, no refinement to the exposure assessment is made specifically to consider the volatilization of hexachlorobenzene from water.

3.2.3.4.4. Other Modeling Efforts

The U.S. EPA/OPP often conducts relatively elaborate modeling in support of pesticide risk assessments or other related analyses. This is not the case for either picloram or hexachlorobenzene. In the Reregistration Eligibility Decision document for picloram (U.S. EPA/OPP 1995a, p. 74), the EPA provides an estimated environmental concentration for picloram of 42.7 µg a.i./L for a 6-foot deep pond following an application of potassium picloram at 2 lbs a.i./acre. Other then specifying the water depth and application rate, U.S. EPA/OPP (1995a) does not provide a detailed discussion of the model or models used in developing this estimate, and no discussion was located in other support documents (U.S. EPA/OPP 1994a,b). Normalizing the EPA estimate of 42.7 µg a.i./L for an application rate of 1 lb/acre, the estimate corresponds to a WCR of about 21.35 µg a.i./L per lb a.i./acre. Because both the application rate and concentration are expressed as active ingredient, the WCR can also be expressed as 21.35 µg a.e./L per lb a.e./acre. This water contamination rate is well within the concentrations modeled using Gleams-Driver—i.e., a central estimate of about 10 µg/L with an upper bound of about 150 µg/L.

While the U.S. EPA/OPP (1998a, pp. 20-21) considers cancer risks associated with hexachlorobenzene residues in food following picloram applications, cancer risks associated with drinking water are not explicitly considered. Hexachlorobenzene, however, is a contaminant in picloram as well as several other pesticides, and the EPA conducted a generic drinking water assessment for hexachlorobenzene associated with hexachlorobenzene in picloram as well as atrazine, clopyralid, chlorothalonil, chlorpyrifos-methyl, dacthal, endosulfan, pentachloronitrobenzene, pentachlorophenol, and, simazine. This document, however, focuses on monitoring data rather than modeling. Based on a consideration of these data, the EPA concluded that longer-term concentrations of hexachlorobenzene in surface water are not likely to exceed 0.01 µg/L. Again, however, this estimate does not appear to be associated specifically with contamination of surfaces water with hexachlorobenzene in the application of any of the pesticides explicitly considered in U.S. EPA/OPP (1998a).

3.2.3.4.5. Monitoring Data

Picloram is not frequently detected in surface water. The U.S. Geological Survey has an extensive program of monitoring pesticides in surface water. In the most recent compendia of this monitoring program in which picloram is noted (Gilliom et al. 2007), picloram was not detected (LOD = 0.04 µg/L) in water samples taken from streams in agricultural areas (n=1465),

urban areas (n=520), and undeveloped areas (n=101). Picloram was detected in 0.08% of 800 streams (6 detects/800 samples) in streams designated as mixed use areas, and the maximum concentration was 0.01 µg/L (Gilliom et al. 2007a, Appendix 7, Table 7A-1). These monitoring data, however, represent concentrations of picloram in surface water that cannot be associated with specific applications of picloram and thus cannot be used to assess the quality of the Gleams-Driver modeling.

As summarized in Table 12, however, there are three studies which involve monitoring of picloram from streams in areas where defined applications of picloram were made—i.e., Davis and Ingebo (1973), Michael and Neary (1993), Watson et al. (1989). One of the monitored samples —i.e., 79 µg/L normalized for an application rate of 1 lb a.e./acre from Michael and Neary (1993)—involved concentrations in a stream during an aerial application. This monitored concentration appears to have been associated with either direct spray or spray drift to the stream and is very close to the estimated concentration of 91 µg/L based on the standard scenario for the direct spray of a stream at an application rate of 1 lb a.e./acre. The post-application monitoring from Michael and Neary (1993) and Davis and Ingebo (1973) yields estimated concentrations, normalized for an application rate of 1 lb a.e./acre, in the range of 2 to 43 µg/L. The geometric mean of this range is about 9.3 µg/L, which is very close to the central estimate in streams from Gleams-Driver—i.e., 14 µg/L.

In the study by Watson et al. (1989), no picloram was monitored in a stream (detection limit of 0.5 µg/L), after the application of picloram at rates of 0.28 kg a.e./ha (about 0.25 lb/acre) or 1.12 kg a.e./ha (1 lb/acre) in areas with loam or sandy loam soil. As noted by Watson et al. (1989), the cumulative rainfall over a period of 90 days following the picloram application was only 172 mm (≈6.7 inches). This cumulative rainfall corresponds to an average annual rainfall of about 26.8 inches. As summarized in Table 9, an annual rainfall of 26.8 inches is below the rainfall rates for areas of average precipitation used in the Gleams-Driver modeling. As summarized in Appendix 7 (Table A7-5), the central estimates of the peak concentrations of picloram in streams in areas with loam soil texture and moderate precipitation range from 0 to 1 µg/L. Thus, the failure of Watson et al. (1989) to detect picloram in streams is not discordant with the Gleams-Driver simulations.

The above discussion is not intended to suggest any formal validation of the Gleams-Driver simulations with the available monitoring studies. To validate or even meaningfully evaluate Gleams-Driver with the available monitoring studies would require a relatively substantial analysis which is beyond the scope of the current effort. Nonetheless, the available monitoring data for picloram do not contradict and are concordant with the Gleams-Driver simulation and suggest that the Water Contamination Rates from Gleams-Driver are plausible.

No monitoring studies of hexachlorobenzene in surface water following applications of picloram have been encountered. Consequently, the estimates of hexachlorobenzene in surface water from Gleams-Driver cannot be evaluated directly.

3.2.3.4.6. Concentrations in Water Used for Risk Assessment

The concentrations of picloram and hexachlorobenzene in surface water used in the current risk assessment are summarized in Table 14. The concentrations are specified as water contamination rates (WCRs)—i.e., the concentrations in water expected at a normalized

application rate of 1 lb/acre, converted to units of ppm or mg/L per lb /acre. For picloram, the WCRs are expressed as mg a.e./L per lb a.e./acre. For hexachlorobenzene, the WCRs are expressed as mg HCB/L per lb HCB/acre. In the modeling and monitoring summary tables (i.e., Table 12 for picloram and Table 13 for hexachlorobenzene) the units of exposure are expressed as ppb or µg/L, as a matter of convenience. In Table 14, however, ppb is converted to ppm because ppm (mg/L) is the unit of measure used in the EXCEL workbook for contaminated water exposure scenarios in both the human health and ecological risk assessments. The water contamination rates are entered in Worksheet B04Rt in Attachment 1 (the EXCEL workbook picloram) and Attachment 2 (the EXCEL workbook for hexachlorobenzene. The values in Worksheet B04Rt are linked to worksheet B04a, which provides the expected concentrations of picloram and hexachlorobenzene in surface water based on the application used in the workbook. As discussed is Section 3.2.1, both workbooks are based on an application rate of 1 lb a.e./acre for picloram, which corresponds to a functional application rate for hexachlorobenzene of 0.000003 lb/acre.

For picloram, the peak WCRs are taken as 0.011 (0.001 to 0.18) mg a.e./L per lb a.e./acre. The central estimate is the arithmetic average of the central estimates of the modeled concentrations for streams and ponds [((0.0088 + 0.014) ÷ 2) = 0.0114 mg/L] rounded to two significant figures. The upper bound is taken at 0.18 mg/L, which is the upper bound concentration from Gleams-Driver for streams rounded to two significant figures. The most reasonable estimate of the lower bound concentration for picloram in water may be viewed as zero (i.e., the lower 25^{th} percentile of the lower bound concentrations from the Gleams-Driver simulations is zero). By convention, however, the lower bound concentrations used in Forest Service risk assessments are nonzero. The lower bound of 0.001 is simply the central estimate divided by 10 and rounded to one significant figure. The longer-term concentrations for picloram are taken as 0.00085 (0.00009 to 0.01) mg a.e./L. These concentrations are derived in the same manner as the peak concentrations.

The longer-term concentrations for hexachlorobenzene in water are taken as 0.00039 (0.00004 to 0.005) mg/L per lb/acre. The central estimate is the arithmetic average of the central estimates of the modeled concentrations for streams and ponds [((0.00032 + 0.00046) mg/L per lb/acre ÷ 2) = 0.00039 mg/L per lb/acre]. The upper bound of 0.005 mg/L per lb/acre is the upper bound from Gleams-Driver for streams, which is modestly higher than the upper bound for ponds – i.e., 0.004 mg/L per lb/acre. The lower bound is the central estimate divided by 10 and rounded to one significant figure. As discussed in Section 3.2.3.4.3.2.2, the Gleams-Driver modeling for hexachlorobenzene used metabolic half-lives for hexachlorobenzene in water (2.7 to 5.4 years) rather than the much lower half-lives based on volatilization (<1 to 7 days). Consequently, the exposure assessments for hexachlorobenzene based on concentrations in water are extremely conservative overestimates. As discussed further in Section 3.4.3, these intentional overestimates of concentrations of hexachlorobenzene in water do not lead to HQs for carcinogenicity that exceed the level of concern. Because the only endpoint considered quantitatively for hexachlorobenzene is carcinogenicity, no acute WRCs for hexachlorobenzene are derived.

3.2.3.5. Oral Exposure from Contaminated Fish

Many chemicals may be concentrated or partitioned from water into the tissues of aquatic animals or plants. This process is referred to as bioconcentration. Generally, bioconcentration is

measured as the ratio of the concentration in the organism to the concentration in the water. For example, if the concentration in the organism is 5 mg/kg and the concentration in the water is 1 mg/L, the bioconcentration factor (BCF) is 5 L/kg [5 mg/kg ÷ 1 mg/L]. As with most absorption processes, bioconcentration depends initially on the duration of exposure but eventually reaches steady state. Details regarding the relationship of the bioconcentration factor to standard pharmacokinetic principles are provided in Calabrese and Baldwin (1993).

For picloram, three standard sets of exposure scenarios are presented: one set for acute exposures following an accidental spill (Worksheets D08a and D08b), one set for acute exposures based on expected peak concentrations of imazamox in water (Worksheets D09c and D09d), and another set for chronic exposures based on estimates of longer-term concentrations in water (Worksheets D09a and D09b). The two worksheets for each set of scenarios are included to account for different consumption rates of caught fish among the general population and subsistence populations. Details of these exposure scenarios are provided in Section 3.2.3.5 of SERA (2007). For hexachlorobenzene, only the chronic exposure scenarios are developed (Worksheets D09a and D09b).

Picloram has a relatively low potential for bioconcentration. Bidlack (1980a) attempted to measure the bioconcentration factor of ^{14}C-picloram in bluegill sunfish over a 28-day exposure period at concentrations of 0.1 and 1 mg/L in water. Only trace amounts of ^{14}C were recovered in fish and Bidlack (1980a) concluded that the bioconcentration factor of picloram is less than 1. Similar results were obtained with channel catfish (Bidlack 1980b) and rainbow trout (Rieger et al. 1985). For this risk assessment a bioconcentration factor of 1 L/kg is used. This assumption will overestimate exposure but has no substantial impact on the risk assessment (Section 3.4).

Hexachlorobenzene is highly lipophilic and will bioconcentrate substantially in fish. As reviewed in ATSDR (2002), the reported bioconcentration factors in fish range from about 2000 to 20,000. For the current Forest Service risk assessment, the upper bound bioconcentration factor of 20,000 is used for the longer-term exposure scenarios involving the consumption of contaminated fish.

The scenarios associated with consumption of contaminated fish are based on the same concentrations of picloram and hexachlorobenzene in water as those used for exposure assessments associated with the consumption of contaminated water (Section 3.2.3.4).

3.2.3.6. Dermal Exposure from Swimming in Contaminated Water

Some geographical sites maintained by the Forest Service or Forest Service cooperators include surface water in which members of the general public might swim. 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). The concentrations of picloram in water are identical to those used in other exposure scenarios involving contaminated water (Table 14). Conceptually and computationally, this exposure scenario is virtually identical to the contaminated gloves scenario used for workers (Section 3.2.2.2)—i.e., a portion of the body is immersed in an aqueous solution of the compound at a fixed concentration for a fixed period of time.

As in the corresponding worker exposure scenario, the 1-hour period of exposure is 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 HQ that is twice as high as that associated with an exposure period of 1 hour. In cases in which this or other similar exposures approach a level of concern, further consideration is given to the duration of exposure in the risk characterization (Section 3.4). For picloram, however, the risks are far below the level of concern.

In Forest Service risk assessments, the ingestion of water during swimming is not considered explicitly. U.S. EPA/OPP (2003) uses a model for swimming exposures based on essentially the same approach to dermal absorption used in Worksheet D11. The EPA model, however, incorporates the assumption that an adult will consume water while swimming at a rate of 50 mL/hour. This assumption is based on data from ingestion rates in swimming pools. Based on more recent studies of water ingestion while swimming in pools (Dorevitch et al. (2010; Dufour et al. 2006), the EPA assumption of 50 mL/hour is a plausible upper bound.

3.2.3.7. Oral Exposure from Contaminated Vegetation

3.2.3.7.1. Picloram

Applications of picloram associated with Forest Service programs will not involve crop treatment. Under normal circumstances and in most types of applications, it is extremely unlikely that humans will consume substantial amounts of vegetation contaminated with picloram. Nonetheless, any number of accidental or incidental scenarios could be developed involving either spraying of crops, gardens, or edible wild vegetation. Again, in most instances and particularly for longer-term scenarios, treated vegetation would probably show signs of damage from exposure to picloram (Section 4.3.2.5), thereby reducing the likelihood of consumption which might lead to significant levels of human exposure.

Notwithstanding the above reservations, all forest service risk assessments involving foliar applications currently include two sets of standard exposure scenarios: one set for the acute and longer-term consumption of contaminated fruit and the other set for the acute and longer-term consumption of contaminated broadleaf vegetation. For picloram, these scenarios are detailed in Attachment 1 (the EXCEL workbook for picloram) in Worksheets D03a (fruit) and D03b (broadleaf vegetation) for acute exposure and Worksheets D04a (fruit) and D04b (broadleaf vegetation) for longer-term exposure. This is an elaboration to the scenarios from the previous Forest Service risk assessment on picloram (SERA 2003) which considers only exposure scenarios for the consumption of contaminated fruit.

In most Forest Service risk assessments, the pesticide concentration on contaminated fruit and vegetation is estimated using the empirical relationships between application rate and concentration on different types of vegetation (Fletcher et al. 1994). The rates provided by Fletcher et al. (1994) are based on a reanalysis of data originally compiled by Hoerger and Kenaga (1972) and represent estimates of pesticide concentration in different types of vegetation (mg chemical/kg vegetation) after a normalized application rate of 1 lb a.i./acre. Although the human health risk assessments conducted by the EPA do not consider these exposure scenarios,

the approach used in the current Forest Service risk assessment is very similar to that used by U.S. EPA/OPP (1994a, p. 39) in the ecological risk assessment of picloram which supports the EPA Reregistration Eligibility Decision for picloram (U.S. EPA/OPP 1995a).

The residue rates recommended by Fletcher et al. (1994) are given in Table 15 of the current Forest Service risk assessment. Fletcher et al. (1994) and Hoerger and Kenaga (1972) provide only central and upper bound estimates of residue rates. Accordingly, the lower bound estimates in Table 15 are made under the assumption that the ratio of the central estimate to the upper bound estimate is identical to the ratio of the lower bound estimate to the central estimate (i.e., the variability is log-symmetrical).

While initial residues on fruit and other commodities are likely to be the same or nearly so for most pesticides, the dissipation of residues will clearly vary among pesticides and different types of vegetation. As discussed in Section 3.2.3.4.3. (Gleams-Driver Modeling) and summarized in Table 10 (inputs for Gleams-Driver modeling), the dissipation half-life for picloram is taken as 8 (6 to 23) days, with the central estimate taken from Knisel and Davis (2000) and the range taken from field studies (Newton et al. 1990; Zhao et al. 2011).

For the longer-term exposure scenario (Worksheets D04a and D04b), a duration of 90 days is used. This is a standard assumption for systemic toxicity used in all Forest Service risk assessments for the longer-term consumption of plant materials—i.e., fruit and broadleaf vegetation. Although the duration of exposure of 90 days is somewhat arbitrarily chosen, this duration is intended to represent the consumption of contaminated fruit which might be available over a reasonable period of time for one season. Longer durations could be used for certain kinds of vegetation, but doing that would lower the estimated dose (i.e., would reduce the estimate of risk). In the longer-term exposure scenarios, the dissipation of picloram on vegetation is modeled using the half-lives of picloram on vegetation that are used in Gleams-Driver modeling (Table 10 for picloram and Table 11 for hexachlorobenzene).

The Forest Service is particularly concerned with pesticide exposures associated with the consumption of contaminated vegetation by Native Americans or other individuals who may forage in forests. Specific information about picloram residues in food items which might be consumed by Native Americans is not available. Furthermore, there is no information on picloram in a survey of herbicide residues on plants which are important to Native Americans (Segawa et al. 1997). Nonetheless and as illustrated in the recent Forest Service risk assessment on triclopyr (SERA 2011b), the residue rates from Fletcher et al. (1994) are generally much higher than the residue rates that can be derived from Segawa et al. (1997). Thus, the use of the Fletcher et al. (1994) residues rates should encompass potential exposures to pesticides that may be associated with forestry applications.

As summarized in Worksheet E03 of Attachment 1 (the EXCEL workbook for picloram), the longer-term dietary exposures range from about 0.0005 mg/kg bw/day (the lower bound for contaminated fruit) to 0.5 mg/kg bw/day (the upper bound for the consumption of contaminated vegetation). The upper bound of this range is much greater than the anticipated dietary exposures developed by the U.S. EPA/OPP for picloram —i.e., 0.0009 to 0.0043 mg/kg bw/day (U.S. EPA/OPP 1999, p. 422). This type of discrepancy is a very common pattern in

comparisons between dietary exposure estimates in EPA and Forest Service risk assessments. Dietary exposure estimates from the U.S. EPA/OPP are based on the assumption that exposures occur through the consumption of agricultural commodities in which the concentration of the pesticide is no greater than the pesticide tolerance set by the U.S. EPA. As discussed above and detailed in SERA (2007a), the dietary exposure assessments in Forest Service risk assessments are based on the assumption that individuals forage within a forest in which the pesticide has been applied at a specific application rate (e.g., 1 lb a.e./acre in the case of picloram).

Comparisons of the acute dietary exposures given the current assessment with those from EPA assessment cannot be made because the U.S. EPA/OPP did not conduct an acute dietary exposure analysis for picloram (U.S. EPA/OPP 1994a, p. 18).

3.2.3.7.2. Hexachlorobenzene

Two sets of custom exposure scenarios are developed for exposures to hexachlorobenzene associated with the consumption of contaminated vegetation: longer-term residues associated with deposition (Worksheets D04a for fruit and D04b for broadleaf vegetation in Attachment 2) and exposures associated with the uptake of hexachlorobenzene from soil into tubers such as wild sweet potatoes or onions. As with other aspects of the exposure assessment and for the same reasons, only longer-term exposure assessments are developed for hexachlorobenzene, and these exposure assessments are applied only to the potential carcinogenicity of hexachlorobenzene.

3.2.3.7.2.1. Deposition

Reservations with the deposition scenarios are identical to those discussed in Section 3.2.3.7.1 for picloram. Picloram is an effective herbicide; accordingly, significant longer-term exposures to hexachlorobenzene are not likely, given the damaging effect of picloram on the treated vegetation. As discussed in Section 3.2.3.7.1, the averaging period for longer-term exposures to picloram is taken as 90 days. For systemic toxicity, this averaging period is reasonable. For hexachlorobenzene, however, the endpoint of concern is carcinogenicity. As discussed in the U.S. EPA's guidelines for cancer risk assessment (U.S. EPA/RAF 2005), cancer potency factors are typically derived based on lifetime exposures in experimental mammals, which are typically applied to estimates of lifetime average daily doses. This approach is used in U.S. EPA/OPP (1994a, p. 23) in the cancer risk assessment for hexachlorobenzene as an impurity in picloram. While there are uncertainties in the application of lifetime average daily doses to the assessment of less than lifetime exposures, reasonable alternative approaches for hexachlorobenzene have not been identified, and the EPA approach in using the lifetime average daily dose is adopted in the current Forest Service risk assessment. Consequently, the averaging period for hexachlorobenzene is taken as 365 days (i.e., the annual average concentration) rather than 90 days.

An additional adjustment for the lifetime average daily dose must also be made for the number of years that picloram (with hexachlorobenzene) might be applied to a single location. The likelihood of multiple applications to the same site is variable within the Forest Service. For example, annual applications of picloram to the same site over a period of several years are avoided in Forest Service Region 6, the Pacific Northwest (Bautista, personal communication). In Forest Service Region 8, the Southern Region, picloram may be applied annually for up to 6 years for the control of kudzu (Mistretta, personal communication). In the EXCEL workbook

released with this risk assessment, Worksheet A01 has a custom entry for the number of years that picloram will be applied and the estimated human lifespan. These values are used in Worksheets B05a and B05b to calculate the lifetime-weighted average concentration of hexachlorobenzene in fruit and broadleaf vegetation. These worksheets are linked to Worksheets D04a and D04b in which the lifetime-weighted average doses are calculated for a young woman consuming the contaminated commodities.

Also in the EXCEL workbook released with this risk assessment, the number of years over which picloram is applied is set to 6 years with a reference lifespan of 70 years. As noted above, this is the maximum number of years that picloram would be applied in the same location. As discussed further in the risk characterization for the general public (Section 3.4.3), this most extreme application regimen does not lead to exposures that exceed the level of concern.

3.2.3.7.2.2. Soil Uptake

Most Forest Service risk assessments include only exposure scenarios for deposition and do not include separate exposure scenarios for the uptake of the pesticide from the soil into plants. For hexachlorobenzene, however, this exposure scenario is justifiable. As discussed in the ATSDR (2002, p. 212 ff) toxicological profile for hexachlorobenzene, hexachlorobenzene may bioconcentrate from soil to plants. The greatest bioconcentration factor from soil to edible plants is 19—i.e., the bioconcentration from soil to carrots from the study by Smelt and Leistra (1974, Table II, p. 69). Other edible items, such as potatoes and sugar beets, evidenced much lower bioconcentration factors ranging from about 0.23 to 1.24.

A particular limitation with this soil exposure scenario for hexachlorobenzene contamination subsequent to applications of picloram involves the potential for the human consumption of contaminated tubers from soil. Preliminary discussions with Forest Service personnel suggested that incidental (i.e., very minor) consumption of wild onions, sweet potatoes, or ginseng are plausible. It is much less clear that the longer-term consumption of substantial amounts of contaminated tubers is likely or even remotely so. Specifically, no particular tuber which might be consumed by individuals over prolonged periods of time from foraging in a treated forest has been identified; therefore, it is not possible to estimate the amount of material which might be consumed.

Nonetheless and as discussed in Section 3.2.3.7.1, the Forest Service has a concern for Native Americans or other individuals who may forage in forests. Consequently, a custom worksheet (i.e., Worksheet D04Soil) is included in Attachment 2 which will allow for the calculation of lifetime daily average doses associated with the consumption of contaminated tubers for soil containing hexachlorobenzene as a result of picloram applications. The concentrations of hexachlorobenzene in soil are based on the Gleams-Driver simulations detailed in Section 3.2.3.4.3. As summarized in Appendix 8 (Table A8-2), the peak concentrations of hexachlorobenzene in the top 12 inches of soil following an application of picloram at a rate of 0.1 lb a.e./acre are estimated at 0.181 (0.175 to 0.195) ppm—i.e., mg hexachlorobenzene/kg soil dry-weight. These concentrations are entered directly into Worksheet D04Soil and are used to calculate the concentration of hexachlorobenzene in soil under the assumption that picloram is applied at 1 lb a.e./acre and that the concentration of hexachlorobenzene in picloram is 3 ppm (Section 3.1.15.1).

As noted above, it is not possible to estimate the amount of a contaminated tuber which an individual might consume long term, given that no such specific tuber has been identified. For the current risk assessment, the assumption is made that the consumption rate for a tuber would be identical to the consumption rate used for contaminated fruit. While this is not the most extreme assumption that could be made, it seems reasonable to suggest that the consumption of foraged tubers would not exceed the typical consumption rates for fruit.

In Worksheet D04Soil, no adjustment for soil degradation or dissipation is made. In other words, the concentration of hexachlorobenzene in the top 12 inches of soil is based on the peak rather than average concentrations over a 1-year period. This very conservative approach, similar to the use of the biological rather than volatilization half-life for water (Section 3.2.3.4.3.1) is taken as a very conservative screen-level approach. As discussed further in Section 3.4.3, cancer risks associated with this exposure scenario are below the level of concern; thus, a refinement of this exposure scenario is not warranted.

In preliminary review of this scenario, concern was expressed for the possible buildup of hexachlorobenzene in soil in the event of annual applications of picloram made over of the course of several years. As discussed above, some Forest Service regions may apply picloram to the same site over the course of up to 6 years. Given the long half-live of hexachlorobenzene in lower soil layers, the accumulation of hexachlorobenzene over the course of several yearly applications is reasonable. As noted in Section 3.2.3.4.3.1, however, the Gleams-Driver simulations involve only two applications over a period of only 1½ years following the first application of picloram. To address this concern, auxiliary Gleams-Driver simulations were conducted over a period of 8 years with 8 applications made at 1-year intervals. A typical profile of hexachlorobenzene concentrations in soil is given in Figure 6. In this figure, the y-axis reflects the concentration in soil relative to the initial peak concentration following the first application. As illustrated in Figure 6, the concentration of hexachlorobenzene in soil does increase for the second application (which is included in all of the Gleams-Driver simulations discussed above) but does not increase substantially in subsequent years.

The failure of hexachlorobenzene to accumulate substantially in soil is clearly attributable to the rapid volatilization of hexachlorobenzene from the soil surface. For soil accumulation, the processes involved in the relatively rapid approach to steady-state are somewhat more complex than the plateau principle discussed in Section 3.1.3.3 because more processes are involved—i.e., volatilization, downward dispersion into the soil column, and biodegradation. In the example given in Figure 6, the apparent plateau is about 1.1.

While the exposure assessment for the uptake of hexachlorobenzene from soil to a tuber has many limitations, this exposure scenario is maintained in the event that a situation arises in a site-specific or region-specific assessment in which the uptake of hexachlorobenzene from soil into a plant is a scenario of concern. In this case, it should be relatively simple for Forest Service personnel to modify Worksheet D04Soil to address this concern.

3.3. DOSE-RESPONSE ASSESSMENT

3.3.1. Overview

Table 16 summarizes the toxicity values used in the current Forest Service risk assessment for human health effects. When the U.S. EPA/OPP adopts toxicity values for human health, which is the case for picloram, those values are typically adopted and used directly in Forest Service risk assessments. For picloram, the U.S. EPA/OPP (1995a, 1999) has a chronic RfD of 0.2 mg/kg bw/day. This RfD is modestly higher than an earlier RfD of 0.07 mg/kg bw/day proposed by U.S. EPA/ORD (1992). The more recent RfD of 0.2 mg/kg bw/day is well documented and is adopted in the current risk assessment. U.S. EPA/OPP has not derived an acute RfD for picloram. Other offices within the EPA—i.e., the Office of Drinking Water and the Office of Water—have proposed acute health advisories for picloram, and these values are used to derive a surrogate acute RfD of 2 mg/kg bw. Both of the chronic RfD and the surrogate acute RfD are based on NOAELs from studies in experimental mammals divided by an uncertainty factor of 100. While the dose-severity data on picloram are limited to studies in experimental mammals, these studies suggest that modest excursions above the acute and chronic RfDs would not be of substantial concern.

Technical grade picloram contains small amounts of hexachlorobenzene. Acute and chronic RfDs can be developed for hexachlorobenzene. In the current risk assessment, however, the available toxicity data on technical grade picloram is used directly to encompass the systemic toxicity of both picloram and hexachlorobenzene as an impurity in technical grade picloram. This approach is consistent with that of U.S. EPA/OPP in their risk assessments on picloram as well as the EPA guidelines for the risk assessment mixtures. In addition, a quantitative consideration of the acute and chronic RfDs for both picloram and hexachlorobenzene and the relative exposures to the two agents clearly indicates that picloram is of greater concern than hexachlorobenzene in terms of systemic toxicity by a factor of over 1000.

While picloram is not classified as a carcinogen, hexachlorobenzene is classified as a carcinogen. The EPA proposes a cancer potency factor of 1.02 $(mg/kg\ bw/day)^{-1}$ for hexachlorobenzene (U.S. EPA/OPP 1998b, 1999). Based on this cancer potency factor, the dose associated with a risk level of 1 in one million is 0.00000098 mg/kg bw/day. The dose associated with a 1 in one million risk level is used to derive HQs associated with the potential carcinogenicity of hexachlorobenzene as a contaminant in technical grade picloram.

3.3.2. Chronic RfD

The most recent RfD for picloram is 0.2 mg/kg/day, a value derived by the Health Effects Division of the U.S. EPA's Office of Pesticide Programs (U.S. EPA/OPP 1994a,d). This RfD is based on a NOAEL of 20 mg/kg/day from a 2-year rat feeding study (Landry et al. 1986). The RfD uses an uncertainty factor of 100—i.e., 10 for species-to-species extrapolation multiplied by a factor of 10 for sensitive individuals. At doses of 60 and 200 mg/kg/day, changes in the staining properties of liver cells, but no frank signs of toxicity, were noted. This RfD is also cited in the RED for picloram (U.S. EPA/OPP 1995a) as well as proposed pesticide tolerances for picloram (U.S. EPA/OPP 1999).

An earlier RfD of 0.07 mg/kg/day is listed on IRIS (U.S. EPA/ORD 1992). This RfD is based on a no-observed-effect level (NOEL) of 7 mg/kg/day from a 6-month dog feeding study (Barna-

Lloyd et al. 1982), also discussed in Section 3.1.5. This RfD also was derived using an uncertainty factor of 100. This earlier RfD is discussed in the peer-review report for the more recent RfD of 0.2 mg/kg bw/day (U.S. EPA/OPP 1994d). While this report does not specifically discuss the rationale for adopting the higher RfD of 0.2 mg/kg/day, the 2--year rat study was probably preferred because dogs are generally considered a poor animal model for human health risk assessment because of a decreased ability of dogs to secrete weak acids via the kidney.

Forest Service risk assessments generally adopt the most recent RfD from the U.S. EPA unless there is a compelling basis to do otherwise. On the basis of the well-documented review of the more recent RfD of 0.2 mg/kg bw/day in U.S. EPA/OPP (1994d) as consideration of the earlier RfD by U.S. EPA/OPP (1994d), the current Forest Service risk assessment adopts the more recent RfD of 0.2 mg/kg bw/day.

3.3.3. Acute RfD

The U.S. EPA/OPP will sometimes, particularly in more recent risk assessments, derive acute RfDs for some pesticides. Typically, acute RfDs are based on developmental studies under the assumption that the endpoint observed in the developmental study could be associated with a single dose of the pesticide. For picloram, however, U.S. EPA/OPP (1994a, 1995a, 1999) has not derived an acute RfD. In discussing the available acute toxicity data on picloram, U.S. EPA (1999) concludes that:

> *Acute dietary risk assessments are performed for a food-use pesticide if a toxicological study has indicated the possibility of an effect of concern occurring as a result of a 1 day or single exposure. No toxicological effect that could be attributable to a single oral exposure was identified, and therefore picloram is not expected to present an acute dietary hazard.*
>
> U.S. EPA/OPP 1999, p. 421, Section C.1.i.

As noted in Section 3.2.3.7.1, the dietary assessments developed by the U.S. EPA/OPP are based on pesticide tolerances in agricultural commodities rather than the types of acute exposures (both accidental and incidental) considered in Forest Service risk assessments.

The U.S. EPA's Office of Water (U.S. EPA/OW 1992) and the U.S. EPA's Office of Drinking Water (U.S. EPA/ODW 1987) propose a 10-day health advisory of 20 mg/L for a 10 kg child and recommend that the 10-day health advisory be used to assess concerns with exposure periods as short as 1 day. These short-term health advisories are intended to be used to manage emergency situations such as accidental spills (U.S. EPA/ODW 1987, p. 1). In this respect, Offices of Water and Drinking Water are considering events that are analogous to the acute exposures considered in Forest Service risk assessments. The 10-day health advisory of 20 mg/L is based on the NOAEL of 200 mg/kg bw/day from a 9-day acute bioassay in dogs (Dow Chemical 1980). As summarized in Table 5 of the current risk assessment, this study is supported by a 14-day NOAEL of about 575 mg/kg bw/day in rats (Hayes et al. 1986). In deriving the health advisory, an uncertainty factor of 100 is used, as in the derivation of the chronic RfD —i.e., 10 for species-to-species extrapolation multiplied by a factor of 10 for sensitive individuals. Thus, the 10-day health advisory of 20 mg/L is analogous to an acute RfD of 2 mg/kg bw/day [200 mg/kg bw/day ÷ 100]. In the absence of an acute RfD from U.S.

EPA/OPP, 2 mg/kg bw/day is be used as a surrogate acute RfD in the current Forest Service risk assessment.

3.3.4. Dose-Severity Relationships

Forest Service risk assessments of pesticides may consider dose-severity relationships if required to more fully characterize potential risks in exposure scenarios where estimated acute or chronic exposures exceed the corresponding RfD. As discussed further in Section 3.4.3, there are no exposure scenarios, including accidental exposure scenarios, that result in dose estimates that exceed the RfD. Consequently, a detailed elaboration of dose-severity relationships is not required for picloram. Nonetheless, it is worth noting that the dose-severity relationships for picloram do not appear to be particularly marked. As discussed in Section 3.1.5, the study on which the chronic RfD is based (Landry et al. 1986) notes only modest responses—i.e., increased liver weight and altered staining properties in the liver—at doses that exceed the chronic NOAEL of 20 mg/kg bw/day by factors of 3 and 10. Similarly, no overt signs of toxicity in dogs were noted at doses of picloram that exceed the acute NOAEL of 200 mg/kg bw/day by factors of 2 and 4.

Ratios of NOAELs to LOAELs in experimental mammals are not ideal for assessing and may not be directly applicable to dose-severity relationships in humans. Confidence in dose-severity relationships is enhanced if supplemented by data involving human exposures. No such data are available for picloram. The limited data on picloram suggest that modest and perhaps even substantial excursions above the acute or chronic RfDs, while clearly undesirable, might not be associated with overt signs of toxicity in humans.

3.3.5. Hexachlorobenzene Potency (Systemic Toxicity) Relative to Picloram

As discussed in Section 3.1.15.1, technical grade picloram contains hexachlorobenzene. Consequently, exposures to technical grade picloram involve exposures to a mixture of picloram and hexachlorobenzene. As discussed in the U.S. EPA guidance for mixtures risk assessment (U.S. EPA/ORD 2000), two general approaches can be taken to the risk assessment of mixtures, including the use of data on whole mixtures or the use of data on components in the mixture. If adequate data are available on the whole mixture, these data can and should be used directly in a risk assessment. For systemic toxic effects, this is the approach taken in the current risk assessment on picloram as well as in the EPA risk assessments on picloram (U.S. EPA/OPP 1994a, 1995a).

Nonetheless, a consideration of a component-based approach can be useful in addressing any residual concerns with the systemic toxicity of picloram, relative to that of hexachlorobenzene, by considering exposure-weighted relative potency. Specifically, the U.S. EPA has developed a chronic RfD of 0.0008 mg/kg bw/day for hexachlorobenzene (U.S. EPA/ORD 1996a). As discussed in Section 3.3.2, the chronic RfD for picloram is 0.2 mg/kg bw/day. In terms of potency (i.e., the ratio of equitoxic doses), hexachlorobenzene may be viewed as more potent than picloram by a factor of 250 [0.2 mg/kg bw/day ÷ 0.0008 mg/kg bw/day]. Thus, for an exposure that consisted of a 1-to-1 (1:1) mixture of picloram and hexachlorobenzene, the toxic agent of concern would be hexachlorobenzene (by a factor of 250).

As also discussed in Section 3.1.15.1, technical grade picloram is not a 1:1 mixture. Hexachlorobenzene is present in technical grade picloram at a concentration of no more than 3

ppm or a proportion of 0.000003. Thus, the exposure-weighted relative potency of hexachlorobenzene in technical grade picloram is 0.00075 [250 x 0.000003]. In other words, the agent of concern for systemic toxicity in technical grade picloram is picloram itself rather than hexachlorobenzene, and the relative concern for picloram is greater than that for hexachlorobenzene by a factor of over 1000 [$1 \div 0.00075 \approx 1{,}333.333\ldots$].

The U.S. EPA has not derived an acute RfD for hexachlorobenzene. ATSDR (2002), however, derived an acute MRL (minimum risk level, which is analogous to an RfD) for hexachlorobenzene of 0.008 mg/kg/day. This is a factor of 10 above the chronic RfD for hexachlorobenzene derived by U.S. EPA. As discussed in Section 3.3.3, the surrogate acute RfD for picloram is taken as 2 mg/kg bw/day, which is also a factor of 10 above the chronic RfD. Thus, in terms of exposure-weighted relative potency, the mathematics are the same as for chronic toxicity, and the relative concern for picloram is a factor of over 1000 greater than concerns for hexachlorobenzene.

3.3.6. Hexachlorobenzene Cancer Potency

As discussed in Section 3.1.10.2, the EPA classifies hexachlorobenzene as a carcinogen (U.S. EPA/OPP 1998b). Cancer risk is quantified by the U.S. EPA and many other organizations using a cancer potency factor (often designated as a Q_1^*) in units of reciprocal dose such as $(\text{mg/kg bw/day})^{-1}$. In most cancer risk assessments, the EPA (e.g., U.S. EPA/RAF 2005) assumes that cancer is a nonthreshold response and that the risk is linearly related to dose. Under this assumption, cancer risk over a lifetime (***P***) is calculated as the product of the lifetime daily dose (***d***) over a lifetime and the potency parameter ($\mathbf{Q_1^*}$):

$$P = d\, Q_1^*$$

and the lifetime daily dose associated with a given risk level is:

$$d = P \div Q_1^*$$

The U.S. EPA derived a cancer potency factor for hexachlorobenzene of 1.02 $(\text{mg/kg bw/day})^{-1}$ (U.S. EPA/OPP 1998b, 1999).

Forest Service risk assessments defer to the U.S. EPA in the derivation of cancer potency factors. In deriving cancer potency factors, the EPA has full access to the studies on which the cancer potency factors are based; furthermore, the derivations of the potency factors undergo extensive EPA review. Consequently, the current risk assessment uses the potency factor of 1.02 $(\text{mg/kg bw/day})^{-1}$ from U.S. EPA/OPP (1998b, 1999).

In Forest Service risk assessments, risk characterization for systemic toxic effects is expressed as a hazard quotient (HQ)—i.e., the ratio of the exposure to the RfD. To employ the same basic approach for carcinogens, Forest Service risk assessments calculate a dose associated with a 1 in one million (i.e., $1 \div 10^6 = 10^{-6}$) risk of cancer. The dose associated with a risk of 1 in one million is then used to derive an HQ similar to that used for systemic toxicity. For hexachlorobenzene, the dose is calculated as above using the potency factor of 1.02 $(\text{mg/kg bw/day})^{-1}$ and rounding to two significant digits:

$$d = 10^{-6} \div 1.02\ (\text{mg/kg bw/day})^{-1} = 0.00000098\ \text{mg/kg bw/day}.$$

It is important to note that the above dose is the lifetime average dose (i.e., the individual is assumed to be exposed to this dose from birth to death). From a practical perspective, daily exposures to any chemical from birth to death are unlikely. As discussed in Section 3.2, the daily dose is adjusted by the fraction of the lifespan over which exposures are assumed to occur to calculate the lifespan adjusted daily dose.

3.4. RISK CHARACTERIZATION

3.4.1. Overview

Workers are not at substantial risk from exposures to either picloram or hexachlorobenzene—i.e., all of the upper bound HQs are less than one at the maximum anticipated application rate for picloram of 1 lb a.e./acre. Confidence in this assessment is relatively high. For workers, the risk characterization is based on exposure rates used in all Forest Service risk assessments, and these rates are derived from studies which include worker applications of picloram (Section 3.2.2.1).

For members of the general public, the only exposure scenario that leads to an HQ above the level of concern (HQ=1) is the upper bound HQ for the longer-term consumption of contaminated vegetation (HQ=2) at the maximum anticipated application rate of 1 lb a.e./acre. This scenario would not lead to an exceedance in the level of concern at more typical application rates of 0.5 lb a.e./acre or less. While a modest exceedance in the level of concern cannot be viewed as acceptable, there is no basis for asserting that detectable adverse effects would be noted. In addition, the scenario for the longer-term consumption of contaminated vegetation may not be plausible in most instances because picloram will cause visible damage to vegetation that is directly sprayed.

Irritation and damage to the eyes can result from exposure to relatively high levels of picloram (i.e., placement of picloram directly onto the eye). In addition, repeated exposures to a Tordon formulation has lead to skin sensitization in experimental mammals. From a practical perspective, eye irritation is likely to be the only overt toxic effect as a consequence of handling picloram. This effect can be minimized or avoided by prudent industrial hygiene practices during the handling of picloram formulations. Reports of skin sensitization in workers handling picloram are not documented in the literature. Atypical dermal responses in a worker during the course of picloram applications would warrant evaluation by a clinician.

3.4.2. Workers

The quantitative risk characterization for workers is summarized in Table 17. This table is based on Worksheets E02 in Attachment 1 (the systemic toxicity of picloram) and E02 in Attachment 2 (the potential carcinogenicity of hexachlorobenzene). The HQs for picloram are based on the maximum anticipated application rate of 1 lb a.e./acre. The HQs for hexachlorobenzene are also based on an application rate of 1 lb a.e./acre for picloram under the assumption that the technical grade picloram in the formulation is contaminated with hexachlorobenzene at a concentration of 3 ppm. In addition, the HQs for hexachlorobenzene are calculated as the ratio of the estimated absorbed dose divided by the dose of hexachlorobenzene associated with a cancer risk of 1 in 1-million (Section 3.3.6).

Based on both systemic toxicity and carcinogenicity, there is no indication that workers are at risk at during applications of picloram. The highest HQs are associated with upper bound estimates of exposure in workers applying picloram in ground broadcast applications—i.e., an HQ of 0.8 for the systemic toxicity of picloram and 0.5 for the potential carcinogenicity of hexachlorobenzene.

While the accidental exposure scenarios are not the most severe one might imagine (e.g., complete immersion of the worker or contamination of the entire body surface for a prolonged

period of time) the accidental exposure scenarios are representative of reasonable accidental exposures considered in all Forest Service risk assessments. None of these HQs approach a level of concern, even at the upper bounds of the estimated exposures. The simple verbal interpretation of this quantitative characterization of risk is that under the most protective set of exposure assumptions, workers would not be exposed to unacceptable levels of picloram, so long as reasonable and prudent handling practices are followed.

As discussed in Section 3.1.11.3, picloram may cause moderate and transient eye irritation. Quantitative risk assessments for eye irritation are not derived; however, from a practical perspective, effects on the eyes are likely to be the only overt toxic effects as a consequence of accidental exposures to picloram. These effects can be minimized or avoided by prudent industrial hygiene practices during the handling of picloram.

As discussed in Section 3.1.11.2, Tordon 22K has been associated with skin sensitization (i.e., delayed contact hypersensitivity) in guinea pigs. No case reports of skin sensitization in humans associated with exposures to Tordon formulations have been encountered in the literature. Unlike irritant effects, responses associated with hypersensitivity may occur at very low doses and may be more difficult to mitigate than general irritant effects. If workers involved in applications of picloram formulations show signs of atypical skin sensitivity to the formulations, clinical evaluations could be warranted. This type of recommendation, however, is generic and would apply to the use of any pesticide formulation.

3.4.3. General Public

The quantitative risk characterization for members of the general public is summarized in Table 18. Analogous to the corresponding table for workers discussed in the previous subsection, Table 18 is based on Worksheets E04 in Attachment 1 (the systemic toxicity of picloram) and E04 in Attachment 2 (the potential carcinogenicity of hexachlorobenzene). Also as with the corresponding table for workers, the HQs are based on the maximum anticipated application rate of 1 lb a.e./acre for picloram and the assumption that the technical grade picloram in the formulation is contaminated with hexachlorobenzene at a concentration of 3 ppm.

Only one HQ exceeds the level of concern – i.e., the upper bound HQ of 2 for the longer-term consumption of contaminated vegetation. As discussed in Section 3.2.3.7.1, the exposure scenario for the longer-term consumption of contaminated vegetation is a standard scenario used in all Forest Service risk assessments involving foliar applications of pesticides. Nonetheless and as also discussed in Section 3.2.3.7.1, this exposure scenario may be viewed as extreme and unlikely to occur. This exposure scenarios assumes that the food item is directly sprayed with picloram at the application rate of 1 lb a.e./acre. As detailed further in Section 4.4.2.5.1 (risk characterization for terrestrial plants), the direct spray of plants that might be consumed by humans (i.e., dicots) are likely to be severely damaged. That individuals would consume damaged vegetation over a long-term period of time does not seem likely.

Notwithstanding the implausibility of the exposure scenario, there appears to be no basis for asserting that a modest excursion above the chronic RfD (i.e., an HQ of 2) would lead to substantial adverse effects. As discussed in Section 3.3.3, the chronic RfD is based on a NOAEL of 20 mg/kg bw/day with a LOAEL of 60 mg/kg bw/day. At the dose of 60 mg/kg

bw/day, the only effect noted was an alteration of staining properties in liver cells. Thus, while any excursion above the RfD should be viewed with concern, it does not appear that HQs of up to 3 would be associated with detectable adverse effects.

The upper bound HQ of 2 for the consumption of contaminated vegetation is associated with an application rate of 1 lb a.e./acre, the maximum application that is anticipated in Forest Service programs. The HQ for this scenario is linearly related to the application rate. Thus, at application rates of 0.5 lb a.e/acre, the HQ for this exposure scenario would not exceed the level of concern. As discussed in Section 2.4, the typical application rates used in Forest Service programs are likely to be below 0.5 lb a.e./acre.

All of the HQs for carcinogenicity associated with hexachlorobenzene as a contaminant in technical grade picloram are also below the level of concern. The highest HQ associated with hexachlorobenzene is 0.4, the upper bound for the consumption of contaminated fish by subsistence populations. This exposure scenario is driven by the concentration of hexachlorobenzene in water. As discussed in Section 3.2.3.4.3.1, the Gleams-Driver modeling for hexachlorobenzene is conservative in that the rapid volatilization of hexachlorobenzene from surface water is not quantitatively incorporated into the exposure assessment. Consequently, the HQs for the consumption of contaminated fish given in the current risk assessment may be viewed as overestimates. For dietary exposures associated with broadcast deposition onto vegetation, the higher HQ is 0.004, below the level of concern by a factor of 250. This very low HQ requires no elaboration. The higher HQ associated with the consumption of a contaminated tuber is 0.1, below the level of concern by a factor of 10. This exposure scenario is driven by the estimated concentration of hexachlorobenzene in soil. As also discussed in Section 3.2.3.7.2.2, this exposure scenario is based on peak rather than average concentrations of hexachlorobenzene in soil. Thus, as with the HQs for the consumption of fish, the HQs associated with the consumption of tubers may also be viewed as conservative.

3.4.4. Sensitive Subgroups

There is no information to suggest that specific groups or individuals may be especially sensitive to the systemic effects of picloram. As discussed in Sections 3.1 and 3.3.2, the likely critical effect of picloram in humans cannot be identified clearly. In animals, the most sensitive effect of picloram involves changes in the staining characteristics of liver cells. These effects, however, were only noted in one study and are not consistent among species or even between different studies in the same species. Thus, it is unclear if individuals with pre-existing liver disease would be particularly sensitive to picloram exposures, although individuals with any severe disease condition could be considered more sensitive to many toxic agents.

As with most weak acids, picloram is excreted primarily by the kidney (Section 3.1.3.3). Individuals with kidney disease could have an impaired ability to excrete picloram, as well as many other weak acids. No reports, however, linking picloram exposures with adverse effects in individuals with kidney disease were identified in the literature.

Some individuals report a high degree of sensitivity to multiple chemicals, resulting in a broad-spectrum of effects, many of which are similar to allergic reactions. This condition is generally referred to as *Multiple Chemical Sensitivity* (e.g., ATSDR 1995). The literature does not include

any association between exposure to picloram and adverse effects in individuals who report having Multiple Chemical Sensitivity.

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

As detailed in this risk assessment, the use of picloram will involve concurrent exposures to hexachlorobenzene. As discussed in this risk assessment, the systemic toxicity of hexachlorobenzene is encompassed by the use of toxicity studies on technical grade picloram (Section 3.1.15.1) and considerations of the amount of hexachlorobenzene in technical grade picloram as well as the systemic toxicity of both picloram and hexachlorobenzene indicate that picloram is the agent of concern in terms of systemic toxicity (Section 3.3.5). Nonetheless, hexachlorobenzene is classified as a carcinogen, and potential carcinogenic risk is not encompassed by considerations of the data on picloram. Consequently, this risk assessment develops both exposure and dose-response assessments for hexachlorobenzene. As discussed in the previous subsection, the potential carcinogenic risks associated with exposures to hexachlorobenzene in the use of picloram formulations is below the level of concern.

3.4.6. Cumulative Effects

Cumulative effects involve the consideration of co-exposure to picloram and other agents that may impact or add to the risks of exposures to picloram. 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 picloram, and to do so quantitatively would require a complete set of risk assessments on each of the other agents to be considered.

Addressing cumulative effects, within the context of the Food Quality Protection Act, requires the assessment of chemicals with a similar mode of action. In the most recent assessment of cumulative effects associated with picloram, the U.S. EPA states:

> *EPA does not have, at this time, available data to determine whether picloram has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, picloram 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 picloram has a common mechanism of toxicity with other substances.*
>
> – U.S. EPA/OPP, 1999, p. 422.

Cumulative effects may also be considered to include the consequences of repeated exposures, which are explicitly considered in the current risk assessment in terms of both the systemic toxicity picloram and the potential carcinogenicity of hexachlorobenzene.

4. ECOLOGICAL RISK ASSESSMENT

4.1. HAZARD IDENTIFICATION

4.1.1. Overview

As with any effective terrestrial herbicide, picloram poses potential hazards to nontarget terrestrial plants. In general, picloram is more toxic to dicots than to monocots and is more toxic by foliar than soil exposures (i.e., it is more effective as a post-emergent rather than a pre-emergent herbicide). This assessment of hazards to terrestrial vegetation is based primarily on two registrant-submitted studies (Schwab 1995; Weseloh and Stockdale 1989). While both of these studies appear to have been well conducted, there are substantial differences between the results of these studies for some of the same species. The inexplicable differences add uncertainty to the identification of tolerant and sensitive plant species.

Potential hazards to terrestrial animals are less apparent. As discussed in the human health risk assessment, experimental mammals are not particularly sensitive to picloram, although adverse effects may be induced at high doses. As with all groups of nontarget receptors, the hazard identification for mammals in the ecological risk assessment is limited due to a lack of available data on all but a relatively few species of mammals. This limitation, albeit noteworthy, is common to virtually all ecological risk assessments. Based on a relatively standard set of avian studies required by the U.S. EPA, which are supplemented by additional studies in the open literature, picloram does not appear to be highly toxic to birds or terrestrial invertebrates. There is no information available on the toxicity of picloram to terrestrial-phase amphibians.

A relatively substantial proportion of the data on aquatic organisms is from the older literature, some of which cannot be used directly in the current risk assessment because of reporting deficiencies, particularly in terms of the agent tested and the units of measure in which the data are expressed. Conversely, the available studies on the acute toxicity of picloram to fish are robust, with multiple and largely internally consistent bioassays available on several species of fish. These data indicate that the lake trout and cutthroat trout are the fish species most sensitive to picloram and that rainbow trout appear to be intermediate in their sensitivity to picloram and less sensitive than channel catfish. Bluegills and minnows are among the more tolerant species of fish. The chronic toxicity of picloram to fish is also well characterized with early life-stage studies available in four species of fish. Species sensitivity differences among fish in chronic studies appear to be similar to those observed in acute studies. The toxicity of picloram to aquatic invertebrates is less well characterized, and there do not appear to be substantial differences in sensitivity among species. While the useful data on aquatic plants are limited to a few registrant-submitted studies, these studies define a wide-range of sensitivities in algae. The useful data on aquatic macrophytes are limited to a single study in a species of duckweed.

Applications of picloram, an effective herbicide, are likely to alter terrestrial and certain aquatic vegetation. These effects may impact terrestrial and aquatic animals by altering food availability and habitat quality, which may be beneficial to some animal species and deleterious to others. These types of secondary effects are common to all herbicides. Except where specific data are available on secondary effects associated with picloram applications, these potential but poorly defined secondary effects are not discussed further in this risk assessment.

4.1.2. Terrestrial Organisms

4.1.2.1. Mammals

Several standard toxicity studies have been conducted with experimental mammals as part of the registration process for picloram and these studies are relevant to the hazard identification for mammalian wildlife. As discussed in Sections 3.1.4 and 3.1.5 and summarized in Table 6, no clear organ-specific pathological effects are associated with picloram, and the most sensitive endpoints appears to be nonspecific alterations in the staining properties of liver tissue with altered liver and kidney weights noted at higher doses.

Because picloram is a weak acid, there is concern for the potential increased sensitivity of dogs and other canid species. As discussed in the Forest Service risk assessments for triclopyr (SERA 2011b), dogs have an impaired capacity to excrete some weak acids and, as a result, are sometimes much more sensitive than other mammals to weak acids. With some other weak acid herbicides, like aminopyralid (SERA 2007c), there is no indication that dogs are more sensitive than other mammalian species. As summarized in Table 5 and detailed further in Appendix 1 (Table A1-2), the 6-month feeding study by Barna-Lloyd et al. (1982) notes a NOAEL of 7 mg/kg bw/day with a corresponding LOAEL of 35 mg/kg bw/day based on increased liver weights with no corresponding liver pathology. In rats, the corresponding subchronic NOAEL and LOAEL doses for the same endpoint are 50 and 150 mg/kg bw/day (Gorzinski et al. 1982). In chronic studies, however, the corresponding NOAEL/LOAELs for rats and dogs are not substantially different—i.e., 35/175 mg/kg bw/day for dogs (MRID 40834301) and 30/60 mg/kg bw/day for rats (Landry et al. 1986). Comparisons of subchronic and chronic NOAEL/LOAELs between species, however, are inherently imprecise because of differences in the durations of exposure used for rats and dogs in nominally *chronic* studies as well as differences in the dose levels used, which are in some ways artifacts of the doses selected by the different investigators designing and conducting the studies. Given the similarities in the chronic NOAELs for dogs and rats, as well as the failure of the 6-month dog study to note any clear adverse effect, the significance of apparent differences in the subchronic NOAELs and LOAELs for dogs and rats is questionable. Thus, based on the subchronic and chronic toxicity studies, there appears to be no compelling basis for asserting that dogs and other canid species are more sensitive than other mammals to picloram. No acute toxicity studies are available on dogs. This data gap is not uncommon for pesticides. As discussed in Section 3.1.4, the limited acute oral LC_{50} values on several other nonstandard test species for acute toxicity studies (i.e., rabbits, guinea pigs, sheep, mice, and cows) do not suggest any systematic difference in sensitivity to picloram based on body weights.

The application of any effective herbicide will damage at least some vegetation, and this damage, in turn, may alter (either positivity or negatively) the suitability of the treated area for mammalian wildlife in terms of habitat or food supply. Several field studies note such secondary effects on mammals following the application of picloram either alone or with other herbicides (Brooks et al. 1995; Nolte and Fulbright 1997; Pearson and Callaway 2008). The studies by Brooks et al. (1995) and Pearson and Callaway (2008), indicate that the observed decreases in the populations of small mammals were apparently due to decreases in food supply rather than any direct toxic effect of picloram to mammals. No effect on populations of small mammals are noted in the study by Nolte and Fulbright (1997); however, as noted in the

discussion by Nolte and Fulbright (1997), this study involved relatively few replicates and observation periods. Consequently, the statistical power of the study is limited.

4.1.2.2. Birds

For most pesticides, including most herbicides, the U.S. EPA typically requires a standard set of toxicity studies in a game bird (usually bobwhite quail) and a water fowl (usually mallard ducks) which include acute gavage, acute dietary, and one-generation dietary reproduction studies (U.S. EPA/OCSPP 2011). As summarized in Appendix 2, standard acute oral gavage studies (Table A2-1) and acute dietary studies (Table A2-2) are available on picloram. Studies relating to potential reproductive effects consist of two standard reproduction studies (Mach 2002; Stevenson 1965a,b) and two open literature publications involving exposure of bird eggs (Table A2-3).

4.1.2.2.1. Acute Gavage Toxicity

As summarized in Appendix 2 (Table A2-1), all of the standard acute oral gavage LD_{50} studies in birds report indefinite LD_{50} values of >2000 mg/kg bw. According to the classification scheme used by U.S. EPA/OPP, picloram would be classified as practically nontoxic to birds, based on acute gavage dosing.

There are minor inconsistencies and uncertainties in the available data on acute gavage toxicity. One definite LD_{50} of 6000 mg/kg bw is reported for chickens in the Hazardous Substances Database (HSDB 2011); however, no details of the study have been identified. In Appendix 2 (Table A2-1), LD_{50} values in birds from studies with designated MRID (Master Record Identification) numbers are reported only for mallards. The EPA ecological risk assessment (U.S. EPA/OPP 1994b) conducted in support of the Reregistration Eligibility Decision for picloram (U.S. EPA/OPP 1995a) lists an LD_{50} of >2250 mg/kg bw for quail referenced to MRID No. 164727. A gavage oral LD_{50} in quail with a value designated as >2250 mg/kg bw has not been identified in the conduct of the current risk assessment. Based on the bibliography in the Reregistration Eligibility Decision for picloram (U.S. EPA/OPP 1995a, p. 177), the MRID referenced in U.S. EPA/OPP (1994b, p. 47) is a dietary study in mallards (Beavers 1986), as discussed further below.

Few details are available on the three gavage oral LD_{50} studies in Tucker and Crabtree (1970), which is a compendium of avian toxicity studies conducted and compiled by the Fish and Wildlife Service. The two MRID studies, one on picloram acid (Beavers 1983) and the other on potassium picloram (Beavers 1985) are documented in detail, and full copies of these studies were available in the conduct of the current risk assessment. While both studies report oral LD_{50} values of greater than about 2000 mg a.e./kg bw, the NOAEL for picloram acid (≈400 mg a.e./kg) is much lower than the NOAEL for the potassium salt of picloram (≈1943 mg a.e./kg bw). At doses of 631 mg a.e./kg bw and greater, picloram acid caused general signs of toxicity, including lethargy, incoordination, and limb weakness (Beavers 1983). These effects were not noted in any of the 30 birds exposed to comparable or higher doses of potassium picloram—i.e., the three higher dose groups in Beavers (1986).

4.1.2.2.2. Acute Dietary Toxicity

As summarized in Appendix 2 (Table A2-2), the acute dietary toxicity studies on picloram consist of one well-documented study in quail (Beavers 1986), an early study in mallards

(Stevenson 1965c), and several summary reports on various species of birds from the U.S. Fish and Wildlife Service (Hill and Camardese 1986; Heath et al. 1972; Hill et al. 1975). All of the dietary LC_{50} values are >5000 ppm. As with the acute gavage toxicity studies, these values can be used to classify picloram as virtually nontoxic to birds, according to the categorization system typically employed by U.S. EPA/OPP. U.S. EPA/OPP (1994b) references several additional acute dietary studies with indefinite LC_{50} values ranging from >5620 to >10,000 ppm. Citations for these studies, however, are not provided in U.S. EPA/OPP (1994b), and the MRID numbers specified for the studies in U.S. EPA/OPP (1994b, pp. 21 to 22) do not correspond to MRID numbers given in the Reregistration Eligibility Decision for picloram (U.S. EPA/OPP 1995a). Because these studies report high LC_{50} values and would not have an impact on the current Forest Service risk assessment, the studies are not further considered.

As with the acute gavage studies, two well-documented acute dietary studies are available, one using picloram acid (Stevenson 1965c) and the other using potassium picloram (Beavers 1986), and full copies of both of these studies were available in the preparation of the current risk assessment. As detailed in Appendix 2 (Table A2-2), both of these are registrant-submitted studies. Neither study notes any signs of toxicity associated with exposure to picloram. Stevenson (1965c) calculates an LC_{50} of 56,711 ppm. Given the low mortality and lack of any concentration-response relationship (i.e., a maximum mortality of 1/10 animals in any single dose group), the calculated LC_{50} has little meaning. The LC_{50} for this study should be viewed as >10,000 ppm. As detailed in Appendix 2 (Table A2-2), the cumulative mortality in all treated groups combined is 6/80. Using the Fisher Exact test, this incidence is marginally significant, relative to the cumulative control mortality of 0/50. Nonetheless, there is clearly no concentration-response relationship with no mortality observed in the group exposed to the highest concentration tested (10,000 ppm). Based on reported food consumption and body weights, the NOAEC of 10,000 ppm corresponds to a NOAEL of about 2500 mg/kg bw/day, which is substantially greater than the gavage NOAEL for picloram acid in mallards—i.e., 398 mg a.e./kg bw from the study by Beavers (1983).

In the acute dietary study in which quail were exposed to potassium picloram (Beavers 1986), no treatment-related effects were observed in any of the exposed groups. Thus, the NOAEC is 5620 ppm, the highest concentration tested. Based on reported food consumption and body weights, the NOAEC of 5620 ppm corresponds to a NOAEL of about 1600 mg/kg bw/day. Because of the lack of treatment-related toxicity in this study, the lower NOAEL (relative to the above study on picloram acid) does not suggest that potassium picloram is more toxic than picloram acid. The differences simply reflect the differences in the dietary concentrations used in the two studies.

4.1.2.2.3. Reproductive Effects

Two standard reproductions studies (Mach 2002; Stevenson 1965a,b) are available. The study by Stevenson (1965a,b with MRID numbers 41470 and 41909) is not cited in the relevant EPA risk assessments on picloram (U.S. EPA/OPP 1994b, 1995a). As detailed in Appendix 3 (Table A3-3), the DER for this study indicates that the U.S. EPA/OPP judged the study to be inadequate for risk assessment because of major reporting deficiencies.

No standard reproduction studies involving dietary exposures of male and female birds prior to and during mating were identified in the literature on picloram. Two studies (Hoffman and

Albers 1984; Somers et al. 1978) are available, and both involve exposures of eggs to picloram solutions (Appendix 2, Table A2-3). Full copies of Stevenson (1965a,b) were available for the current risk assessment, and the judgment by U.S. EPA/OPP is appropriate. The study by Stevenson (1965a,b) is not clearly detailed, and the information in the study cannot be used.

Since the early EPA risk assessments on picloram (U.S. EPA/OPP (1994b, 1995a) were conducted, a reproduction study in quail has been conducted (Mach 2002). As summarized in Appendix 2 (Table A2-3), adult quail were exposed to picloram acid at dietary concentrations of 0, 375, 750, and 1500 ppm (mg a.e./kg diet). The offspring were observed for 14-days post-hatching but were fed only control diets. This study does not appear to have been submitted to the U.S. EPA/OPP and no Data Evaluation Record (DER) for this study is available. The study, however, has been submitted to and reviewed by the European Union (2007).

In the Mach (2002) study, no effects were noted in adults. In addition, no overt signs of toxicity were noted in offspring. Based on analysis of variance of body weight in offspring on Day 14, however, a statistically significant decrease in body weights was noted in all three treatment groups. Experimental details and statistical analyses of these data are given in Appendix 10. As summarized in Appendix 10, the magnitude of the decreases in hatching body weight in the three dose groups was about 9% and was not dose-related. In discussing the decrease in body weight, Mach (2002) notes the following:

> *A difference of 3 grams would be considered biologically negligible. Brooder arrangement was examined as a potential cause of the anomaly, but weekly analysis of the data does not consistently identify an effect. The data appears to be an aberration, as it cannot be explained by dose response, associated hatchling effect, or study design.*
>
> Mach (2002, p. 24)

The review of this study by the European Union (2007) concurs with the above assessment:

> *The biological relevance of the differences in mean bodyweight of the 14 day old chicks of 2 to 3 grams in the test substance groups is not known. Brooder arrangement was examined as a potential cause of the anomaly, but weekly analysis of the data does not consistently identify an effect. The data appears to be an aberration, as it cannot be explained by dose response, associated hatchling effect, or study design.*
>
> European Union (2007, p. 293)

No effect on body weights were noted on Day 0 chicks (i.e., the day of hatching), and observations on weights in chicks were not made beyond 14 days after hatching, which is regrettable, because it cannot be determined if the slight decrease in body weights was transient. A longer observation period would have improved the ability to interpret the potential toxicological significance of the slight reduction of Day 14 body weights in chicks. This matter is discussed further in the dose-response assessment for birds (Section 4.3.2.2).

The quail assay by Mach (2002) included several standard endpoints relating to the health and survival of chicks. Mach (2002) noted a significant difference (based on ANOVA) in 14-day hatchling survival per number of normal hatchlings This effect, however, was not viewed as biologically significant because Bonferroni's t-test did not show any differences (Mach 2002, p. 42). Conversely, 14-day mortality in hatchlings per total number of eggs laid did not show any significant differences when analyzed by ANOVA but the high dose group did evidence a significant decrease in survivorship. The review of the Mach (2002) study by European Union (2007, p. 293) concurs with the statistical analyses by Mach (2002) and cites the 1500 ppm dose group as a LOEL based on decreased hatchling survival with a corresponding NOEL of 750 ppm. Details of these as well as other related endpoints are also discussed further in Appendix 10. Unlike body weight, these effects are quantal – all or none – and other statistical tests specifically designed by quantal data are applied in Appendix 10. Based on these statistical methods, several endpoints related to survival appear to indicated effects on mortality in hatchlings that are statistically significant. This is discussed further in the dose-response assessment.

The study by Hoffman and Albers (1984) is essentially a screen assay that involves submersing mallard eggs for 30 seconds in a pesticide solution and then observing mortality and hatching. This assay involved exposure to several individual pesticides. For picloram, the LC_{50} is reported as 100 lbs per 100 gallons, which is equivalent to a concentration of about 200,000 mg/L [100 lb = 45360 g / 100 gal = 378.5 L = 198.841 g/L = 198,841 mg/L]. In terms of sublethal toxicity, the only observation in Hoffman and Albers (1984) is decreased growth in survivors at doses greater than the LC_{50}. While this study may be viewed as a reasonable screening and comparative toxicity evaluation, the study is of limited relevance to the current risk assessment. As detailed in Worksheet A01 of the EXCEL workbook for picloram (Attachment 1), the highest anticipated field solution for picloram of 1 lb/acre at an application volume of 5 gallons/acre is about 24 mg/mL or 24,000 mg/L. As detailed further in Worksheet B04b of Attachment 1, the highest concentration of picloram in a small pond following an accidental spill is about 18 mg/L. Thus, the levels of exposure used by Hoffman and Albers (1984) are far higher than those anticipated in Forest Service programs. In addition, and as discussed further in Section 4.2.2, incidental contamination of bird eggs is conceivable, but the major route of exposure to birds as well as mammals involves the consumption of contaminated water and vegetation.

The study by Somers et al. (1978) does not clearly describe the nature of the exposures to bird eggs. The study notes that fertile eggs from *Gallus domesticus* were sprayed with 10 times the recommended dosage of Tordon 22K either prior to incubation or 4 and 18 days after incubation. No adverse effects were noted in the hatched chicks. The study appears to be summarized in U.S. EPA/OPP (1994b, p. 22); however, the summary is not specifically referenced to Somers et al. (1978). The EPA interprets the exposure as equivalent to a NOEL of 11.2 kg/ha, approximately 10 lb/acre. This interpretation is consistent with the maximum anticipated application rate of 1 lb a.e./acre and the exposure description given by Somers et al. (1978). As with the study by Hoffman and Albers (1984), the study by Somers et al. (1978) cannot be used directly in assessing the consequences of longer-term exposures of birds to picloram in contaminated food or water.

4.1.2.3. Reptiles and Amphibians (Terrestrial-Phase)

There is no information in the picloram literature regarding its toxicity to reptiles or terrestrial-phase amphibians. Neither the database maintained by Pauli et al. (2000) nor the open literature includes information on the toxicity of picloram to reptiles or terrestrial-phase amphibians. In addition, no discussion of the effects of picloram on this group of organisms is provided in the EPA risk assessment on picloram (U.S. EPA/OPP 1994b, 1995a).

4.1.2.4. Terrestrial Invertebrates

4.1.2.4.1. Honeybees

In the United States, the registration requirements for testing the effects of herbicides on terrestrial invertebrates are relatively modest, and registrants typically submit only tests on honey bees.

For the potassium salt of picloram, the 48-hour contact LD_{50} value in the honey bee (*Apis mellifera*) was determined to be greater than 100 µg a.i/ bee and the no-observed-effect dose was 22 µg a.i./bee (Hoxter et al. 1989, MRID 41366902). Based on a control mortality of 4/100 and a mortality rate of 7/100 in the 22 µg/bee dose group, Hoxter et al. (1989) report a NOAEL of 22 µg/bee. This determination is appropriate based on the Fisher Exact test (p=0.268569). At the next higher dose, mortality was 13/100 (p=0.019894). The NOAEL for mortality of 22 µg a.i./bee is equivalent to about 19 µg a.e./bee. The mean body weight of the bees used in this study is reported as 82 mg (Hoxter et al. 1989, Table 1). Using this body weight, the NOAEL of 19 µg a.e./bee corresponds to a dose of about 270 mg a.e./kg bw [0.022 mg ÷ 0.000082 kg ≈ 268.29 mg/kg bw], similar to the reported NOAELs in mammals and birds.

More recently, Hoberg (2001) conducted a study on picloram acid involving both contact and oral exposures. In this study, groups of 30 bees were exposed to average doses of 1.0, 10 and 100 µg a.i./bee in the contact assay and a dose of 100 µg a.i./bee in the oral assay – i.e., picloram in sucrose. In the contact assay, no dose-response relationship was observed based on cumulative mortality at 48-hours – i.e., 3.3% (controls), 10% (1 µg/bee) , 3.3% (10 µg/bee) and 6.7% (100 µg/bee). In addition, the combined mortality of 2/60 in the pooled control and solvent control groups was not significantly different from the mortality of 2/30 in the high-dose group – i.e., p=0.407388 using the Fisher Exact test. In the oral study, cumulative mortality in the combined control (0%) and solvent control group (3.3%) was 1/60 and cumulative mortality in the 100 µg/bee group was 1/30, which is also statistically insignificant – i.e., p=0.558052 using the Fisher Exact test. Thus, in both assays, the NOAEC for mortality is 100 µg/bee. While these types of acute bioassays in honeybees do not involve elaborate assays for sublethal effects, no sublethal effects were noted in terms of activity patterns. For the positive control compound, dimethoate, sublethal observations included lethargy in all surviving bees. This effect was not noted in bees exposed to picloram.

The study by Hoberg (2001) does not report the body weights of the bees. Typical body weights for worker bees range from 81 to 151 mg (Winston 1987, p. 54). Taking 116 mg as an average body weight, a dose of 100 µg/bee corresponds to about 860 mg a.e./kg bw [0.1 mg a.e./bee ÷ 0.000116 kg/bee ≈ 862.07 mg/kg bw]. This dose is about a factor of about 3 higher than the 270 mg a.e./kg bw in the contact assay of potassium picloram from the study by Hoxter et al. (1989) [860 mg/kg bw ÷ 270 mg a.e./kg bw ≈ 3.185].

Atkins et al. (1975) provide a compendium of contact toxicity studies in honeybees conducted by the University of California. In this compendium, a dose of 14.5 µg/bee for picloram (Tordon 22K) is associated with a mortality rate of 7.4%. Additional details of the study are not provided. Specifically, mortality in the matched control group is not specified, and it is not clear if the dose is expressed as picloram acid, potassium picloram, or Tordon 22K. Thus, this study is not directly useful in the current risk assessment.

4.1.2.4.2. Other Terrestrial Invertebrates

Very little information is available on the toxicity of picloram to other terrestrial invertebrates. At dietary concentrations of about 5000 mg/kg over a 14-day period, picloram (acid) did not increase mortality in the brown garden snail, *Helix aspersa* (Schuytema et al. 1994).

Jacobs et al. (2000) conducted a field study to determine if picloram applications had an impact on a beneficial weevil (*Cyphocleonus achates*) used to control spotted knapweed (*Centaurea maculosa*). Low application rates of 0.03, 0.06, and 0.09 kg/ha had no impact on the weevil. Application rates of 0.12 and 0.15 kg/ha, however, reduced weevil numbers by about 50%. This effect does not appear to be a direct impact of picloram on the weevil; it is, however, associated with the effect of picloram on spotted knapweed cover. The publication does not specify the formulation of picloram or form of picloram. In addition, it is not clear if the application rates are expressed in units of a.e., a.i., or formulation. Thus, this study is not directly useful in the current risk assessment.

4.1.2.5. Terrestrial Plants (Macrophytes)

Picloram is a typical auxin-binding herbicide. In this respect, picloram is similar to other structurally related carboxylic acid herbicides such as aminopyralid, clopyralid, fluroxypyr, and triclopyr (Figure 1) and is mechanistically similar to other auxin-like herbicides, like 2,4-D, dichlorprop, mecoprop, dicamba, and quinclorac (Retzinger and Mallory-Smith 1997). As discussed in risk assessments of aminopyralid (SERA 2007), clopyralid (SERA 2004), fluroxypyr (SERA 2009), and triclopyr (SERA 2011b), the pyridine carboxylic acid herbicides mimic indole auxin plant growth hormones and cause uncontrolled growth in plants. At sufficiently high levels of exposure, the abnormal growth is so severe that vital functions cannot be maintained and the plant dies (Grossmann et al. 2001; Hansen and Grossmann 2000; Webb and Hall 1995).

The testing requirements for the effects of herbicides on terrestrial plants are relatively rigorous since terrestrial vegetation is the typical target group for herbicides. As detailed further in the following subsections, the testing requirements involve bioassays for vegetative vigor, seedling emergence as well as seed germination in several species of dicots and monocots.

4.1.2.5.1. Vegetative Vigor

Vegetation vigor studies involve foliar applications, and these studies are used in the current risk assessment to assess the consequences of exposures associated with direct spray of or drift to nontarget plants (Sections 4.2.4.1 and 4.2.4.2). Two assays on vegetative vigor, Schwab (1996) and Weseloh and Stockdale (1989), are summarized in Appendix 3 (Table A3-1). The study by Weseloh and Stockdale (1989) is used in the EPA ecological risk assessment on picloram (U.S. EPA/OPP 1994b). The study by Schwab (1996) was submitted after the preparation of the

Reregistration Eligibility Decision for picloram (U.S. EPA/OPP 1995a) and the supporting ecological risk assessment (U.S. EPA/OPP 1994b). Nonetheless, the study by Schwab (1996) has been submitted to and reviewed by the U.S. EPA/OPP. Based on the Data Evaluation Record prepared by the U.S. EPA/OPP, the U.S. EPA/OPP … *has determined that this study is scientifically sound and fulfills the guideline requirements for a vegetative vigor of non-target terrestrial plants study (GLN 123-1b) and is classified as core* (Mullins 2001).

As also summarized in Appendix 3 (Table A3-1), a third study on vegetative vigor was conducted by Schwab (1994). This study involved far fewer doses and fewer species than the Schwab (1996) although the results of this study are consistent with the later and more complete study by Schwab (1996). While the earlier study by Schwab (1994) has been submitted to the U.S. EPA/OPP – i.e., the study has been assigned an MRID number – no Data Evaluation Record (DER) for Schwab (1994). While somewhat speculate, the lack of a DER suggests that Schwab (1994) may have been classified as an exploratory study for the later and more complete study by Schwab (1996) as well as the Schwab (1995) study on seedling emergence. Because of limitations in the Schwab (1994) study, the lack of an Agency evaluation of this study, and because the Agency has accepted the Schwab (1996) as core, the earlier study by Schwab (1994) is not considered further.

The EC_{25} values for vegetative vigor from the studies by Weseloh and Stockdale (1989) and Schwab (1996) are summarized in Table 19. The values given in Table 19 for the study by Schwab (1996) differ from those in Appendix 3 (Table A3-1). Schwab (1996) assayed Tordon K and reports the EC_{25} values in units of g a.i./ha. These values are given in Appendix 3 (Table A3-1). In Table 19, however, the values are converted to units of g a.e./ha, consistent with the units reported by Weseloh and Stockdale (1989). In the dose-response assessment (Section 4.3.2.5), application rates are converted to lb a.e./acre, which is the unit of measure for application rates used by convention in all Forest Service risk assessments. Units of g a.e./ha are used in the following discussion simply to maintain reasonable consistency with the values reported in the two studies.

As with the study by Schwab (1996), Weseloh and Stockdale (1989) used potassium picloram. Weseloh and Stockdale (1989) indicate that the test material contained 0.2885% picloram, which appears somewhat unusual in terms of the dilution—i.e., 28.85% or a proportion of 0.2885 would be closer to the picloram concentration in most commercial formulations. No DER for the study by Weseloh and Stockdale (1989) is available on the EPA web site of cleared reviews (http://www.epa.gov/pesticides/foia/reviews.htm); moreover, it is not clear whether the concentration of 0.2885% is correct. In any event, the g a.e./ha values reported in Weseloh and Stockdale (1989) are identical to the value used in U.S. EPA/OPP (1994b).

The earlier study by Weseloh and Stockdale (1989) gives EC_{25} values for only a single general endpoint—i.e., *a detrimental change or alteration* (Weseloh and Stockdale 1989, p. 13 of study). As detailed in Appendix 3 (Table A3-1), the later study by Schwab (1996) follows the more current practice of reporting separate toxicity values for visual signs of phytotoxicity (equivalent to the endpoint reported in Weseloh and Stockdale 1989), shoot length and shoot weight. This reporting difference has no impact on the current risk assessment, because the most sensitive

endpoint for picloram in the study by Schwab (1996) is visual signs of phytotoxicity, equivalent to the endpoint reported in Weseloh and Stockdale (1989).

Figure 7 provides an overview of the cumulative frequency distributions of EC_{25} values for monocots from the study by Schwab (1996) and dicots from the studies by both Schwab (1996) as well as Weseloh and Stockdale (1989). As discussed further below and detailed in Table 19, the monocot data from the study by Weseloh and Stockdale (1989) are not include in Figure 7 because most of the EC_{25}s are reported as indefinite values – i.e., the values are reported as greater than the highest application rate that was tested.

In Figure 7, the x-axis plots the EC_{25} values and the y-axis plots the cumulative frequency of the EC_{25} values. The individual values for the cumulative frequency are based on the following equation:

Equation 3

$$Freq_i = \frac{1-0.5}{N}$$

where $Freq_i$ is the cumulative frequency for the i^{th} value and N is the number of values in the data set. The x-axis in Figure 7 represents the toxicity values on a logarithmic scale, under the standard assumption that EC_{25} values and LC_{50} and EC_{50} values will be distributed lognormally. While the dose-response assessment for nontarget species (Section 4.3) is focused on NOAECs, the comparisons of toxicity in the hazard identification use values such as EC_{25}, EC_{50} and LC_{50} values, because these types of values estimate population means and are more amenable to comparisons, relative to NOAECs, which are strongly influenced by the choice of concentrations used in experiments. The cumulative frequency distributions of toxicity values are related to figures often referred to as *species sensitivity distributions* (e.g., Awkerman et al. 2008; Posthuma et al. 2002). As discussed by Posthuma et al. (2002), species sensitivity distributions can be used quantitatively as tools in probabilistic risk assessment. Probabilistic methods are not routinely used in Forest Service risk assessments. Nonetheless, cumulative distribution plots, like those in Figure 7, are useful for illustrating differences in and among different agents or groups of organisms.

As illustrated in Figure 7 and summarized in Table 19, dicots are generally more sensitive than monocots to picloram. As discussed in the following subsections on terrestrial plants, this pattern also holds for toxicity based on seedling emergence and seedling germination. While this difference in sensitivity is evident in the study by Schwab (1996) as well as the study by Weseloh and Stockdale (1989), the EC_{25} values for monocots differ markedly between the two studies. With the exception of wheat, Weseloh and Stockdale (1989) report EC_{25} values for monocots of >560 g a.e./ha. Both studies report definite EC_{25} values for wheat—i.e., 29.4 g a.e./ha in Schwab (1996) and 310 g a.e./ha in Weseloh and Stockdale (1989). Weseloh and Stockdale (1989) also report EC_{25} values for dicots. Some of the EC_{25} values for a given species of dicot are not remarkably different in the two studies—e.g., soybeans and radish. The toxicity values for sunflowers, however, are strikingly different—i.e., an EC_{25} of 0.081g a.e./ha in Schwab (1996) which is a factor of about 85 below the EC_{25} of 6.9 g a.e./ha reported in Weseloh and Stockdale (1989).

The reason for the substantial differences in the EC_{25} values for monocots and some dicots in the studies is not apparent from a review of the information presented in the studies by Weseloh and Stockdale (1989) and Schwab (1996). Wright (1995), however, has presented a detailed comparison of earlier study by Weseloh and Stockdale (1989) with the later studies by Schwab (1994, 1995) and has suggested a large number of factors that may have contributed to the differences between the two studies including differences in growing conditions as well as the possibility of cross contamination in the earlier study by Weseloh and Stockdale (1989). A more recent commentary on these studies by Jachetta (2011c) also suggests that cross contamination probably occurred in the earlier study by Weseloh and Stockdale (1989). From a practical perspective, these concerns do not have a substantial impact on the current risk assessment in terms of the data on vegetative vigor. As illustrated in Figure 7 and discussed further in Section 4.3.2.5.1 (dose-response assessment for foliar exposures), the study by Schwab (1996) provides a more conservative basis for the dose-response assessment and this study is used to derive toxicity values for terrestrial vegetation.

Figure 8 provides an alternate view of the vegetative vigor EC_{25} values on monocots and dicots including only the data from Schwab (1996). One possibly noteworthy consideration in this illustration is the difference between the patterns of the cumulative distributions for monocots and dicots. The cumulative distribution for monocots is smooth, suggesting that the assumption of a lognormal distribution of tolerances among monocots is reasonable, which is not the case for dicots. The EC_{25} for radishes (36.3 g a.e./ha) appears to be an outlier (i.e., at the far right of the plot for dicots). The high EC_{25} does not necessarily suggest any irregularity in the study. An equally reasonable supposition is that there may be a subgroup of dicots (which would include the radish) that are relatively tolerant to picloram (i.e., as tolerant as the more sensitive monocots). A similar, albeit more tenuous, supposition for very a sensitive subgroup of dicots is suggested by the clustering of the low EC_{25} for sunflowers and pinto beans (i.e., on the left side of the plot for dicots). Given the small number of species tested in the study by Schwab (1996) as well as the inconsistencies between the study by Schwab (1996) and the study by Weseloh and Stockdale (1989), these suggestions are speculative, and a more formal analysis does not seem justified.

4.1.2.5.2. Seedling Emergence

Seedling emergence studies involve exposures of seeds to contaminated soil, and these studies are used in the current risk assessment to assess the consequences of exposures associated with runoff of herbicides to nontarget fields (Sections 4.2.4.1 and 4.2.4.2). As with studies on vegetative vigor, two standard seedling emergence studies are available on picloram, and these studies—i.e., Weseloh and Stockdale (1989) and Schwab (1995)—are summarized in Appendix 3 (Table A3-2). As discussed in the previous subsection, the earlier study by Weseloh and Stockdale (1989) is cited and used in the Reregistration Eligibility Decision for picloram (U.S. EPA/OPP 1995a) and the supporting ecological risk assessment (U.S. EPA/OPP 1994b). The study by Schwab (1995) is not cited in the EPA assessments and was probably not available to the EPA when the assessments were conducted. This study, however, has been reviewed by the U.S. EPA/OPP and is classified as core (Mullins 2001).

The EC_{25} values for the seedling emergence studies are summarized in Table 20. The data for monocots is illustrated in Figure 9 and the data for dicots is illustrated in Figure 10. Unlike the

case with the vegetative vigor studies, the study by Weseloh and Stockdale (1989) yields consistently lower EC_{25} values for the seedling emergence in both monocots and dicots, compared with the more recent study by Schwab (1995). In Figure 9, it should be noted that several of the higher monocot and dicot EC_{25} values are indefinite values—i.e., >560 and >1120 g a.e./acre. For monocots, the most sensitive and tolerant species (i.e., wheat and corn, respectively) are consistent in the two studies. For wheat, the EC_{25} from Weseloh and Stockdale (1989) is a factor of about 6 less than the corresponding EC_{25} from Schwab (1995) [136 ÷ 23.5 g a.e./ha ≈ 5.787]. For corn, both EC_{25} values are indefinite—i.e., >560 g a.e./ha from Weseloh and Stockdale (1989) and >1120 g a.e./ha from Schwab (1995). Because of the indefinite nature of the values, these EC_{25} values are essentially consistent. For dicots, overlap in the EC_{25} values for the various species is apparent. Nonetheless, in every instance in which the same species is assayed, EC_{25} values from Weseloh and Stockdale (1989) are greater than the corresponding EC_{25} values from Schwab (1995)—i.e., factors of about 1642 for soybean, 13 for tomato, and 373 for sunflower. The differences for soybean are particularly striking.

As discussed in Section 4.1.2.5.2, the studies by Weseloh and Stockdale (1989) and Schwab (1995) follow superficially similar protocols but the discussions by Wright (1995) and Jachetta (2011c) suggest that the earlier study by Weseloh and Stockdale (1989) may be flawed due to cross contamination. In a seedling emergence study, cross contamination could account for the apparently greater sensitivity of both monocots and dicots in the study by Weseloh and Stockdale (1989) relative to the later study by Schwab (1995). This interpretation seems reasonable particularly because Weseloh and Stockdale (1989) concurrently assayed not only picloram but also mixtures of picloram with both triclopyr and 2,4-D. The issue of cross contamination is discussed further in the dose-response assessment for soil exposures (Section 4.3.2.5.2).

4.1.2.5.3. Seed Germination

The seed germination studies conducted only by Weseloh and Stockdale (1989) are summarized in Appendix 3 (Table A3-3). These studies involve Petri dish exposures—i.e., the seeds are placed on filter paper in a Petri dish, sprayed with the herbicide at various application rates, and then water is added to support germination. These studies are not used directly in most herbicide risk assessments because the exposure method is not directly relevant to plausible exposures involving the use of most herbicides. For picloram, the EC_{25} values for seedling germination are higher than the EC_{25} values for vegetative vigor and seedling emergence. While the seed germination studies from Weseloh and Stockdale (1989) are included in Appendix 3 for the sake of completeness, these studies are not discussed further in this risk assessment.

4.1.2.5.4. Other Data

Picloram has been used as a pesticide for more than 50 years, and its efficacy is documented in numerous published studies (e.g., Bovey et al. 1979; Campbell and Nicol 2000; Canode 1974; Hamill et al. 1972; Harrington et al. 1998; Lym 1993; Lym and Messersmiht 1981; Jacoby et al. 1990; McCarty 1979; Meyer et al. 1983; Miller et al. 1999; Reece and Wilson 1983; Sheets and Harrell 1986). Despite the importance of efficacy studies to the practical considerations of herbicide use, efficacy studies are generally considered in risk assessments only to the extent that the help to identify sensitivities in nontarget species. To that end, the studies by Jacoby et al. (1990) and Sheets and Harrell (1986), which are summarized in Appendix 3 (Table A3-4), are most relevant to the current risk assessment. Both of these studies indicate significant adverse

effects in nontarget vegetation—i.e., ≈96 g a.e./ha for cotton (Jacoby et al. 1990), about 2.2 g a.e./ha in tobacco after broadcast applications, and 0.22 g a.e./ha to tobacco when applied as contaminated fertilizer to soil (Sheets and Harrell 1986). Horsman et al. (2007) also note that wild tobacco is very sensitive to picloram at an application rate of 5 g a.e./ha, which is only moderately higher than the application rates used by Sheets and Harrell (1986). By comparison to the standard test species, cotton appears to be a relatively tolerant species. Tobacco is much more sensitive than cotton; however, the most sensitive test species (based on EC_{25} values) for dicots appear to be more sensitive than tobacco —i.e., the EC_{25} of 0.081 g a.e./acre in sunflowers following foliar application (Schwab 1996) and the EC_{25} of 0.014 g a.e./acre in soybeans following soil application (Weseloh and Stockdale 1989). In terms of a practical impact on the current risk assessment, the field studies are somewhat reassuring in that the standard studies used by the U.S. EPA/OPP encompass the apparent toxicity of picloram in field studies of efficacy.

The development of resistance to herbicides is obviously related to efficacy, and several studies focus on assessing or explicating the mechanisms of resistance to picloram in target and nontarget species (Horsman et al. 2007; Sabba et al. 2003; Walsh et al. 200; Yajima et al. 2004). In terms of the current risk assessment, resistance is important primarily in identifying tolerant subpopulations. In this respect, the study by Fuerst et al. (1996) is relevant. These investigators examined resistance to picloram in populations of yellow starthistle, *Centaurea solstitialis* and noted that resistant plants are more tolerant by factors ranging from about 10- to 35-fold, compared with non-resistant plants (Fuerst et al. 1996, Table 1). Fuerst et al. (1996) report EC_{50} rather than EC_{25} values, as discussed above for the standard bioassays. For normal (i.e., nonresistant) populations, the EC_{50} values range from 25 to 31 g a.e./ha. As summarized in Appendix 3, these values would classify normal populations of yellow starthistle as relatively tolerant to picloram. In resistant populations of yellow starthistle, EC_{50} values range from 310 g a.e./ha for foliar exposures to 2100 g a.e./ha for soil exposures. The EC_{50} of 310 g a.e./ha for foliar exposures is consistent with the highest EC_{50} for test dicots in the standard studies—i.e., >280 g a.i./ha or >240 g a.e./ha for radishes in the study by Schwab (1996). EC_{50} of 2100 g a.e./ha for soil exposures in starthistle only modestly higher than the highest EC_{50} of 1083 g a.i./ha or 935 g a.e./ha in standard test dicots —i.e., rape (*Brassica napus*) in the study by Schwab (1995). Thus, while resistance to picloram may develop in subpopulations of some plants, the results of the standard studies required by U.S. EPA/OPP (as detailed in the previous subsections) appear to encompass hazards to terrestrial plants that may develop resistance to picloram.

Based on growth inhibition in sunflower seedlings, picloram is more toxic than its metabolites by factors of about 300 to 3000 (Grover et al. 1975).

4.1.2.6. Terrestrial Microorganisms

The persistence of picloram in soil increases with increasing application rates or soil concentrations, which suggests that picloram is toxic to soil microorganisms. In soil column studies conducted over a 30-day period, Krzyszowska et al. (1994) notes that the soil half-life of picloram is directly related to the application rate. Application rates of 0.47, 0.97, and 1.85 kg/ha (about 0.4, 0.86, and 1.6 lb/acre) are associated with half-lives in soil of 13, 19, and 23 days, respectively. As would be expected, the toxicity of picloram to soil microorganisms is

inversely related to the extent that picloram is bound to soil, relative to the concentration of picloram in pore water (Prado and Airoldi 2003).

Data regarding the effects of picloram on soil microorganisms are mostly from assays of microbial activity in soils with defined concentrations of picloram. Consistent with the study by Krzyszowska et al. (1994), USDA/ARS (1995) notes a direct relationship between aerobic soil half-lives and picloram concentrations in soil: 18 days at a concentration of 0.0025 ppm, 29 days at a concentration of 0.025 ppm, 150 days at a concentration of 0.25 ppm, and 300 days at a concentration of 2.5 ppm. At a level of 10 ppm in sandy loam soil, picloram — and several other herbicides—caused a transient decrease in nitrification after 2 but not 3 weeks of incubation (Tu 1994). As discussed by this investigator, the decrease in nitrification is relatively mild and does not suggest the potential for a substantial or prolonged impact on microbial activity. In the same study, picloram had no effect on ammonia formation or sulfur oxidation. Prado and Airoldi (2001) assayed the effect of picloram on mixed microbial activity using microcalorimetry, which measures changes in heat production from soil treated with glucose (microbial food source) and various concentrations of picloram. Time to peak heat production was attenuated, and the magnitude of peak heat production was reduced by picloram concentrations as low as 1 ppm. In cell culture (i.e., artificial growth media), *Lipomyces kononenkoae*, a species of soil fungi, completely degrades picloram at a concentration of 0.05 ppm within 48 hours (Sadowsky et al. 2009).

Welp and Bruemmer (1999) describe the pH dependence of toxicity measurements of picloram (acid) in soil as determined by Fe(III) reduction test. The results show that the EC_{50} ranged from 1.93 mmol/kg [about 465 ppm] soil to more than 16.6 mmol/kg [about 4000 ppm] soil over a pH range of 3.5 to 7.8 (Welp and Bruemmer 1999). This publication does not detail the relationship between toxicity and pH for picloram but does indicate that pH was positively correlated with EC_{50} values. In other words, picloram toxicity increased in more acidic soils (in which picloram should be more highly protonated). As discussed further in Section 4.1.3.1.1.1, an opposite pattern – i.e., increasing toxicity with increasing pH – has been noted in trout by Woodward (1976).

Unlike the case with terrestrial macrophytes (Section 4.1.2.5.4), the metabolism of picloram may result in increased rather than decreased toxicity in some microorganisms. In three species of fungi, EC_{50} values for growth inhibition by picloram acid were >1600 ppm (the highest concentration tested). Corresponding values for the decarboxylated metabolite, 4A-TCP, were 50 to 80 ppm. In two species of bacteria, *Arthrobacter globiformis* and *Pseudomonas pictorum*, differences in toxicity were not substantial and ranged between 60 and 380 ppm for picloram acid and 4A-TCP (Baarschers et al. 1988). As discussed above, Welp and Bruemmer (1999) determined EC_{50} values ranging from 1.93 to >16.6 mMoles/kg soil, which corresponds to a range from about 466 to somewhat greater than 4000 mg/kg soil [MW=241.48].

4.1.3. Aquatic Organisms

4.1.3.1. Fish

4.1.3.1.1. Acute Toxicity

4.1.3.1.1.1. General Considerations

As with terrestrial species, the acute lethal potency of picloram to fish is relatively well defined. These values are typically expressed as time-specific LC_x values where *x* is the estimate of the proportion of fish that die—e.g., 96-hour LC_{50}. For picloram, numerous acute LC_{50} values have been determined for various species of fish in both registrant-submitted studies and studies published in the open literature. Similar to the approach taken in the hazard identification for terrestrial plants (Section 4.1.2.5), the discussion of differences in sensitivities among fish species is focused on LC_{50} values rather than NOAECs, because LC_{50} values estimate population means and are more amenable to quantitative comparisons, relative to NOAECs, which are simply exposure concentrations used in experiments. NOAECs for fish, which are the basis for the dose-response assessment, are discussed further in Section 4.3.3.1.

The acute toxicity data for fish data summarized in Appendix 4 (Table A4-1). By convention, the Forest Service and U.S. EPA/OPP risk assessments classify the salts of weak acids (in this case potassium picloram) as the active ingredient (a.i.). In order to facilitate comparisons, LC_{50} values reported in units of mg a.i./L are converted to units of mg a.e./L using the conversion factor of 0.8637 a.e./a.i. from Table 1. Similarly, LC_{50} values reported in units of mg formulation/L are converted to mg a.e./L based on the percent a.i. or a.e. specified in the study for the formulation tested. In some cases, these conversions are problematic because of a lack of clarity in studies. As noted in Section 2.2, picloram was developed in the 1960s. Many of the studies summarized in Appendix 4 (Table A4-1) are from the early literature on picloram, and several of these studies have reporting limitations not typically found in the more recent literature. Some of the more serious limitations involve a lack of clarity in the identification of the test material and the units in which the LC_{50} values are reported—i.e., whether the LC_{50} values are reported in units of mg formulation/L, mg a.i./L, or mg a.e./L.

Two studies summarized in Appendix 4 (Table A4-1) are excluded from further consideration in the current risk assessment—i.e., Alabaster (1969) and Johnson (1978)—due to limitations in the way in which the data are reported. Alabaster (1969) assayed Tordon 22K (24% a.e.) in Harlequin fish and reports an LC_{50} of 66 mg/L. This is the only study on Harlequin fish, and the units of the reported LC_{50} cannot be determined. Johnson (1978) assayed Tordon 50-D in Mosquito fish and reports an LC_{50} of 120 mg/L. The units of this LC_{50} also cannot be determined. In addition, while Johnson (1978) indicates that the formulation contained picloram, the concentration of picloram in the formulation is not specified. A cursory search for information on Tordon 50-D indicates that this formulation is a mixture of the triethanolamine salts of picloram and 2,4-D, which is registered in Australia and New Zealand (Dow AgroSciences NZ Ltd 1999). The study by Johnson (1978) appears to have been conducted in Australia and funded by an Australian foundation.

Some of the studies in Appendix 4 are useful for assessing differences in exposure conditions that impact toxicity. For example, no substantial differences are apparent in the toxicity of picloram acid and the potassium salt of picloram in bluegills based on reports by Mayes and Dill

(1984) and Johnson and Finley (1980) – i.e., the ratios of the LC_{50} values for the potassium salt (expressed in a.e. equivalents) to the acid are about 1.2 and 1.009, respectively. The report by Mayes and Dill (1984) appears to involve matched bioassays (i.e., studies conducted at the same time by the same investigators). Johnson and Finley (1980) is a compendium of early studies conducted by the Fish and Wildlife Service, and it is not clear that the bioassays were conducted by the same investigators. Similarly, in the matched assay in rainbow trout by Mayes and Dill (1984), the LC_{50} values for the potassium salt (expressed as a.e. equivalents) and picloram acid are identical—i.e., 18 mg a.e./L.

Fish size and/or life stage can sometimes have an impact on sensitivity to pesticides. Mayer and Ellersieck (1986) conducted assays in fry of channel catfish and rainbow trout at different stages. As summarized in Table 21 and detailed further in Appendix 4 (Table A4-1), rainbow trout exhibited relatively little difference in sensitivity among progressively more mature fry (i.e., yolk sac fry, swim up fry, and advanced fry). Channel catfish, on the other hand, displayed more substantial differences in sensitivity with yolk sac fry yielding the lowest LC_{50} for this species (5.8 mg a.e./L) and advanced fry yielding the highest LC_{50} for this species (16 mg a.e./L).

Woodward (1976) conducted matched assays in both cutthroat and lake trout focused on the effect of temperature, pH, and water hardness. As detailed in Appendix 4 (Table A4-1), the toxicity of picloram generally increases with increasing temperature, although the differences over a range of 5 to 15°C are less than a factor of 2. Water hardness has relatively little impact of the toxicity of picloram. The greatest impact on toxicity is apparent with pH. Over a pH range of 6.5 to 8.5, the toxicity of picloram increased by over a factor of 2 as pH increased.

The increase in the toxicity of picloram with increasing pH is not intuitive. For a weak acid, the degree of ionization will increase at increasing pH. A reasonable expectation is that the toxicity of picloram to fish would decrease because ionized picloram should be less readily absorbed than protonated picloram. More specifically, the proportion of a weak acid that is non-ionized at a given pH may be calculated as:

Equation 4

$$P_{Non-ionized} = 1-(1+10^{pH-pKa})$$

Taking 2.3 as the estimate of the pKa picloram (Tomlin 2004a, Baker 1989c; Health Canada 2007), the proportion of picloram that is non-ionized is about 6.31×10^{-7} at pH 8.5 and 6.31×10^{-5} at pH 6.5 – i.e., a 100 fold increase in the concentration of non-ionized picloram.

As discussed in Section 4.1.3.1.1.2, one early study by McCarty et al. (1977) suggests that a guanidine impurity in technical grade picloram may be toxic to bluegill sunfish and significantly contribute to the toxicity of technical grade picloram. Guanidine is a base rather than an acid, and the toxicity of guanidine derivatives might be expected to increase with increasing pH. While highly speculative, the impact of pH on a guanidine impurity might account for the observations by Woodward (1976) on the toxicity of technical grade picloram.

Excluding the studies by Alabaster (1969) and Johnson (1978) discussed above, Table 21 provides an overview of the 96-hour LC_{50} from Appendix 4 (Table A4-1). LC_{50} values for other durations (i.e., 24, 48, and 72 hours) are provided in some studies (e.g., Alexander and

Batchelder 1965; Fogels and Sprague 1977). As would be expected, 96-hour LC_{50} values are lower than 24- or 48-hour LC_{50} values by factors of about 2 to 4. The emphasis on 96-hour LC_{50} values reflects the fact that they are the most commonly reported values and are used by convention in discussing acute toxicity in fish.

The distributions of LC_{50} values for fish species are illustrated in Figure 11 for species on which multiple bioassays of picloram are available. This figure is similar to other plots of sensitivity distributions as discussed in Section 4.1.2.5.1. The only species from Table 21 not included in Figure 11 are the species for which only a single 96-hour LC_{50} is available. For the most part, the cumulative frequencies for different species of fish are reasonably smooth and consistent with lognormal distribution of tolerances. The only possible exception is the somewhat atypically low LC_{50} of 1.5 mg a.e./L reported by Johnson and Finley (1980) for cutthroat trout. This value, however, is only about a factor of 2 below the LC_{50} of 3.45 mg a.e./L reported by Woodward (1976).

With the exception of the atypically low LC_{50} for cutthroat trout reported by Johnson and Finley (1980), the LC_{50} values for different species of fish for which multiple bioassays are available are remarkably consistent within species, with the ranges within species spanning a factor of only about 2 to 3. Variations of this magnitude are not uncommon in inter- and intralaboratory comparisons of acute toxicity assays in aquatic organisms (e.g., Rue et al. 1998).

Figure 12 illustrates cumulative frequency of the ordered geometric means of the LC_{50} values for the species of fish for which multiple LC_{50}s are available. This figure, which contains only one value per species, is analogous to a species sensitivity distribution (e.g., Awkerman et al. 2008; Posthuma et al. 2002), discussed in Section 4.1.2.5.1. As illustrated in Figure 12, the cumulative frequency distribution is reasonably smooth, suggesting a lognormal distribution of tolerances. In other words, the available data on fish species for which multiple LC_{50} values are available does not suggest that any of species display abnormal (i.e., statistically non-normal) sensitivities. Of the six species represented in Figure 12, cutthroat trout are most sensitive (mean LC_{50} = 4.3 mg a.e./L) and fathead minnow are the least sensitive (mean LC_{50} = 62.4 mg a.e./L) with the difference in the mean LC_{50} values spanning a factor of about 15 [62.4 mg a.e./L ÷ 4.3 mg a.e./L ≈ 14.512].

Figure 12 does not include species for which only a single 96-hour LC_{50} is available. As summarized in Table 21, these species include flagfish (a tropical fish species) with an LC_{50} of 22.6 mg a.e./L and bull trout (*Salvelinus confluentus*, a cold water salmonid fish) with an LC_{50} of 16 mg a.e./L. Of the fish included in Figure 12, both of these fish with only single toxicity values are intermediate in sensitivity between rainbow trout (mean LC_{50} of 13.2 mg a.e./L) and bluegills (mean LC_{50} of 25.8 mg a.e./L).

Sheepshead minnow is another species for which only a single toxicity value is available. In this species, no mortality and no signs of toxicity were apparent at concentrations of up to 27.2 mg a.e./L in an assay of Tordon 22K (Boeri et al. 1995b). In Table 21, this study is listed with an indefinite LC_{50} of >27.2 mg a.e./L. Thus, this saltwater/estuarine minnow is clearly less sensitive to picloram than all of the species included in Table 21, except for the fathead minnow (a freshwater species of fish), which has reported LC_{50} values of 52 mg a.e./L for picloram acid

(Mayes and Dill 1984) and 75 mg a.e./L for potassium picloram (Mayes and Dill 1985). While somewhat speculative, it appears that sheepshead minnow may be as tolerant as its freshwater counterpart is to picloram.

4.1.3.1.1.2. Impurities

As discussed in the previous subsection, bioassays by Woodward (1976) in cutthroat and lake trout suggest that the toxicity of technical grade picloram increases with increasing pH (i.e., increasing alkalinity). This is the opposite of the effect that would be expected for a weak acid—i.e., decreasing pH will increase the extent of protonation of the weak acid which should, in turn, increase absorption by and toxicity to aquatic organisms. The opposite, however, would be true for a weak base.

One possible explanation for observations by Woodward (1976) on the effect of pH on the toxicity of technical grade picloram involves an impurity that apparently occurred in technical grade picloram in the late 1970s. As summarized in Appendix 4 (at the end of Table A4-1), McCarty et al. (1977) assayed bluegills using three different batches of technical grade picloram containing differing amounts of N''-(3,4,5,6-tetrachloro-2-pyridinyl)-guanidine. One batch contained very little of the guanidine derivative (0.05%) and the LC_{50} of this batch was 32.9 mg a.e./L with confidence intervals of 23.7 to 58.2 mg a.e./L. The other two batches contained the guanidine derivative at concentrations of 0.221 and 0.25%, and the LC_{50} values were 17.7 mg and 19.4 mg a.e./L with confidence intervals that did not overlap (in one case) with or barely overlapped (in another case) with the confidence intervals of the batch containing less of the guanidine derivative. Notably, the batch containing the low concentration of the guanidine impurity is less toxic than the other batches by factors of about 2. Perhaps coincidentally, this factor is roughly the same as in the trout study by Woodward (1976) in which the pH range is 6.5 to 8.5.

The association between the observations by Woodward (1976) in trout and by McCarty et al. (1977) in bluegills is plausible, yet tenuous. Moreover, this information may not be relevant to technical grade picloram as currently produced. The Reregistration Eligibility Decision for picloram (U.S. EPA/OPP 1995a) includes a citation to but no discussion of the McCarty et al. (1977) study. In addition, the ecological risk assessment prepared in support of the Reregistration Eligibility Decision (U.S. EPA/OPP 1994b) does not discuss the McCarty et al. (1977) study. One can only speculate that the EPA may consider the earlier study on the guanidine impurity irrelevant to more recent production methods for technical grade picloram.

4.1.3.1.1.3. Sublethal Toxicity

Relatively little information is available on the sublethal toxicity of picloram to fish from relatively short-term exposures. As summarized in Appendix 4 (Table A4-2), Woodward (1976) conducted prolonged exposure studies in trout; however, these studies focus on temporal relationships rather than sublethal effects.

In another unusual study, also summarized in Appendix 4 (Table A4-2), Woodward (1979) conducted short-term, variable exposure studies in cutthroat trout to mimic exposures that might occur in streams. Exposure regimes in which the peak concentration of picloram in water did not

exceed 0.29 mg a.e./L had no effect on trout fry, based on mortality as well as fry weight and growth. This study is discussed further in the risk characterization for fish (Section 4.4.3.1).

Many of the acute toxicity studies summarized in Appendix 4 (Table A4-1) report NOAELs for mortality or overt signs of toxicity. These NOAELs, however, do not necessarily reflect sensitive sublethal endpoints and are not typically used in Forest Service risk assessments. This issue is discussed further in the dose-response assessment for fish (Section 4.3.3.1).

4.1.3.1.2. Longer-Term Toxicity

Two types of longer-term toxicity studies in fish may be required by the U.S. EPA/OPP for the registration of pesticides, full-life cycle studies and early life-stage studies (U.S. EPA/OCSPP 2011). As the name implies, full-life cycle studies involve exposures from the egg stage through mating and egg-laying—i.e., at least one full life-cycle. These studies are analogous to multi-generation reproduction studies in mammals (Section 3.1.9.2.). Early life-stage studies, also referred to as egg-to-fry studies, involve shorter periods of exposures of fertilized eggs, which are continued through development until the fish are free swimming.

There are no full-life cycle studies available on picloram. This data gap is not unusual for a pesticide that does not appear to be highly toxic to fish or for pesticides for which the levels of anticipated longer-term exposures are below the apparent NOAECs from early life-stage studies. Several early life-stage studies are available on picloram. As detailed in Appendix 4 (Table A4-3) and summarized in Table 22, these include assays in lake trout, rainbow trout, bull trout, and fathead minnows. Table 22 includes the NOAECs for the early life-stage studies, the duration of the studies, and the corresponding LC_{50} values. As with acute toxicity, the most sensitive species is lake trout. For this species, an NOAEC has not been defined. At the lowest concentration tested (0.035 mg a.e./L), adverse effects included decreases in fry survival and growth (Woodward 1976). Also as with the definitive acute LC_{50} values, the most tolerant species is the fathead minnow with an NOAEC of 7.19 mg a.e./L (Weinberg et al. 1996). The longer-term NOAELs for rainbow trout and bull trout do not correlate precisely with the LC_{50} values, but the deviations are not substantial.

As discussed further in Section 4.3.3.1, the information on the most sensitive and most tolerant species form the basis for the dose-response assessment in fish.

4.1.3.2. Amphibians (Aquatic-Phase)

The only information on the toxicity of picloram to aquatic-phase amphibians is from Johnson (1976). In this study, acute bioassays were conducted using tadpoles of two species of amphibians, *Adelotus brevis* and *Limnodynastes peroni*. Both of these species are native to Australia. As with the Johnson (1978) study in mosquito fish, discussed in Section 4.1.3.1.1.1, the test material used in the study as well as the reporting units (i.e., a.e., a.i., or formulation) are not clear. The test material is specified as Tordon 50-D, an Australian formulation that contains picloram and 2,4-D. Like the Johnson (1978) study, the Johnson (1976) study appears to have been conducted in Australia and was funded by an Australian foundation. While Johnson (1976) presents results as if picloram were the only agent tested, 2,4-D may have been in the mixture. Because of these limitations, the Johnson (1976) amphibian study is not used directly in this risk assessment.

Notwithstanding the above, the studies of Johnson (1978) in fish and Johnson (1976) in amphibians may be used to compare responses in fish and amphibians under the assumption that the units reported and the agent tested are the same in both studies. Based on this assumption, a summary of the acute LC_{50} values reported in both publications is given in Table 23. For all durations of exposure and all bioassays on amphibians, there are no remarkable differences in the toxicity of the test material to amphibians and fish.

4.1.3.3. Aquatic Invertebrates

Information on the toxicity of picloram to aquatic invertebrates is summarized in Appendix 5, and an overview of the relevant studies is given in Table 24. While acute toxicity values in fish are almost always expressed as LC_{50} values (lethality), the toxicity values for invertebrates are sometimes expressed as EC_{50} values for immobility. Immobility is typically used for microcrustaceans, like daphnids. For larger invertebrates, mortality is often the endpoint used. For the picloram assays on the fiddler crab, however, complete loss of equilibrium is used as the endpoint for calculating the EC_{50} values. Endpoints for bivalves may be expressed in several different ways, depending on the life-stage assayed. For picloram, the assays are based on oyster larvae development —i.e., normal development to the straight-hinge stage within 48 hours after exposure. The interpretation of the differences in the severity of these endpoints is discussed further in the dose-response assessment (Section 4.3.3.3.1).

Compared with the rather extensive data on fish (Section 4.1.3.1), there is relatively little information on the toxicity of picloram and potassium picloram to aquatic invertebrates—i.e., three registrant-submitted studies (Gersich et al. 1984; Heitmuller 1975a,b), an early study by Dow in the open literature (Mayes and Dill 1984), and some early studies conducted by the U.S. Fish and Wildlife Service (Johnson and Finley 1980; Sanders 1969; Sanders and Cope 1968).

The publication by Johnson and Finley (1980) is a compendium of studies from U.S. Fish and Wildlife Service rather than a primary publication. A serious limitation in this compendium is that the toxicity values provided are not explicitly linked to specific Fish and Wildlife Service studies. Instead, a list of studies is included at the end of the compendium. For picloram, this limitation is problematic. As detailed in Appendix 5 (Table A5-1), Johnson and Finley (1980) give two toxicity values which appear to be in error, including a 96-hour LC_{50} in *Gammarus fasciatus* of 0.027 (0.020-0.037) mg/L and a 96-hour LC_{50} in a species of stonefly (*Pteronarcys*) of 0.048 (0.037-0.062) mg/L.

Neither of the above toxicity values from Johnson and Finley (1980) can be confirmed in the primary literature; furthermore, they are far lower than toxicity values cited in the primary literature. In a primary literature publication from the Fish and Wildlife Service, Sanders (1969) reports a 96-hour LC_{50} of 27 (20-37) mg a.e./L for *Gammarus lacustris*. It is worth noting that this LC_{50} and the associated confidence interval are exactly a factor of 1000 higher than the corresponding values for *Gammarus fasciatus* given in Johnson and Finley (1980). Similarly, the primary literature study by Sanders and Cope (1968) reports a 96-hour LC_{50} of 48 (37-62) mg a.e./L for *Pteronarcys californica*. Again, this LC_{50} and the associated confidence interval are exactly a factor of 1000 higher than the corresponding values for a *Pteronarcys* species given in Johnson and Finley (1980). As detailed in Appendix 5 (Table A5-1), other details associated with these studies (e.g., animal size and temperatures used) are identical or nearly so. Given the implausibility of the very low toxicity values reported in Johnson and Finley (1980) as well as

the precise 3-order of magnitude difference in these values relative to other better documented values, the atypically low toxicity values for *Gammarus* and *Pteronarcys* species reported by Johnson and Finley (1980) are interpreted as reporting errors and excluded from further consideration in this risk assessment.

The matched studies by Mayes and Dill (1984) on picloram acid and potassium picloram suggest that the salt is less toxic than the acid. While the difference is not substantial (about a factor of 1.6), the difference is statistically significant based on the confidence limits in the LC_{50} values. The reason for the difference in toxicity is not apparent but is not likely to result from increased pH in the test with the acid, since Mayes and Dill (1984) report that the pH of the test solutions ranged from 6.9 to 8.1 but do not report any differences in pH for the assays on the acid and potassium salt (Mayes and Dill 1984, p. 265).

Based on the studies by Heitmuller (1975a,b) Tordon 22K is more toxic (based on a.e. equivalents) than a 10% a.e. pellet formulation of picloram to oysters and shrimp. This information suggests that Tordon 22K might contain an inert that enhances the acute toxicity of Tordon 22K to aquatic organisms. Alternatively, the 10% a.e. pellet formulation may contain an inert that reduces the toxicity of the formulation to aquatic organisms—e.g., reduced bioavailability. Without a matched study on the potassium salt and Tordon K and/or Tordon 22K in the same organism, it is not certain that the toxicity studies on picloram acid and the potassium salt of picloram encompass the toxicity to Tordon 22K to daphnids. Notwithstanding this uncertainty, the available toxicity data in fish (Section 4.1.3.1.1, Table 21) indicate no substantial or consistent differences in the toxicities to fish of picloram acid, the potassium salt of picloram, the Tordon formulations covered in the current risk assessment.

There are no toxicity studies involving the exposure of daphnids to Tordon K or Tordon 22K in the available literature. U.S. EPA/OPP (1994b, p. 25) cites an LC_{50} of 226 mg/L for an unspecified 88.6 % a.i. formulation. No MRID number for this study is given, and the LC_{50} of 226 mg formulation/L has not been identified in a primary study or secondary source. In addition, the active ingredient in the formulation is not identified. Consequently, the LC_{50} for the formulation cannot be converted to units of mg a.e./L.

One daphnid study is available on a South American formulation of potassium picloram – i.e., the Perina and Pedrolli (1996) on Tordon 24K using *Daphnia similis*. Based on the product label (http://www.jedys.com.ar/data/HojaDeSeguridad_777.pdf) and an MSDS for this formulation (http://www.dowagro.com/PublishedLiterature/dh_04c0/0901b803804c0778.pdf), Tordon 24K is a formulation produced by Dow AgroSciences Argentina S.A. The study by Perina and Pedrolli (1996) was funded by Dow Elanco Industrial Ltda., Brazil. A full copy of this study, including laboratory notes, was provided for the conduct of the current risk assessment by Dow AgroSciences, Indianapolis, Indiana. This study is not listed in the U.S. EPA/OPP bibliography for picloram (obtained under a FOIA request). Thus, this study does not appear to have been submitted to the U.S. EPA/OPP. This is not unusual in that the U.S. EPA/OPP is concerned only with U.S. formulations of pesticide.

The study by Perina and Pedrolli (1996) appears that have been well-conducted, including the use of a reference toxicant, and the data are clearly reported. The only atypical feature relative to

a U.S. study is that only nominal but not measured concentrations are reported. As summarized in Table 24 and detailed further in Appendix 5 (Table A5-1), these investigators report a 48-hour LC_{50} of 50.29 (44.23 to 57.19) mg formulation/L. Correcting for acid equivalents, this corresponds to an LC_{50} of about 12 (10.6 to 13.7) mg a.e./L. This LC_{50} is lower than the reported LC_{50}s in *Daphna magna* by factors of about 4 to 6 for picloram acid and about 7 to 14 for potassium picloram.

In the absence of information on the similarities of Tordon 24K (the South American formulation) to the U.S. formulations, Tordon K and Tordon 22K, the relevance of the study by Perina and Pedrolli (1996) to the current risk assessment is uncertain. Nonetheless, this study enhances the concern for the lack of a matched study on potassium picloram and the U.S. formulations. As discussed below and in Section 4.3.3.3.1.1, the dose-response assessment for sensitive species of aquatic invertebrates is based on an assay of Tordon 22K in larvae of the eastern oyster Heitmuller (1975b). Consequently, concerns for the sensitivity of daphnids to the Tordon formulations do not quantitatively impact the current risk assessment.

Based on the longer-term study (Gersich et al. 1984), the NOAEC for reproductive effects in *Daphnia magna* is 11.8 mg a.e./L. Gersich et al. (1984) also assayed the acute toxicity of picloram acid to *Daphnia magna* and report an acute EC_{50} of 68.3 mg a.e./L and an acute NOAEC of 34.5 mg a.e./L for immobility. The proximity of the acute NOAEC for mortality to the longer-term NOAEC for reproductive effects suggests an only modest/insubstantial duration-response and dose-severity relationship in daphnids.

Based on the reported toxicity values expressed as acid equivalents, the most sensitive species/life stage is larvae of the eastern oyster from the study by Heitmuller (1975b) with Tordon 22K. While Heitmuller (1975b) does not calculate an EC_{50} for abnormal development in oyster larvae because of the very sharp increase in response from the second to the highest concentration – i.e., 4% response at 18 ppm formulation – and the highest concentration – i.e., 100% response at 32 ppm formulation. As a crude approximation, an estimated EC_{50} could be taken as the geometric mean of this range – i.e., 24 ppm formulation or about 5.2 mg a.e./L. Using the U.S. EPA/OPP classification system for toxicity to aquatic species (SERA 2007a, Table 4-1), this approximate EC_{50} would classify Tordon 22K as moderately toxic to oyster larvae. All other EC_{50}s/LC_{50}s given in Table 24 would classify picloram, potassium picloram, or Tordon 22K as either *Slightly Toxic* (>10 to 100 mg/L) or *Practically Nontoxic* (>100 mg/L).

Two life-cycle studies in *Daphnia magna* are available on picloram. As noted above, the study by Gersich et al. (1984) yielded an NOAEC of 11.8 mg a.e./L. The more recent study by Boeri et al. (2002a) yields a somewhat but not remarkably lower NOAEC of 6.79 mg a.e./L. As illustrated in Table 22 for rainbow trout, a factor of 2 in the variability of NOAECs from longer-term studies in aquatic animals is not unusual.

No field studies are available on the toxicity of picloram to aquatic invertebrates. An unusually high number of gonadal neoplasms was identified in softshell clams from three Maine estuaries contaminated with herbicides, including picloram, 2,4-D, and 2,4,5-T (Gardner et al. 1991). Neither this report nor a later study by Van Beneden (1993) implicate picloram (or any specific herbicide directly) with the development of these tumors.

4.1.3.4. Aquatic Plants

4.1.3.4.1. Algae

The available studies on the toxicity of picloram and Tordon formulations to algae are summarized in Appendix 6 (Table A6-1), and an overview of these studies is given in Table 25. These studies consist of both registrant-submitted studies (Boeri et al. 1994b,c,d) as well as several studies published in the open literature. As with open literature studies on other groups of aquatic organisms, many of the open literature studies are of limited use because the form of picloram that was tested is not clear.

The most striking feature of the data on algae is the sensitivity of *Navicula pelliculosa* (EC_{50} = 0.97 mg a.e./L) and *Skeletonema costatum* (EC_{50} = 3.4 mg a.e./L) and the tolerance of *Anabaena flos aquae* (EC_{50} = 142 mg a.e./L) to Tordon K. All of these studies were submitted by the registrant, and there is no uncertainty regarding the test agent or the units in which the results are reported. The open literature study by Turbak et al. (1986) reports an EC_{50} of 44.8 mg/L for *Selenastrum capricornutum*, but the reporting units (a.e., a.i., or formulation) are not clear.

The greatest number of EC_{50} values is reported for *Selenastrum capricornutum*. While *Selenastrum capricornutum* is a common test species in registrant-submitted studies, all of the assays of picloram using this species are from the open literature. The study by Garten and Frank (1984) is relatively well reported with an approximate EC_{50} of about 100 mg a.e./L, which does not appear to be based on a formal dose-response assessment. Instead, the estimate is characterized as a test concentration that caused 50% or greater inhibition. Even if this were a standard EC_{50}, reporting deficiencies in the other studies on *Selenastrum capricornutum* preclude an assessment of the differences in the response of algae to picloram acid and potassium picloram relative to Tordon K or Tordon 22K.

While the data on algae are limited and not as robust as the data on fish, the deficiencies in the open literature studies do not have a substantial impact on the hazard identification. Full copies of the well-documented studies by Boeri et al. (1994b,c,d) were available for the conduct of this risk assessment, and these studies appear to define ranges of sensitivity that encompass 2 orders of magnitude. In addition and as discussed further in the dose-response assessment (Section 4.3.3.4.1), the studies by Boeri et al. (1994b,c,d) also report NOAECs, and these values can be used directly for the risk characterization of algae.

4.1.3.4.2. Aquatic Macrophytes

Appendix 6 (Table A6-2) summarizes three studies on the effects of picloram on aquatic macrophytes (Kirk et al. 1994; Nishiuchi 1974; Forsyth et al. 1997). The study by Kirk et al. (1994) is a well-documented registrant-submitted study on Tordon K that defines both an EC_{50} (47.8 mg a.e./L) and an NOAEC (12.2 mg a.e./L) in *Lemna gibba*, a standard test species commonly used in U.S. EPA/OPP and Forest Service risk assessments. The study by Kirk et al. (1994) does not appear to have been available for the EPA ecological risk assessment on picloram (U.S. EPA/OPP 1994b), and this study is not cited in the Reregistration Eligibility Decision for picloram (U.S. EPA/OPP 1995a).

The other studies cited in Appendix 6 (Table A6-2) are not directly useful. The study by Nishiuchi (1974) does not specify the test agent other than to refer to a *technical product*, and the

reporting units are not clear. The study by Forsyth et al. (1997) uses a form of picloram (i.e., the diethanolamine salt) and a formulation of picloram (i.e., Tordon 202C) not encompassed by the current Forest Service risk assessment.

In terms of the hazard identification, the availability of only a single study on a single species raises concerns for the distinction between sensitive and tolerant species. As noted in the previous subsection, the differences in sensitivity of algal species span two orders of magnitude. As discussed in Section 4.1.2.5 and illustrated in Figures 7 through 9, similar variability is reflected in the range of sensitivities of terrestrial plants to picloram. In the absence of additional relevant studies on the toxicity of Tordon formulations to other species of aquatic macrophytes, the position of *Lemna gibba* in the spectrum of sensitivities for aquatic macrophytes cannot be determined.

4.2. EXPOSURE ASSESSMENT

4.2.1. Overview

A standard set of exposure assessments for terrestrial and aquatic organisms is provided in Attachment 1 for terrestrial applications made at the maximum anticipated application rate of 1 lb a.e./acre. As in the human health risk assessment, three general types of exposure scenarios are considered: accidental, acute non-accidental, and longer-term.

Exposure assessments for mammals and birds are summarized in Worksheet G01 of the EXCEL workbooks that accompany this risk assessment. The highest short-term exposures are associated with the consumption of contaminated insects by a small bird (224 mg/kg bw) and the consumption of contaminated grasses by a small bird 1,710 mg/kg bw). For both acute and chronic exposures, consumption of contaminated water leads to dose estimates far below those associated with consumption of contaminated vegetation. This pattern, which is common in many herbicide exposure assessments, reflects the consequences of direct applications to vegetation.

For terrestrial plants, five exposure scenarios are considered quantitatively: direct spray, spray drift, runoff, wind erosion, and the use of contaminated irrigation water. Unintended direct spray is expressed simply as the application rate. As with terrestrial animals, all exposure assessments used in the workbooks that accompany this risk assessment are based on the maximum anticipated application rate of 1 lb a.e./acre. The consequences of using other application rates are discussed in the risk characterization.

Exposures of aquatic plants and animals to picloram are based on essentially the same information used to assess the exposure to terrestrial species from contaminated water.

4.2.2. Terrestrial Vertebrates

All exposure scenarios for terrestrial animals are summarized in Worksheet G01 in the EXCEL workbook for picloram that accompanies this risk assessment (Attachment 1). An overview of the mammalian and avian receptors considered in the current risk assessment is given in Table 26. These data are discussed in the following subsections. Because of the relationship of body weight to surface area as well as to the consumption of food and water, small animals will generally receive a higher dose, in terms of mg/kg body weight, relative to large animals, for a given type of exposure. The exposure assessment for mammals considers five nontarget mammals of varying sizes: small (20 g) and medium (400 g) sized omnivores, a 5 kg canid, a 70 kg herbivore, and a 70 kg carnivore. Four standard avian receptors are considered: a 10 g passerine, a 640 g predatory bird, a 2.4 kg piscivorous bird, and a 4 kg herbivorous bird. Because of differences in presumed food items that are consumed, all of the mammalian and avian receptors are not considered in all of the exposure scenarios (e.g., the 640 g predatory bird is not used in the exposure assessments for contaminated vegetation). Toxicity data are not available on terrestrial-phase amphibians (Section 4.1.2.3); accordingly, exposure assessments for these terrestrial vertebrates are not developed.

4.2.2.1. Direct Spray

The unintentional direct spray of wildlife during broadcast applications of a pesticide is a credible exposure scenario, similar to the accidental exposure scenarios for the general public

discussed in Section 3.2.3.2. In a scenario involving exposure to direct spray, the amount of pesticide absorbed depends on the application rate, the surface area of the organism, and the rate of absorption.

For this risk assessment, two direct spray or broadcast exposure assessments are conducted for terrestrial applications. The first spray scenario (Worksheet F01a) concerns the direct spray of half of the body surface of a 20 g mammal during pesticide application. This exposure assessment assumes first-order dermal absorption. The second exposure assessment (Worksheet F01b) assumes complete absorption over Day 1 of exposure. This assessment is included in an effort to encompass increased exposures due to grooming.

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

4.2.2.2. Dermal Contact with Contaminated Vegetation

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

For picloram, as well as most other herbicides and insecticides applied in broadcast applications, the failure to quantify exposures associated with dermal contact adds relatively little uncertainty to the risk assessment, because the dominant route of exposure will be the consumption of contaminated vegetation, which is addressed in the following subsection.

4.2.2.3. Ingestion of Contaminated Vegetation or Prey

In foliar applications, the consumption of contaminated vegetation is an obvious concern. Exposure assessments for the consumption of contaminated vegetation are developed for all mammals and birds listed in Table 26, except for the large carnivorous mammal and the predatory bird. Both acute and chronic exposure scenarios are developed for the consumption of contaminated fruit (Worksheets F04a-e for acute and Worksheets F10a-e for chronic) and the consumption of short grass (Worksheets F05a-e for acute and Worksheets F11a-e for chronic).

As summarized in Table 27, fruit and short grass are the food items that comprise the commodities with the lowest pesticide residue rates (fruit) and the highest pesticide residue rates (short grass). Fruit and short grass are selected to represent the types of vegetation likely to be consumed by various mammals and birds and which encompass the range of plausible picloram concentrations on vegetation.

For both the acute and chronic exposure scenarios, the assumption is made that 100% of the diet is contaminated. This may not be a realistic assumption for some acute exposures and will probably be a rare event in chronic exposures—i.e., animals may move in and out of the treated areas. While estimates of the proportion of the diet that is contaminated could be incorporated into the exposure assessment, the estimates would be an essentially arbitrary set of adjustments. Because the proportion of the diet that is contaminated is linearly related to the resulting HQs, the impact of variations in the proportion of the diet that consists of contaminated food is discussed further in the risk characterization (Section 4.4.2.1).

The initial concentrations of picloram in the food items are based on the U.S. EPA/OPP (2001) adaptation of the residue rates from Fletcher et al. (1997), as summarized in Table 27. The methods of estimating the peak and time-weighted average concentrations of picloram are identical to those used in the human health risk assessment (Section 3.2.3.7.1 for picloram).

The estimated food consumption rates by various species of mammals and birds are based on field metabolic rates (kcal/day), which, in turn, are based on the adaptation of estimates from Nagy (1987) by the U.S. EPA/OPP (1993). These allometric relationships account for much of the variability in food consumption among mammals and birds. There is, however, residual variability, which is remarkably constant among different groups of organisms (Nagy 1987, Table 3). As discussed further by Nagy (2005), the estimates from the allometric relationships may differ from actual field metabolic rates by about ±70%. Consequently, in all worksheets involving the use of the allometric equations for field metabolic rates, the lower bound is taken as 30% of the estimate and the upper bound is taken as 170% of the estimate.

The estimates of field metabolic rates are used to calculate food consumption based on the caloric value (kcal/day dry weight) of the food items considered in this risk assessment and estimates of the water content of the various foods. Estimates of caloric content are summarized in Table 39. Most of the specific values in Table 39 are taken from Nagy (1988) and U.S. EPA/ORD (1993).

Along with the exposure scenarios for the consumption of contaminated vegetation, similar sets of exposure scenarios are provided for the consumption of small mammals by either a predatory mammal (Worksheet F08a) or a predatory bird (Worksheet F08b) as well as the consumption of contaminated insects by a small mammal, a larger (400 g) mammal, and a small bird (Worksheets F07a-c).

4.2.2.4. Ingestion of Contaminated Water

The methods for estimating picloram 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 consumed. As with the estimates of food consumption, water consumption rates are well characterized in terrestrial vertebrates. The water consumption rates are based on allometric relationships in mammals and birds, as summarized in Table 26. Based on these estimates, exposure scenarios involving the consumption of contaminated water are developed for mammals and birds for accidental spills (Worksheets F02a-e), expected peak expected concentrations (Worksheets F06a-e), and expected longer-term concentrations (Worksheets F12a-e).

As with food consumption, water consumption in birds and mammals will vary substantially with diet, season, and many other factors; however, there are no well-documented quantitative estimates regarding the variability of water consumption by birds and mammals in the available literature. Accordingly, the variability in water consumption rates of birds and mammals is not considered in the exposure assessments. As summarized in upper section of Table 14, however, the upper and lower bound estimates of picloram concentrations in surface water vary by a factor of 180 for acute exposures and over 110 for longer-term exposures. Given this variability in the concentrations of picloram in surface water, it is unlikely that a quantitative consideration of the variability in water consumption rates of birds and mammals would have a substantial impact on the risk characterization.

4.2.2.5. Ingestion of Contaminated Fish

In addition to the consumption of contaminated vegetation, insects, and other terrestrial prey (Section 4.2.2.3), the consumption of contaminated fish by piscivorous species is a viable route of exposure to picloram; accordingly, sets of exposure scenarios are developed for an accidental spill (Worksheets F03a-b), expected peak exposures (Worksheets F09a-c), and estimated longer-term concentrations (Worksheets F13a-c). These exposure scenarios are applied to 5 and 70 kg carnivorous mammals as well as a piscivorous bird. The 70 kg carnivorous mammal would be typical of a black bear (which does not actively hunt fish) but could be representative of a small or immature Great Plains Grizzly Bear (*Ursus arctos horribilis*), which is an endangered species that actively feeds on fish (Reid 2006).

Exposures to picloram in contaminated fish are dependent not only on the concentration of picloram in water but also on the bioconcentration factor for picloram. The concentrations of picloram in water are identical to those discussed in Section 4.2.2.4. As discussed in Section 3.2.3.5, picloram does not bioconcentrate in fish. Consequently and as in the human health risk assessment, the bioconcentration factor for fish is taken as 1 L/kg for all exposure scenarios involving mammals and birds.

4.2.3. Terrestrial Invertebrates

4.2.3.1. Direct Spray and Drift

Estimated levels of exposure associated with broadcast terrestrial applications of picloram are detailed in Worksheet G09 of Attachment 1 (terrestrial applications of picloram). This is a custom worksheet which includes aerial, ground broadcast (high boom and low boom), and backpack applications.

Honeybees are used as a surrogate for other terrestrial insects, and honeybee exposure levels associated with broadcast applications are modeled as a simple physical process based on the application rate and surface area of the bee. The surface area of the honeybee (1.42 cm^2) is based on the algorithms suggested by Humphrey and Dykes (2008) for a bee with a body length of 1.44 cm.

The amount of a pesticide deposited on a bee during or shortly after application depends on how close the bee is to the application site as well as foliar interception of the spray prior to deposition on the bee. The estimated proportions of the nominal application rate at various distances downwind given in G09 are based on Tier 1 estimates from AgDRIFT (Teske et al.

2002) for distances of 0 (direct spray) to 900 feet downwind of the treated site. Further details of the use of AgDRIFT are discussed in Section 4.2.4.2 (Off-Site Drift) with respect to nontarget vegetation.

In addition to drift, foliar interception of a pesticide may occur. The impact of foliar interception varies according to the nature of the canopy above the bee. For example, in studies investigating the deposition rate of diflubenzuron in various forest canopies, Wimmer et al. (1993) report that deposition in the lower canopy, relative to the upper canopy, generally ranged from about 10% (90% foliar interception in the upper canopy) to 90% (10% foliar inception by the upper canopy). In Worksheet G09, foliar interception rates of 0% (no interception), 50%, and 90% are used.

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

4.2.3.2. Ingestion of Contaminated Vegetation or Prey

Like terrestrial mammals and birds, terrestrial invertebrates may be exposed to picloram through the consumption of contaminated vegetation or contaminated prey. For broadcast foliar applications, estimates of residues on contaminated vegetation or prey are based on estimated residue rates (i.e., mg/kg residues per lb applied) from Fletcher et al. (1994), as summarized in Table 15.

An estimate of food consumption is necessary to calculate a dose level for a foraging herbivorous insect. Insect food consumption varies greatly, depending on the caloric requirements in a given life stage or activity of the insect and the caloric value of the food to be consumed. The derivation of consumption values for specific species, life stages, activities, and food items is beyond the scope of the current analysis. Nevertheless, general food consumption values, based on estimated food consumption per unit body weight, are readily 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).

Details concerning estimated exposure levels for the consumption of contaminated vegetation by herbivorous insects are provided in Worksheets G07a, G07b, G07c, and G07d of the EXCEL workbook for terrestrial foliar applications of picloram (Attachment 1). These levels pertain to the four food items included in the standard residue rates provided by Fletcher et al. (1994).

4.2.4. Terrestrial Plants

Generally, the primary hazard to nontarget terrestrial plants associated with the application of most herbicides is unintended direct deposition or spray drift. In addition, herbicides may be transported off-site by percolation or runoff or by wind erosion of soil. As noted in Section 4.1.2.5 (Hazard Identification for Terrestrial Plants) and discussed further in Section 4.3.2.5 (Dose-Response Assessment for Terrestrial Plants), the toxicity data on picloram are sufficient to interpret risks associated with these exposure scenarios. Consequently, exposure assessments are developed for each of these exposure scenarios, as detailed in the following subsections. These exposure assessments are detailed in Worksheet G04 (runoff), Worksheet G05 (direct spray and drift), Worksheet G06a (contaminated irrigation water), and Worksheet G06b (wind erosion) of the attachments for broadcast foliar applications—i.e., Attachment 1 for picloram.

4.2.4.1. Direct Spray

Unintended direct spray will result in an exposure level equivalent to the application rate. For many types of herbicide applications, it is plausible that some nontarget plants immediately adjacent to the application site could be sprayed directly. This type of scenario is modeled in the worksheets that assess off-site drift (see below).

4.2.4.2. Off-Site Drift

Because off-site drift is more or less a physical process that depends primarily on droplet size and meteorological conditions rather than specific properties of the compound being sprayed, estimates of off-site drift can be modeled using AgDRIFT. These estimates are summarized in Worksheet G05 of the EXCEL workbook for terrestrial applications of picloram (Attachment 1). This custom worksheet includes estimates of drift for aerial, ground broadcast, and backpack applications.

The drift estimates used in the current risk assessment are based on AgDRIFT (Teske et al. 2002) using Tier 1 analyses for aerial and ground broadcast applications. The term *Tier 1* is used to designate relatively generic and simple assessments that may be viewed as plausible upper limits of drift. Aerial drift estimates are based on Tier 1 using ASAE Fine to Medium drop size distributions. Tier 1 estimates of drift for ground broadcast applications are modeled using both low boom and high boom options in AgDRIFT. For both types of applications, the values are based on Very Fine to Fine drop size distributions and the 90^{th} percentile values from AgDRIFT.

Drift associated with backpack applications (directed foliar applications) are likely to be much less than drift from ground broadcast applications. Few studies, however, are available for quantitatively assessing drift after backpack applications. For the current risk assessment, estimates of drift from backpack applications are based on an AgDRIFT Tier 1 run of a low boom ground application using Fine to Medium/Coarse drop size distributions (rather than very fine to fine) as well as 50^{th} percentile estimates of drift (rather than the 90^{th} percentile used for ground broadcast applications).

The values for drift used in the current risk assessment should be regarded as little more than generic estimates similar to the water concentrations modeled using GLEAMS (Section 3.2.3.4.3). Actual drift will vary according to a number of conditions—e.g., the topography, soils, weather, and the pesticide formulation. All of these factors cannot be considered in this general risk assessment.

4.2.4.3. Runoff and Soil Mobility

Exposures to terrestrial plants associated with runoff and sediment loses from the treated site to an adjacent untreated site are summarized in Worksheet G04 of the EXCEL workbook for terrestrial applications of picloram (Attachments 1).

Any pesticide can be transported from the soil at the application site by runoff, sediment loss, or percolation. Runoff, sediment loss, and percolation are considered in estimating contamination of ambient water. Only runoff and sediment loss are considered in assessing off-site soil contamination. This approach is reasonable because off-site runoff and sediment transport will contaminate the off-site soil surface and could impact non-target plants. Percolation, on the other hand, represents the amount of the herbicide that is transported below the root zone and thus may impact water quality but should not affect off-site vegetation. The GLEAMS modeling used to estimate concentrations in water provides data on loss by runoff. As with the estimates of picloram in surface water, runoff estimates are modeled for clay, loam, and sand at nine sites that are representative of different temperatures and rainfall patterns (Table 9).

For picloram, the results of the standard GLEAMS modeling of runoff and sediment losses are summarized in Appendix 7, Table A7-1. Note that the proportion of runoff as a fraction of the application rate will vary substantially with different types of climates—i.e., temperature and rainfall—as well as soils, with no runoff or sediment loss anticipated in predominantly sandy soils. The input parameters used to estimate runoff are identical to those used in the Gleams-Driver modeling for concentrations of picloram in surface water as discussed in Section 3.2.3.4.3.1 and summarized in Tables 8, 9 and 10.

The runoff for picloram as a proportion of the application rate is taken as 0.0026 (0.00039 to 0.15). The central estimate and upper bound is taken directly from the Gleams-Driver modeling—i.e., the median and empirical upper 95% bound. The lower bound is effectively zero – i.e., for sandy soils. The lower bound value of $5.1x10^{-07}$ is based on the lowest non-zero central estimate – i.e., loam soils in cool locations and average rainfall. Much lower loss rates are plausible – i.e., in areas with predominantly sandy soils – and this consideration is discussed further in the risk characterization (Section 4.4.2.5.2).

4.2.4.4. Contaminated Irrigation Water

As discussed further in Section 4.4.2.5.3, the Reregistration Eligibility Decision for picloram (U.S. EPA/OPP 1995a) as well as the product labels for Tordon K and Tordon 22K note that water contaminated with picloram should not be used for irrigation. Consequently, this standard exposure scenario that is included in all herbicide risk assessments conducted for the Forest Service may not be relevant to picloram. Nonetheless, this exposure assessment is included both for consistency with other herbicide risk assessments as well as to allow for the assessment of the consequences of disregarding the labeled use restrictions.

The levels of exposure associated with this scenario will depend on the pesticide concentration in the ambient water used for irrigation and the amount of irrigation water used. Concentrations in ambient water are based on the peak concentrations modeled in the human health risk assessment, as discussed in Section 3.2.3.4.6 and summarized in the upper portion of Table 14.

The amount of irrigation used will depend on the climate, soil type, topography, and plant species under cultivation. Thus, the selection of an irrigation rate is somewhat arbitrary. In the absence of any general approach for determining and expressing the variability of irrigation rates, the application of 1 inch of irrigation water with a range of 0.25 to 2 inches is used in this risk assessment. Details of the calculations used to estimate the functional application rates based on irrigation using contaminated surface water are provided in Worksheet G06a (Attachment 1).

4.2.4.5. Wind Erosion

Wind erosion can be a major transport mechanism for soil (e.g., Winegardner 1996), and wind erosion is also associated with the environmental transport of herbicides (Buser 1990). Wind erosion leading to off-site movement of pesticides is likely to be highly site-specific. The amount of picloram that might be transported by wind erosion depends on several factors, including application rate, depth of incorporation into the soil, persistence in the soil, wind speed, and topographical and surface conditions of the soil. Under desirable conditions—e.g., relatively deep (10 cm) soil incorporation, low wind speed, and surface conditions which inhibit wind erosion—it is unlikely that a substantial amount of picloram would be transported by wind.

For this risk assessment, the potential effects of wind erosion are estimated in Worksheet G06b. In this worksheet, it is assumed that picloram is incorporated into the top 1 cm of soil, which is identical to the depth of incorporation used in GLEAMS modeling (Table 10). Average soil losses are estimated to range from 1 to 10 tons/ha/year with a typical value of 5 tons/ha/year. These estimates are based on the results of agricultural field studies which found that wind erosion may account for annual soil losses ranging from 2 to 6.5 metric tons/ha (Allen and Fryrear 1977).

As noted in Worksheet G07b, offsite losses are estimated to reach as much as 0.014% of the application rate. Larney et al. (1999), however, report that wind erosion of other herbicides could be associated with losses up to 1.5% of the nominal application rate following soil incorporation or 4.5% following surface application. This difference appears to be a due to the much higher soil losses noted by Larney et al. (1999)—i.e., up to 56.6 metric tons/ha from a fallow field. The losses reflected in Worksheet G06b may be somewhat more realistic for forest or rangeland applications, because herbicide applications are rarely made to fallow areas. In any event, the higher offsite losses reported by Larney et al. (1999) are comparable to exposures associated with offsite drift at distances of about 50 feet from the application site following low boom (0.017) and high boom (0.05) ground broadcast applications (Worksheet G05). All of the estimates for wind erosion and offsite drift are likely to vary dramatically according to site conditions and weather conditions.

4.2.5. Aquatic Organisms

The concentrations of picloram in surface water used to estimate exposures for aquatic species are identical to those used in the human health risk assessment, as discussed in Section 3.2.3.4.6 and summarized in the upper portion of Table 14.

4.3. DOSE-RESPONSE ASSESSMENT

4.3.1. Overview

Table 28 summarizes the toxicity values used in this risk assessment. The derivation of each of these values is discussed in the following subsections. The available toxicity data support separate dose-response assessments in eight classes of organisms: terrestrial mammals, birds, terrestrial invertebrates, terrestrial plants, fish, aquatic invertebrates, aquatic algae, and aquatic macrophytes. Different units of exposure are used for different groups of organisms, depending on the nature of exposure and the way in which the toxicity data are expressed. To maintain consistency with the exposure assessment, which is necessary for the development of HQs in the risk characterization, all toxicity values given in Table 28 are expressed as acid equivalents (a.e.). Where necessary, the conversion factor of 0.8637 a.e./a.i derived in Table 1 is used to convert experimental exposures expressed as active ingredient (a.i.) to corresponding units in acid equivalents (a.e.).

As with most herbicides labeled for terrestrial applications, the most relevant toxicity data on terrestrial plants are contained in studies submitted to the U.S. EPA/OPP in support of the registration of picloram. These studies on terrestrial plants, however, are not consistent and this adds uncertainty to the dose-response assessment for this group of organisms (Section 4.3.2.5). The toxicity data on aquatic plants suggest a wide-range of sensitivity in algae. Data on aquatic macrophytes, however, are sparse and the dose-response assessment for this group is limited to presumably tolerant species.

The dose-response assessments for terrestrial animals are relatively standard and uncomplicated, except for longer-term studies in birds and estimates of acute oral toxicity in herbivorous insects. Only one standard reproduction study is available in birds and this study has not yet been reviewed by the U.S. EPA/OPP. The study is used to estimate a longer-term NOAEL of 65 mg a.e./kg bw. For herbivorous insects, no oral toxicity data are available and no oral toxicity data are available in bees. Consequently, the dose-response assessment for herbivorous insects is based on a contact toxicity study in honeybees. While tenuous, this approach seems preferable to declining to develop a dose-response assessment and subsequent risk characterization for herbivorous insects. No toxicity data are available on terrestrial-phase amphibians and a dose-response assessment for this group of organisms is not derived.

The dose-response assessments for fish and aquatic invertebrates are reasonably complete except that the longer-term data on aquatic invertebrates are sparse and an explicit chronic NOAEC for sensitive species of aquatic invertebrates is not derived. As with terrestrial-phase amphibians, a dose-response assessment for aquatic-phase amphibians is not derived because of inadequacies in the available data.

4.3.2. Terrestrial Organisms

4.3.2.1. Mammals

As with most Forest Service risk assessments, the dose-response assessment for mammalian wildlife is based on the same studies used in the dose-response assessment for human health effects. As discussed in Section 3.3 and summarized in Table 16, the surrogate acute RfD, derived from a 10-day health advisory (U.S. EPA/OW 1992), is based on a 9-day subacute

toxicity study in dogs yielding an NOAEL of 200 mg/kg bw with a corresponding LOAEL 400 mg/kg bw. The chronic RfD is based on a 2-year dietary study in rats with a NOAEL of 20 mg/kg bw/day and a corresponding LOAEL of 60 mg/kg bw/day. As discussed in Section 4.1.2.1, there are no systematic differences in the toxicity of picloram to various groups of mammals. Consequently, the acute NOAEL of 200 mg/kg bw and the chronic NOAEL of 20 mg/kg bw/day are used to characterize risks associated with acute and chronic exposures, respectively, for all groups of mammals.

4.3.2.2. Birds

4.3.2.2.1. Acute Exposures

As discussed in Section 4.1.2.2, picloram and potassium picloram are classified by the U.S. EPA as *practically nontoxic* to birds in terms of acute exposures (U.S. EPA/OPP 1994b, pp. 21-22). Differences are apparent in acute NOAELs for birds in gavage and acute dietary exposures, and some differences are apparent in NOAELs for picloram acid and the potassium salt of picloram. While acute gavage studies with both the acid and salt yield LD_{50} values in mallards of >2000 mg a.e./kg bw, the salt resulted in no adverse effects at the highest dose tested —i.e., NOAEL ≈1943 mg a.e./kg bw from the study by Beavers (1985); whereas, the picloram acid caused marked signs of toxicity at a dose of 631 mg a.e./kg bw with a NOAEL of 398 mg a.e./kg bw (see Beavers, 1983, as summarized in Appendix 2, Table A2-1). The relatively high NOAEL for mallards in the gavage study for the potassium salt of picloram is supported by a dietary NOAEL of approximately 1600 mg a.e./kg bw in quail exposed to the potassium salt (Beavers 1986).

The current risk assessment is focused exclusively on formulations of picloram that contain the potassium salt of picloram as the active ingredient. In this respect, it could be seen as sensible to use the NOAEL of 1600 mg a.e./kg bw from the study by (Beavers 1986). Conversely, once the formulation of picloram is applied, it may not be reasonable to assume that the cation and anion will be similarly transported. In this respect, the more conservative NOAEL of 398 mg a.e./kg bw may be more appropriate. In the EPA ecological risk assessment on picloram (U.S. EPA/OPP 1994b), the acute dietary NOAEL for birds is taken as 5620 mg a.i./kg food from the study by Beavers (1986) (i.e., equivalent to a NOAEL of about 1600 mg a.e./kg bw). This approach, although it may not be the most conservative, is reasonable. Accordingly, the current Forest Service risk assessment defers to U.S. EPA/OPP (1994b), and the NOAEL of 1600 mg a.e./kg bw is used to characterize risks to birds associated with short-term exposure to picloram following applications of formulations of potassium picloram.

4.3.2.2.2. Longer-term Exposures

The chronic toxicity value for picloram is problematic. The only study appropriate for the longer-term dose-response assessment in birds is the recent reproduction study in quail by Mach (2002). A full copy of this study has been available for the conduct of the current Forest Service risk assessment. This study, however, is proprietary and a copy of this study could not be released to Forest Service personnel and other external peer reviewers during the preparation of the current risk assessment. The Mach (2007) study, which appears to have been properly conducted and is well documented, has not been reviewed by the U.S. EPA/OPP but has been reviewed by the European Union (2007).

Another issue with the study by Mach (2002) involves the determination of the NOAEL. As discussed in Section 4.1.2.2.3, Mach (2002) noted no signs of toxicity in adults and no frank signs of compound-related toxicity in chicks. Two effects in chicks, however, were noted – i.e., a decrease in body weight in all dose groups – and a variety of effects relating to hatchability and survival in chicks. As detailed further in Appendix 10, all three dose groups may be classified as LOELs for weight loss but the magnitude of the weight is not substantial. In some respects, the issue with the interpretation of weight loss in the Mack (2002) study seems analogous to the deliberations of U.S. EPA/OPPTS (1994) concerning the toxicological significance of the 7 mg/kg bw/day dose level in dogs in the study by Landry et al. (1986), as discussed in Section 3.1.5. Simply because an effect is observed, does not suggest that the effect is toxicologically significant or that the effect would substantially impact the ability of organisms to survive and reproduce in the field.

As also discussed in Appendix 10, the effects on hatchability and survivability may be analyzed and interpreted in a number of different ways. Based on the statistics presented in the Mach (2002) study, the European Union (2007) has classified the high dose group (1500 ppm) as a LOEL based on the incidence of hatchlings surviving to Day 14 per number of eggs laid. The statistical reanalyses done as part of the current risk assessment (i.e., the quantal methods presented in Appendix 10) suggest that this endpoint is not the most significant response. Nonetheless, the reanalyses suggests that the 1500 ppm exposure groups is a LOAEL based on the incidence of viable embryos that failed to hatch.

For characterizing the risk of longer-term exposures of birds to picloram, the current risk assessment will classify the 1500 ppm dose group as a LOAEL and the 750 ppm dose group as a NOAEL. This is consistent with the approach taken by the European Union (2007) but it based on a different set of statistical analyses and interpretations of the magnitude of the responses (Appendix 10). Estimating doses in terms of mg/kg bw/day from dietary exposures is an inexact process. As detailed in Appendix 2 (Table A2-3), the estimates provided by the European Union (2007) are modestly lower than the estimates made in the conduct of the current risk assessment. Consequently and as a conservative approximation, the estimates from the European Union (2007) are used and the NOAEL is estimated at 65 mg a.e./kg bw/day and the LOAEL is estimated at 127.6 mg a.e/kg bw/day.

Forest Service risk assessments will generally defer to EPA/OPP risk assessments because Forest Service risk assessments do not involve the levels of resources and review that are typical in U.S. EPA/OPP risk assessments. The most recent ecological risk assessment on picloram (U.S. EPA/OPP 1994b, p. 43) develops an approximate chronic NOAEL for birds of 3648 ppm a.i., equivalent to about 3150 ppm a.e. This NOAEL is based on …*supplemental studies conducted more than 10 years ago.*… which yield a NOAEL (expressed as an application rate) of 11.2 kg a.i./ha for the potassium salt of picloram. While not specifically referenced in the U.S. EPA/OPP (1994b, p. 43) discussion, the NOAEL of 11.2 kg a.i./ha appears to refer to the study by Somers et al. (1978). As summarized in Appendix 3 (Table 3A-3), this study involved exposures only to eggs, although the offspring were followed for a prolonged period of time. While it seems unlikely that a current U.S. EPA/OPP risk assessment would base a chronic NOAEL on a study like the one conducted by Somers et al. (1978), the risk assessment by U.S. EPA/OPP (1994b) is the most recent Agency assessment on picloram.

4.3.2.3. Reptiles and Amphibians (Terrestrial Phase)

In the absence of information on the toxicity of picloram to reptiles and terrestrial phase-amphibians (Section 4.1.2.3), no dose-response assessment for this group of organisms can be developed.

4.3.2.4. Terrestrial Invertebrates

As discussed in Section 4.1.2.4.1, toxicity data on honeybees are typically used in ecological risk assessments as surrogates for terrestrial insects.

For exposure scenarios involving direct spray or spray drift (Section 4.2.3.1), suitable contact toxicity values include the 270 mg a.e./kg bw contact NOAEL for potassium picloram by Hoxter et al. (1989) and the 860 mg a.e./kg bw contact NOAEL for picloram acid from the study by Hoberg (2001). Because the current risk assessment is concerned with the potassium salt of picloram, the 270 mg a.e./kg bw contact NOAEL will be used. Nonetheless, it should be noted that both NOAELs are essentially free-standing in that a LOAEL for contact toxicity in honeybees has not been established. As discussed further in Section 4.4.2.4.1, however, these considerations have little practical consequence because the use of the lower NOAEL does not lead to hazard quotients that exceed the level of concern (HQ=1).

For exposure scenarios involving the consumption of contaminated vegetation (Section 4.2.3.2), only one oral toxicity study is available Hoberg (2001). As with the contact study by Hoberg (2001), the NOAEL from the oral study is 860 mg a.e./kg bw and this is also a free-standing NOAEL. In the absence of any other useful study, the NOAEL of 860 mg a.e./kg bw is used for the risk characterization of herbivorous insects.

4.3.2.5. Terrestrial Plants (Macrophytes)

As detailed in Section 4.1.2.5, standard Tier 2 studies are available for vegetative vigor (Schwab 1996; Weseloh and Stockdale 1989) and seedling emergence (Schwab 1995; Weseloh and Stockdale 1989). As also detailed in Section 4.1.2.5, the studies by Schwab (1995, 1996) are not concordant with the earlier study by Weseloh and Stockdale 1989).

As also discussed in Section 4.1.2.5, commentary on these studies by Wright (1995) and Jachetta (2011c) suggest that the earlier study by Weseloh and Stockdale (1989) may have been flawed due to cross contamination. The commentary by Jachetta (2011c) was conducted in the peer review of the current Forest Service risk assessment and details of this commentary are given below:

> *While there were numerous flaws in the 1989 non-GLP study* [Weseloh and Stockdale (1989)], *the key problem was the cross-contamination between treatments allowed by the irrigation regime used at that time by the Dow Chemical Agricultural Products Company; all treatments and control were subirrigated in the same tray as was typical for herbicide screening studies done at that point in time, this allowing the movement of picloram between treatments and controls. The dose-response curves derived from the 1989 study are archetype classic for cross-contamination. As Dow AgroSciences, we now study water soluble herbicide candidates very differently. We feel that the 1995 GLP study*

represents the best available data with which to evaluate picloram non-target plant effects. This study meets the current guidelines for non-target plant data requirements and was conducted over a broad range of rates to address. Additionally, this study was conducted under GLP and should replace older non-GLP compliant studies for regulatory risk assessment and decision making.

Jachetta 2011c

As noted in Section 1.1, the U.S. EPA/OPP will be conducting a registration review of picloram, currently scheduled for 2014. There is little doubt that the U.S. EPA/OPP will address the issues associated with the seedling emergence studies on picloram. In the interim, the explanation of the otherwise inexplicable differences between the studies by Weseloh and Stockdale (1989) and Schwab (1995) seems reasonable. Particularly in a seedling emergence assay, the potential for cross contamination due to irrigation of plants from different treatment groups cultivated in the same tray is a compelling basis for excluding the use of the study by Weseloh and Stockdale (1989) in the dose-response assessment.

It should be noted that the exclusion of the study by Weseloh and Stockdale (1989) does not have a uniform effect on the dose-response assessment for terrestrial plants. For foliar application, exclusion of the Weseloh and Stockdale (1989) study decreases the NOAEL for tolerant species but has no impact on the NOAEL for sensitive species. Conversely, for soil exposures, excluding the Weseloh and Stockdale (1989) study does increase the NOAEL for sensitive species but has no impact on the NOAEL for tolerant species.

4.3.2.5.1. Foliar Exposures

4.3.2.5.1.1. Sensitive Species

In the assays for vegetative vigor, the most sensitive species are dicots: sunflowers and tomatoes, based on NOAELs of 0.029 g a.e./ha for both species from the study by Schwab (1996). The application rate of 0.029 g a.e./ha is equivalent to about 2.6×10^{-5} lb/acre [0.029 g a.e./ha x 0.001 kg/g x $0.892_{lb/ac \div kg/ha} \approx 0.000025863$ lb a.e./acre], which is the toxicity value entered in Table 28 for sensitive species with respect to foliar applications of picloram.

4.3.2.5.1.2. Tolerant Species

In terms of tolerant species, the study by Schwab (1996) indicates that corn is the most tolerant species, with a NOAEL of 60.5 g a.e./ha or 0.0605 kg a.e./ha. This NOAEL is equivalent to about 0.05 lb a.e./acre [0.0605 g a.e./ha x $0.892_{lb/ac \div kg/ha} \approx 0.05397$ lb a.e./acre] , which is the toxicity value entered in Table 28 for tolerant species with respect to foliar applications of picloram.

4.3.2.5.2. Soil Exposures

4.3.2.5.2.1. Sensitive Species

As discussed in Section 4.1.2.5.2 and illustrated in Figure 9 (monocots) and Figure 10 (dicots), the two studies available on seedling emergence – i.e., Weseloh and Stockdale (1989) and Schwab (1995) – are not concordant. The study by Weseloh and Stockdale (1989) yields substantially lower toxicity values in terms of both NOAECs and EC_{25}s than the later study by Schwab (1995). As discussed in some detail at the start of Section 4.3.2.5, however, the study by Weseloh and Stockdale (1989) is not used in the dose-response assessment.

In the study by Schwab (1995), the most sensitive species, based on NOAELs, is *Phaseolus vulgaris* (pinto beans) with an NOAEC of 0.27 g a.i./ha – i.e., equivalent to 0.00027 kg a.i./ha or about 0.00024 lb a.i./acre. Converting to acid equivalents, this NOAEL is approximately 0.00021 lb a.e./acre [0.00024 lb a.i./acre x $0.8637_{a.e./a.i.}$ ≈ 0.000208 lb a.e./acre]. The NOAEL of 0.00021 is used to characterize risks to sensitive species of terrestrial plants for soil exposures (Table 28).

4.3.2.5.2.2. Tolerant Species

Relative to sensitive species, the dose-response assessment for tolerant species is simple and unambiguous. In the study by Schwab (1995), the most tolerant species is corn (a monocot) with an NOAEL of 560 g a.i./ha or about 0.5 lb a.i./acre. Again converting to acid equivalents, this NOAEL is approximately 0.43 lb a.e./acre [0.5 lb a.i./acre x $0.8637_{a.e./a.i.}$ = 0.43185 lb a.e./acre]. The NOEAL of 0.43 lb a.e./acre is used to characterize risks to tolerant species of terrestrial plants for soil exposures (Table 28).

4.3.2.6. Terrestrial Microorganisms

Risks to terrestrial microorganisms are not expressed quantitatively in most Forest Service risk assessments, and no formal dose-response assessment is developed for picloram. Potential risks to terrestrial microorganisms, however, are addressed qualitatively in the risk characterization (Section 4.4.2.6).

4.3.3. Aquatic Organisms

4.3.3.1. Fish

4.3.3.1.1. Acute Exposures

As discussed in Section 4.1.3.1.1 and illustrated in Figures 11 and 12, the acute toxicity data on picloram, potassium picloram, and the Tordon formulations covered in this risk assessment are robust and internally consistent. These data are suitable for the application of probabilistic methods (e.g., Posthuma et al. 2002) that could be used to present an elaborated dose-response assessment and risk characterization for fish. Probabilistic methods in ecological risk assessment, however, have not been adopted by the Forest Service and are seldom used in Forest Service or U.S. EPA/OPP pesticide risk assessments. In addition and as detailed in the U.S. EPA's Ecological Committee on FIFRA Risk Assessment Methods (ECOFRAM 1999a,b), probabilistic methods are warranted when more routine and conservative methods, such as those employed in the current risk assessment, suggest a substantial risk and a need to refine the risk assessment to provide more precise guidance on the likelihood and magnitude of the risk. As detailed further in Section 4.4.3.1 (risk characterization for fish), this is not the case with picloram and acute risks to fish appear to be marginal.

4.3.3.1.1.1. Sensitive Species

While the data on the acute lethal potency of picloram in fish are substantial, data on sublethal toxicity are scant (Section 4.1.3.1.1.3). In such cases, Forest Service risk assessments typically divide an LC_{50} by 20 to estimate an NOAEC as a first approximation. As illustrated in SERA (2007a, Table F-1), this approach is consistent with and adopted from the U.S. EPA/OPP method for risk characterizations of aquatic species. For picloram, the most sensitive fish species is lake

trout (Figure 12), and the lowest LC_{50} for this species is 1.55 mg a.e./L from the study by Woodward (1976) using hard water (Table 21). As also summarized in Table 21, the geometric mean of the LC_{50} values for this species is 2.8 mg a.e./L, which is only modestly higher than the lowest LC_{50} for this species. Dividing the LC_{50} of 1.55 mg a.e./L by 20 yields an estimated NOAEC of about 0.08 mg a.e./L [1.55 mg a.e./L ÷ 20 ≈ 0.0775 mg a.e./L].

This initial estimate of the NOAEC for a sensitive species, however, is not sensible. As discussed in Section 4.1.3.1.1.3, Woodward (1979) conducted a very atypical but highly relevant study in which the fry of cutthroat trout, another species that is very sensitive to picloram, were exposed to pulse concentrations (designed to mimic exposures through runoff). In this study, no adverse effects based on fry mortality, weight, and growth were noted at concentrations in water that did not exceed 0.29 mg a.e./L. While this NOAEC does not encompass all possible sublethal effects that might be seen in fish, endpoints based on growth are commonly used as NOAECs in chronic studies (discussed below). While the Woodward (1979) study involved exposures to 0.29 mg a.e./L for only 48 hours, exposures up to 0.140 mg a.e./L occurred on Day 9 and 10 of the study, and the duration of observation covered a 25 day period (i.e., the study might be considered subchronic rather than acute). Thus, it seems reasonable to use 0.29 mg a.e./L as a basis for deriving an acute NOAEC for sensitive species.

As noted above, the study by Woodward (1979) involves cutthroat trout, a sensitive but not the most sensitive species. The most sensitive species is lake trout with a mean LC_{50} of 2.8 mg a.e./L, compared with the mean LC_{50} of 4.3 mg a.e./L in cutthroat trout. Thus, the NOAEC of 0.29 mg a.e./L for cutthroat trout is adjusted to lake trout using the ratio of the LC_{50} values (i.e., 0.29 mg a.e./L x 2.8 mg a.e./L ÷ 4.3 mg a.e./L ≈ 0.1888 mg a.e./L). This adjusted value is rounded to 0.19 mg a.e./L and is used to characterize risks to sensitive species of fish following peak exposures to picloram.

4.3.3.1.1.2. Tolerant Species

Based on definitive LC_{50} values, the most tolerant species of fish is the fathead minnow with an LC_{50} of 75 mg a.e./L for potassium picloram (Mayes and Dill 1985). As an initial approximation of an acute NOAEC, this LC_{50} is divided by 20 to yield an estimated acute NOAEC of [75 mg a.e./L ÷ 20 ≈ 3.75 mg a.e./L]. As discussed below in Section 4.3.3.1.2.2, this estimated NOAEC is not sensible because the longer-term NOAEC in fathead minnow from the early life-stage study by Weinberg et al. (1996) is 7.19 mg a.e./L. As a conservative approach, the chronic NOAEC is rounded to two significant figures and the acute NOAEC is taken as 7.2 mg a.e./L. A more elaborate and less conservative dose-response assessment for tolerant species is unnecessary, because expected peak concentrations of picloram in water are far below the concentration of 7.2 mg a.e./L. Peak concentrations in water following an accidental spill are somewhat higher than this NOAEC, and this matter is discussed further in the risk characterization for fish (Section 4.4.3.1).

As summarized in Table 21, the acute toxicity study by Boeri et al. (1995b) in sheepshead minnow using Tordon 22K yields a NOAEC of 27.2 mg a.e./L. Sheepshead is an estuarine/marine species, and the study by Boeri et al. (1995b) is the only study available on estuarine/marine species. It is not clear that this study would be appropriate as a basis for a dose-response assessment in freshwater species. In practical terms, the use of the higher NOAEC

from Boeri et al. (1995b) would have no impact on the risk characterization of tolerant species of fish and this study is not considered further.

4.3.3.1.2. Longer-term Exposures

4.3.3.1.2.1. Sensitive Species

The dose-response assessment for longer-term exposures in sensitive species of fish is reasonably simple. As discussed above (Section 4.3.3.1.1.1) and illustrated in Figure 12, lake trout are the most sensitive species of fish, based on acute lethal potency. Similarly and as summarized in Table 22, lake trout appear to be the most sensitive species of fish, based on longer-term exposures, with an LOAEC of 0.035 mg a.e./L from the early life-stage study by Woodward (1976).

For estimating a NOAEC, considerations of sensitivity ratios based on acute toxicity do not appear to be appropriate. As summarized in the last column of Table 22, the acute-to-chronic ratios (i.e., the ratio of the acute LC_{50} to the chronic NOAEC) for less sensitive species of fish range from about 10 to 40. The experimental LOAEC for lake trout, however, is a factor of 80 below the acute LC_{50} for lake trout. Consequently, as a default approach, the LOAEC of 0.035 mg a.e./L is divided by 10 to estimate an NOAEC of 0.0035 mg a.e./L.

4.3.3.1.2.2. Tolerant Species

The dose-response assessment for longer-term exposures in tolerant species of fish is also straightforward. As summarized in Table 22, the most tolerant species of fish based on both definitive LC_{50} values and longer-term NOAECs is the fathead minnow with an NOAEC of 7.19 mg a.e./L from the early life-stage study by Weinberg et al. (1996). This NOAEC is rounded to 7.2 mg a.e./L and used to assess the consequences of longer-term exposures in tolerant species of fish.

4.3.3.2. Amphibians (Aquatic-Phase)

As discussed in Section 4.1.3.2, the only toxicity data available on aquatic-phase amphibians is the study by Johnson (1976) in tadpoles of two species of frogs native to Australia. This study is not directly useful in the dose-response assessment, because the identity of the material assayed in this study (i.e., Tordon 50-D) is not clear. While the material tested contained picloram, it may also have contained 2,4-D. In addition, the units in which the toxicity values are reported are not clear—i.e., acid equivalents, active ingredient, or formulation. Based on comparisons with a later paper by Johnson (1978) involving a bioassay of Tordon 50-D in a species of fish, no substantial differences in sensitivity between fish and amphibians are apparent (Table 23). This comparison is discussed further in the risk characterization for aquatic-phase amphibians (Section 4.4.3.2).

4.3.3.3. Aquatic Invertebrates

4.3.3.3.1. Acute Exposures

As discussed in Section 4.1.3.3, the acute toxicity data on picloram, the potassium salt of picloram, and the Tordon formulations considered in the current risk assessment are not as extensive as the data on fish. Nonetheless, the data are reasonably consistent indicating that picloram, potassium picloram, and Tordon 22K are only slightly toxic or practically nontoxic to

most aquatic invertebrates. As discussed in Section 4.1.3.3, the endpoints used in the bioassays for aquatic invertebrates range from lethality to effects on development, and these differences influence the use of the different bioassays in the dose-response assessment.

4.3.3.3.1.1. Sensitive Species

The most sensitive species of aquatic invertebrates appear to be oyster larvae. Oyster larvae are very small organisms that undergo rapid development. As detailed in Appendix 5 (Table A5-1), the bioassay by Heitmuller (1975b) reports no substantial impact on development (normal development to the straight-hinge stage within 48 hours) at concentrations of up to about 3.9 mg a.e./L, the second to the highest concentration tested —i.e., 3/100 in control and 4/100 in exposed, p=0.5 using the Fisher Exact test. At the next lower concentration, 2.15 mg a.e./L, the number of abnormal larvae was 1%. At the highest concentration tested, 6.88 mg a.e./L, the number of abnormal larvae was 100%. All response rates were based on counts of 200 larvae at each exposure level. This assay was reviewed by U.S. EPA/OPP and is classified as *Core* for Tordon 22K (U.S. EPA/OPP 1995a, p. 52).

As discussed in Section 4.1.3.3, an approximate EC_{50} of 5.2 mg a.e./L can be based on the geometric mean of the highest no-effect concentration and the 100% effect concentration [(3.9 mg a.e./L x 6.88 mg a.e./L)$^{0.5}$ ≈ 5.17996 mg a.e./L]. This approximation, however, is made simply to classify the response of the larvae in terms of the U.S. EPA/OPP scheme for categorizing acute toxicity in aquatic organisms. It does not seem sensible, however, to divide the approximate EC_{50} by 20 to estimate an acute NOAEC of 0.26 mg a.e./L [5.2 mg a.e./L ÷ 20]. While the failure of oyster larvae to develop properly may be viewed as equivalent to a lethal response, successful development of oyster larvae may be viewed as a satisfactory NOAEC for sublethal effects. In other words, in terms of oyster larvae, more subtle measures of sublethal toxicity are not generally used and do not seem to be needed. Consequently, the NOAEC of 3.9 mg a.e./L could be regarded as a satisfactory NOAEC. Because of the steepness of the dose-response relationship, however, the current risk assessment uses the next lower concentration of 2.15 mg a.e./L from the bioassay by Heitmuller (1975b) as the NOAEC for sensitive species of aquatic invertebrates.

4.3.3.3.1.2. Tolerant Species

The most tolerant species of aquatic invertebrates appears to be the fiddler crab. As summarized in Table 24 and detailed in Appendix 5 (Table A5-1), Heitmuller (1975b) assayed Tordon 22K at concentrations of up to about 215 mg a.e./L in fiddler crabs. No mortality was noted and no effects were noted on equilibrium or response to prodding. As noted above, U.S. EPA/OPP (1995a, p. 52) classifies the Heitmuller (1975b) assay in oyster larvae as *Core* for Tordon 22K. U.S. EPA/OPP (1994b, 1995a) does not, however, discuss the fiddler crab assay in Heitmuller (1975b).

The concentration of 215 mg a.e./L may be regarded as a sublethal NOAEL for gross behavioral changes in the fiddler crab. It is less clear that this NOAEL would reflect more subtle effects in adult crabs that could be significant. In practical terms, however, this has no significant impact on the current risk assessment. As discussed further in Section 4.4.3.4, the concentrations of picloram in water (including the concentrations associated with an accidental spill) are

substantially below 215 mg a.e./L. Consequently, 215 mg a.e./L is taken as the acute NOAEC for tolerant species of aquatic invertebrates.

4.3.3.3.2. Longer-term Exposures

As discussed in Section 4.1.3.3 and summarized in Table 24, two life-cycle study in *Daphnia magna* with technical grade picloram are available (Gersich et al. 1984; Boeri et al. 2002a). The NOAECs in these studies are reasonably consistent – i.e., 11.8 mg a.e./L in Gersich et al. (1984) and 6.79 mg a.e./L in the study by Boeri et al. (2002a).

As summarized in Table 24, *Daphnia magna* is neither a particularly sensitive nor tolerant species. From a practical perspective, however, this matter has no impact on the current risk assessment because expected longer-term exposures to picloram are a factor of about 1000 less than the lower NOAEC of 6.79 mg a.e./L. Consequently, for longer-term exposures, *Daphnia magna* is treated as a tolerant species and the NOAEL is rounded to 6.8 mg a.e./L. Residual concerns for sensitive species are discussed qualitatively in the risk characterization (Section 4.4.3.4).

4.3.3.4. Aquatic Plants

4.3.3.4.1. Algae

As discussed in Section 4.1.3.4.1, several studies on the toxicity of picloram are available in the open literature, but the most relevant studies for the dose-response assessment are those submitted to the U.S. EPA/OPP in support of the registration of picloram —i.e., the assay in *Navicula pelliculosa* by Boeri et al. (1994c) and the assay in *Anabaena flos aquae* by Boeri et al. (1994b). Both of these studies involve Tordon K, one of the formulations used in Forest Service programs; furthermore, these studies define a substantial range of sensitivities.

The most sensitive species is *Navicula pelliculosa* with a 5-day EC_{50} of 0.93 mg a.e./L for growth and a 5-day LOAEC of 0.23 mg a.e./L (Boeri et al. 1994c). Because an NOAEC is not defined, the LOAEC is divided by 10 to approximate an NOAEC of 0.023 mg a.e./L in sensitive species of algae.

The most tolerant species is *Anabaena flos aquae* with an a 5-day EC_{50} of 590 mg a.e./L for growth and a 5-day NOAEC of 94 mg a.e./L (Boeri et al. 1994b). The NOAEC of 94 mg a.e./L is used directly for assessing potential effects in tolerant species of algae.

4.3.3.4.2. Macrophytes

As discussed in Section 4.1.3.4.2, the data on the toxicity of picloram to aquatic macrophytes are sparse. The only directly useful study is the bioassay of Tordon K in duckweed (*Lemna gibba*) with a 14-day EC_{50} of 47.8 mg a.e./L and an NOAEC of 12.2 mg a.e./L (Kirk et al. 1994). Duckweed is an aquatic dicot. By analogy to terrestrial plants (Section 4.1.2.5), it would be reasonable to speculate that duckweed might be a tolerant species. As illustrated in Figure 7, however, some species of terrestrial dicots may be as tolerant as some species of monocots to picloram. Given the difficulties in interpreting the data on terrestrial plants—i.e., the lack of concordance in the studies by Schwab (1995, 1996) and Weseloh and Stockdale (1989)—no supposition about the sensitivity of duckweed, relative to other aquatic plants, is made. Consequently and as a conservative assumption, NOAEC of 12.2 mg a.e./L is used for

potentially tolerant species of aquatic macrophytes. Potential risks to sensitive species of aquatic macrophytes are discussed qualitatively in the risk characterization (Section 4.4.3.4.2).

4.4. RISK CHARACTERIZATION

4.4.1. Overview

Like most effective herbicides, picloram poses the greatest risks to terrestrial plants. Even so, there are substantial differences in the sensitivity of various species of terrestrial plants to picloram, as reflected in the HQs. For sensitive species of terrestrial plants, particularly some species of dicots, HQs associated with direct spray, spray drift, and runoff are substantially above the level of concern. The exposure assessments on which these HQs are based involve conservative assumptions. Site-specific or region-specific refinements to the exposure assessments would probably lead to lower HQs. Nonetheless, it is apparent that picloram should be applied with care in order to prevent or minimize damage to nontarget species of plants that are sensitive to picloram. Conversely, other species of plants, particularly some species of monocots, are much less sensitive to picloram. For these tolerant species, the HQs are below the level of concern, except in the event of a direct spray.

Risks to terrestrial animals are much less certain than risks to sensitive species of terrestrial plants. Exposures of terrestrial animals to contaminated water do not lead to apparent risks even in the case of an accidental spill. For contaminated vegetation or prey, none of the central estimates of exposure (i.e., the most likely events) result in HQs that exceed the level of concern (HQ=1). At the maximum anticipated application rate of 1 lb a.e./acre, upper bound HQs that exceed the level of concern are associated with the consumption of contaminated grasses (i.e., food items which contain the highest concentrations of picloram) by a small mammal (HQ=3). This HQ would reach a level of concern at an application rate of about 0.33 lb a.e./acre. For longer-term scenarios using longer-term toxicity values, the consumption of contaminated grasses lead to upper bound HQs that exceed the level of concern for a small mammal (HQ=12), a 400 gram mammal (HQ=3), a large mammal (HQ=1.5), and a small bird (HQ=9). At the typical application rate of 0.25 lb a.e./acre, all of these upper bound HQs would be at or below the level of concern except for the small mammal and the small bird. Direct toxic effects on terrestrial invertebrates as well as terrestrial microorganisms cannot be ruled out but do not appear to be substantial. Because of effects on terrestrial vegetation, secondary effects on terrestrial animals may occur due to changes in habitat quality and/or food availability. These secondary effects could be beneficial to some species and detrimental to other species.

Based on expected concentrations of picloram in surface water, all central estimates of the HQs are below the level of concern for fish, aquatic invertebrates, and aquatic plants. No risk characterization for aquatic-phase amphibians can be developed because no directly useful data are available. Upper bound HQs exceed the level of concern for longer-term exposures in sensitive species of fish (HQ=3) and peak exposures in sensitive species of algae (HQ=8). It does not seem likely that either of these HQs would be associated with overt or readily observable effects in either fish or algal populations. In the event of an accidental spill, substantial mortality would be likely in both sensitive species of fish and sensitive species of algae.

4.4.2. Terrestrial Organisms

4.4.2.1. Mammals

The HQs for mammals as well as birds are summarized in Worksheet G02 of Attachment 1, the EXCEL workbook for picloram. For convenience, sections of this worksheet that lead to HQs of greater than 1, the level of concern (LOC), are summarized in Table 30.

None of the accidental exposure scenarios for mammals exceeds the level of concern, as is generally the case with foliar applications of pesticides. Doses to both mammals and birds following foliar applications are generally associated with the consumption of treated vegetation and are far less than doses associated with an accidental spill scenario.

As detailed in the following subsections, all central estimates of the HQs for mammals are below the level of concern. Because the central estimates of the HQs are based on average or mean estimates of the exposure parameters for the different scenarios, the central estimates of the HQs may be viewed as the expected or most likely measures of risk. The upper bound HQs for the consumption of contaminated grasses exceed the level of concern for a small mammal in both acute and chronic scenarios and exceed the level of concern for larger mammals in chronic scenarios. Consequently, the possibility of undesirable exposure levels cannot be ruled out. On the other hand, there is no indication that overt signs of toxicity might be expected.

4.4.2.1.1. Acute Exposures

For acute non-accidental exposures, only the scenario for the consumption of contaminated grass by a small mammal leads to HQs for which the upper bound exceeds the level of concern—i.e., HQs = 0.7 (0.08 to 3). As summarized in Table 15, the residue rates for short grass are substantially higher than those for other types of vegetation. As discussed in the exposure assessment (Section 4.2.2.3), this exposure scenario may be viewed as conservative since it assumes that 100% of the diet is contaminated and that no foliar interception occurs. Because small mammals will range over a relatively limited area, the assumption of 100% contamination of the diet is not extreme. Grasses, however, are not typically sprayed intentionally with picloram. Moreover, the contamination of grasses with picloram will often be subject to at least some foliar interception (i.e., by the target vegetation). Although, these types of considerations could be included in a site-specific assessment, the conservative assumption of direct spray is maintained in the current generic risk assessment.

The upper bound HQ of 3 is associated with a dose of about 690 mg a.e./kg bw (Attachment 1, Worksheet G01). As summarized in Table 16, this dose is modestly higher than the 400 mg e.g./kg bw LOAEL, associated with decreased body weight in dogs, from the study on which the NOAEL for small mammals is based. It is not clear what effects a dose of 690 mg a.e./kg bw might cause in a small mammal. Although not true for picloram, many acute RfDs are based on developmental/teratogenicity studies with the assumption that adverse developmental effects could occur as a result of single day exposures. As summarized in Appendix 1 (Table A1-3), doses of up to 1000 mg a.e./kg bw/day did not cause adverse developmental effects in small mammals. Thus, while subtle signs of toxicity such as a decrease in body weight cannot be ruled out, it does not seem likely that an acute HQ of 3 would be associated with severe adverse effects in a small mammal.

4.4.2.1.2. Longer-term Exposures

Similar to the circumstances of acute exposures, only the longer-term consumption of contaminated grasses results in HQs that exceed the level of concern (HQ=1) for a small mammal (HQ=12), a 400 gram mammal (HQ=3), and a large mammal (HQ=1.5). The toxicological significance of the HQs of 1.5 and 3 appear to be questionable or at least relatively modest. As summarized in Table 16 and discussed in Section 3.3.3, the chronic NOAEL of 20 mg/kg bw/day in rats used in the dose response assessment is associated with a LOAEL of 60 mg/kg bw/day from the study by Landry et al. (1986). This LOAEL corresponds to an HQ of 3. At this dose, the only effect noted in rats involves altered staining properties of liver cells. The toxicological significance of this effect is not clear. In any event, the study by Landry et al. (1986) clearly indicates that overt signs of toxicity would not be expected at a longer-term HQ of 3.

The upper bound HQ of 12 for a small mammal consuming contaminated grass is associated with a dose of about 238 mg a.e./kg bw/day. As summarized in Table 5, this dose is below the NOAEL of 500 mg a.e./kg bw/day in the 2-year feeding study in mice (Stott et al. 1992). Nonetheless, this dose is above several subchronic LOAELs in rats (i.e., 60 to 185 mg a.e./kg bw/day), none of which is associated with frank signs of toxicity.

4.4.2.1.3. Secondary Effects

The secondary effects on populations of mammals noted in field studies are associated with decreases in food supply rather than any direct toxic effect of picloram to mammals (Section 4.1.2.1). The failure of field studies to detect direct toxic effects in mammals is consistent with the risk characterization for mammals in the current risk assessment. As discussed further in Section 4.4.2.4, secondary effects in mammals based on toxic effects to terrestrial invertebrates do not seem likely but cannot be ruled out. More significantly and as discussed in Section 4.4.2.5, secondary effects on mammals attributable to adverse effects in vegetation are plausible and in some cases virtually certain.

4.4.2.2. Birds

The risk characterization for birds is similar to but somewhat less severe than the risk characterization for mammals. As indicated in Table 30, only two scenarios lead to HQs for which the upper bounds exceed a level of concern—i.e., the acute scenario for a small bird consuming contaminated grasses [HQ = 0.2 (0.02 to 1.1)] and the chronic scenario for a small bird consuming contaminated grasses [HQ = 0.7 (0.06 to 9)].

The modest exceedance in the acute exposure scenarios can be dismissed. HQs are typically rounded to one significant digit. For HQs that are greater than 1 but less than 2, two significant digits are displayed in Forest Service risk assessments by convention and in the interest of transparency.

The longer-term upper bound HQ of 9 is of much greater concern. As discussed in Section 4.3.2.2.2 and detailed in Appendix 10, the current risk assessment does not take the most conservative approach that might be considered in the longer-term dose-response assessment for birds. Specifically, the study by Mach (2002) notes marginal but statistically significant weight loss in chicks at Day 14 after hatching at all exposure levels. The current risk assessment uses a NOAEL of 65 mg a.e./kg bw/day as a NOAEL with a corresponding LOAEL of about 127.5

mg/kg bw/day (Appendix 2, Table A2-3 based on dose estimates from the European Union (2007). The HQ of 9 in the exposure scenario for the longer-term consumption of grass by a small bird is associated with a dose of about 588 mg a.e./kg bw. This dose is substantially higher than the LOAEL of 127.5 mg a.e./kg bw/day and the study by Mach (2002) did not assay doses above 127.5 mg a.e./kg bw/day. Consequently, the potential effects of longer-term exposures to doses in the range of 588 mg a.e./kg bw/day cannot be characterized directly.

One obvious reservation with this scenario involves the consumption of grass by small birds. Larger birds, such as geese, will consume grass, although grass is not typically a major proportion of the diet (U.S. EPA/ORD 1993, p. 2-25). This is also the case with some small birds such as robins (U.S. EPA/ORD 1993, p. 2-198). The assumption that a small bird might feed extensively on grasses may be extreme and implausible. Nonetheless, the standard use of grasses (highest residue rates) and broadleaf vegetation (lowest residue rates) are not necessarily intended to be interpreted literally. Residue rates on a large variety of food items have not been developed, and the use of grass and broadleaf vegetation is an extension of the Extreme Value approach (Section 3.2.3.1.1).

The most prudent interpretation of the upper bound HQ of 9 for chronic exposures is that adverse effects in at least young birds cannot be ruled out. The prevalence and severity of these effects cannot be characterized further.

4.4.2.3. Reptiles and Amphibians (Terrestrial Phase)

In the absence of information on the toxicity of picloram to reptiles and amphibians (Section 4.1.2.3), no risk characterization for this group of organisms is developed. In the absence of information on these groups of organisms, the EPA generally uses data on standard test species of birds (i.e., mallard ducks and quail) as surrogates for reptiles and terrestrial phase amphibians (U.S. EPA/OPPTS 2004, p. 32) .

4.4.2.4. Terrestrial Invertebrates

4.4.2.4.1. Contact Exposures in Honeybees

Details of the HQ for direct spray and spray drift are given in Worksheet G09 of the EXCEL workbook for picloram (Attachment 1). This is a custom worksheet that considers all application methods covered in the current risk assessment as well as the impact of foliar interception.

Risks to honeybees associated with direct spray and spray drift appear to be minimal. Confidence in this risk characterization is reasonably high because a contact toxicity study in bees is available (Hoxter et al. 1989 as discussed in Section 4.1.2.4.1). In addition, the HQ associated with direct spray is 0.3, below the level of concern by a factor of 3. Because the direct spray scenario is not of concern, a discussion of the lower HQs associated with spray drift and foliar interception is unnecessary.

4.4.2.4.2. Herbivorous Insects

The HQs associated with the consumption of contaminated vegetation by herbivorous insects are given in Worksheet G08b of the EXCEL workbook for picloram (Attachment 1). Separate sets of HQs are given for each of the standard food items from Fletcher et al. (1997), as detailed in Table 14. All of the central estimates of the HQs are below the level of concern, ranging from

0.01 for fruit to 0.1 for short grass. The upper bounds of the HQs are also below the level of concern ranging from 0.04 for fruit to 0.6 for short grass.

Confidence in the HQs is reduced because of limitations in the available toxicity data. These limitations include a lack of data on herbivorous insects which necessitates the use of data on honeybees, the availability of only a single oral toxicity study in honeybees that does not define a LOAEL (i.e., Hoberg 2001 as discussed in Section 4.3.2.4), and the lack of data on a relevant formulation or the potassium salt of picloram (i.e., the active ingredient).

Qualitatively, a reasonable interpretation of the HQs is that risks to herbivorous insects do not appear to be of concern based on the available data. As discussed further in the following section, some level of damage to sensitive terrestrial plants is likely at least in some instances. The most likely impact on herbivorous insects would probably be associated with damage to plants and subsequent changes in habitat. As with secondary effects in other groups of organisms, the impacts of changes in vegetation could be beneficial or detrimental, depending on the species of insects.

4.4.2.5. Terrestrial Plants

A quantitative summary of the risk characterization for terrestrial plants is presented in the EXCEL workbook for picloram (Attachment 1): Worksheets G04 for runoff, Worksheets G05 for drift, G06a for exposures associated with the used of contaminated irrigation water, and Worksheet G06b for off-site contamination due to wind erosion. In Attachment 1, Worksheet G05 is a custom worksheet that uses four sets of values for drift: aerial application, ground high-boom broadcast application, ground low-boom broadcast application, and ground backpack application. As detailed in Section 4.3.2.5 and summarized in Table 28, all HQs are based on experimental NOAECs. In addition, all HQs for terrestrial plants are based on the unit application rate of 1.0 lb a.e./acre, which is also the maximum anticipated application rate. As discussed at length in Section 4.3.2.5, the two key toxicity studies on terrestrial plants are not concordant with each other. While this lack of concordance adds some uncertainty to the risk characterization, the magnitude of the HQs are sufficiently high for sensitive species and low for tolerant species that the qualitative risk characterization is reasonably unambiguous.

4.4.2.5.1. Direct Spray and Spray Drift

As summarized in Worksheet G05, the highest HQs are associated with foliar applications (i.e., direct spray and spray drift). This is true for many herbicides used in foliar applications. For convenience, the HQs for direct spray and drift based on all four application methods discussed above are summarized in Table 31. For sensitive species, the HQs substantially exceed the level of concern (HQ=1) for all application methods at distances of up to 900 feet downwind. Because of the very high HQ for sensitive species of plants, considerations of variations in the application rate are only marginally relevant. If sensitive species of plants are sprayed directly with picloram, they will die. At distances of up to 900 feet downwind, adverse effects could occur.

A major reservation with the risk characterization for sensitive species of terrestrial plants involves the exposure assessment. As detailed in Section 4.2.4.2, all estimates of drift are based on estimates from AgDRIFT (Teske et al. 2002). As detailed in the documentation for the worksheets (SERA 2010a, 2011a), the drift estimates used in generic (i.e., non-site-specific) risk assessments, including the current risk assessment, are based on Tier 1 analyses for aerial and

ground broadcast applications. The term Tier 1 is used to designate relatively generic and simple assessments that may be viewed as plausible upper limits of drift. Specifically, all of the HQs are based on upper 90th percentile estimates of drift involving very fine to fine droplet sizes. These drift values may overestimate exposures associated with applications in which larger droplet sizes are used.

Reservations with the exposure assessment for backpack applications are extreme. As also detailed in the documentation for the worksheets (SERA 2010a, 2011a), no substantial quantitative analyses of backpack drift have been encountered in the literature. In addition, no quantitative estimates of backpack drift are available from the Forest Service or other groups within the Department of Agriculture. In the absence of data on backpack drift, the following approach is used:

> *…estimates of drift from an AgDRIFT Tier 1 run of a low boom ground application using Fine to Medium/Coarse drop size distributions (rather than very fine to fine) as well as 50th percentile estimates of drift (rather than the 90th percentile used for ground broadcast applications). More appropriate estimates of drift associated with backpack applications are being sought and, if appropriate data are found, these data will be incorporated into future releases of WorksheetMaker.*
>
> SERA 2011a, p. 46.

If damage to nontarget vegetation is an important consideration in a site-specific assessment, site-specific refinements to the exposure assessment using different inputs into AgDRIFT or using other drift models that might better consider site-specific factors would be justified. Regardless of whether or not refinements to the exposure modeling are made, any applications of picloram should attempt to minimize drift to nontarget vegetation.

For tolerant species of plants, the HQs are much lower. The direct spray of a highly tolerant plant would result in a substantial exceedance above the NOAEC (HQ=20), but none of the HQs exceed the level of concern at distances of about 100 feet or greater downwind of the application site.

As discussed in Section 4.1.2.5.1, the distribution of sensitivities of both monocots and dicots follows a continuum ranging from the most sensitive to most tolerant. As an extension of the *Extreme Value* approach (Section 3.2.3.1.1), HQs are derived in the current generic risk assessment for only the extremes (i.e., the apparently most sensitive and most tolerant species). In a site- or region-specific assessment, considerations of species with intermediate sensitivities could be warranted.

4.4.2.5.2. Soil Exposures by Runoff

As summarized in Worksheet G04 of Attachment 1 (the EXCEL workbook for picloram), the HQs for sensitive species of plants are 12 (0.002 to 714) and the corresponding HQs for tolerant species of plants are 0.006 (0.000001 to 0.3).

For tolerant species, the HQs require little elaboration. Tolerant species of nontarget plants do not appear to be at risk from offsite losses of picloram due to runoff.

For sensitive species of plants, the extreme range of the HQs reflects the nature of the generic (non-site-specific) Gleams-Driver modeling on which the exposure assessment is based. As detailed in Section 3.2.3.4.3 and summarized in Table 9, Gleams-Driver simulations are conducted for nine different locations encompassing extremes of temperature and rainfall. For each of these nine sites, three separate sets of simulations are conducted for soils that consist of predominantly of clay, loam, and sand. As detailed in Section 4.2.4.3, with respect to runoff, the estimated exposures of nontarget plants adjacent to the application site are taken as a composite (i.e., a central estimate and a range) for all of the simulations combined. Consequently, the range of HQs for sensitive species does not apply to any specific location but is a composite of HQs that might be seen nationally.

Appendix 7, Table A7-1 should be consulted in any consideration of the consequences of potential risks to sensitive species of nontarget vegetation in a site-specific application. In areas with predominantly sandy soils, the runoff of picloram following foliar applications should be negligible and risks to nontarget plants should also be negligible. Conversely, risks will be greatest in areas with predominantly clay soils and moderate to high rates of rainfall. Risks may also be relatively high in cool locations with predominantly loam soils. Further generalizations do not appear to be warranted because the modeling conducted for the current risk assessment is inherently conservative and a number of site-specific conditions could reduce, and perhaps substantially reduce, estimates of risks to nontarget vegetation.

If risks to nontarget vegetation in an area adjacent to a planned application site are a substantial concern, site-specific modeling with Gleams-Driver or some other appropriate tool would be justified. The only apparent exceptions involve areas with predominately sandy soils or very arid areas with predominantly loamy soils.

4.4.2.5.3. Contaminated Irrigation Water

The product labels for both Tordon K and Tordon 22K contain cautionary language concerning the potential hazards associated with the contamination of water used for irrigation:

> *Do not contaminate water used for irrigation or domestic purposes by cleaning of equipment or disposal of wastes. Do not allow runoff or spray to contaminate well, irrigation ditches or any body of water used for irrigation or domestic purposes.*
>
> Product label for Tordon K, Label Code: D02-112-025, EPA accepted 03/31/09

The above language reflects similar language from the Reregistration Eligibility Decision for picloram (U.S. EPA/OPP 1995a). Based on the standard assessment for irrigation water included in the current risk assessment, this cautionary language is justified, but only for sensitive species of plants.

The HQs for nontarget plants associated with the use of picloram contaminated surface water for irrigation are summarized in Worksheet G06a of Attachment 1 (the EXCEL workbook for picloram)—HQs of 96 (2 to 3,137) for sensitive species and 0.005 (0.0001 to 1.6) for tolerant species.

As with the HQs for runoff, the HQs associated with irrigation water for tolerant species of plants do not require elaboration. The key variables in this exposure scenario are the Water Contamination Rates and the amount of irrigation water applied, which is assumed to be 1 (0.25 to 2) inches. Taking into account reasonable variations that might be made in the exposure scenario, there is little basis for asserting that tolerant species of plants will be at risk.

The apparent risks to sensitive plants are substantial. As with the runoff estimates discussed in the previous section, Water Contamination Rates (WCRs) are taken from the Gleams-Driver modeling and adjusted for an application rate of 1 lb a.e./acre. As detailed in Section 3.2.3.4.3, the WCRs are a composite of all sites and soils considered in the Gleams-Driver modeling. As with the risks associated with runoff discussed in the previous subsection, site- or region-specific Gleams-Driver may be used to derive more relevant HQs. Given the label language discussed above, however, the use of picloram contaminated surface water for irrigation is not an anticipated event – i.e., the use of contaminated water for irrigation is contrary to the cautionary language on the formulation labels.

4.4.2.5.4. Wind Erosion

As summarized in Worksheet G06b of Attachment 1 (the EXCEL workbook for picloram), the HQs for sensitive species of plants are 3 (0.5 to 5) and the corresponding HQs for tolerant species of plants are 0.0001 (0.0003 to 0.003). As detailed in Section 4.2.4.5, substantial uncertainties are associated with this exposure scenario, and the expected loss rates for soil are intended to represent forestry applications. Much higher loss rates could occur if picloram were to be applied inadvertently to fallow soil.

The HQs for tolerant species of plants are below, and for this scenario, far below the level of concern.

For sensitive species of plants, the central estimate and upper bound of the HQs modestly exceed the level of concern at the maximum anticipated application rate of 1 lb a.e./acre. Because of the modest exceedances, considerations of application will qualitatively alter the risk assessment. As discussed in Section 2.4, the average application rate for picloram in Forest Service applications is about 0.25 lb a.e./acre based on the 2004 use statistics, which are the most recent statistics available. At this lower and perhaps more typical application rate, the central estimate of the HQ would be below the level of concern and the upper bound of the HQ would be only modestly above the level of concern (HQ $\approx$ 1.25).

While potential damage to nontarget vegetation due to the erosion of contaminated soil by wind cannot be totally dismissed, the risks associated with this scenario are far below those of other exposure scenarios for plants considered in this risk assessment (i.e., drift, runoff, and irrigation water).

4.4.2.6. Terrestrial Microorganisms

As discussed in Section 4.1.2.6, the effects of picloram on soil microorganisms may involve a direct relationship between the application rate and the soil concentrations of picloram as well as the persistence of picloram in soil. Whether or not this involves a saturation of microbial metabolism, direct toxicity to microbial populations, or a combination of these two factors is not

clear. Additional studies on soil microorganisms suggest that both picloram and picloram metabolites may impact soil microorganisms. Based on the assay by Prado and Airoldi (2001), picloram concentrations as low as 1 mg/kg soil may delay the microbial use of glucose. As summarized in Appendix 7 (Table A7-3), peak concentrations in the top 12 inches of soil will be no more than 0.2 mg a.e./kg soil. While not detailed in Appendix 7, higher concentrations will occur at shallower soil depths for a least a brief period of time following applications of picloram.

Although picloram could have an effect on soil microorganisms, the consequences of such effects are not clear. Picloram has been used as an herbicide since 1964 (U.S. EPA 1995b). No field studies linking adverse effects on soil microorganism with detectable adverse impacts on soil productivity have been encountered.

4.4.3. Aquatic Organisms

The HQs for aquatic organisms are given in Worksheet G03 of the EXCEL workbook for picloram (Attachment 1). As a convenience, this worksheet is reproduced in Table 32. Like all other HQs in Attachment 1, the HQs for aquatic organisms are based on an application rate of 1 lb a.e./acre, the maximum anticipated application rate. The exposures associated with the HQs are based largely on Gleams-Driver modeling. As discussed in some detail in Section 4.4.2.5.2, the range of exposures is a composite of estimates for a wide variety of locations and soil types. In any site-specific or region-specific analysis, HQs of concern could and probably should be addressed by refined exposure assessments based on site-specific or region-specific characteristics.

4.4.3.1. Fish

Exceedances in the level of concern (HQ=1) for fish are limited to accidental exposures and the upper bound HQ for longer-term exposures in sensitive species of fish. The upper bound HQ for expected peak exposures (HQ=0.9) approaches but does not exceed the level of concern.

For longer-term exposures in sensitive species of fish, the HQs are 0.2 (0.03 to 3). The upper bound HQ is applicable to areas in which runoff, sediment loss, and/or percolation are likely to lead to the contamination of surface water. As summarized in Appendix 7 (Tables A7-6 and A7-8), these areas occur primarily in regions with relatively high rainfall rates, regardless of soil characteristics. The upper bound HQ of 3 is also associated with application rates of 1 lb a.e./acre. More typical application rates of about 0.3 lb a.e./acre would lead to upper bound HQs that do not exceed the level of concern.

As summarized in Worksheet G03 and Table 32, the accidental spill scenario entails estimated concentrations of picloram in water of about 1.5 (0.09 to 18) mg a.e./L. As summarized in Table 21 and illustrated in Figure 11, the central and upper bound concentrations associated with an accidental spill exceed the 96-hour LC_{50} values of picloram in several species of trout as well as channel catfish. In the event of a moderate to severe spill, mortality in these species as well as other undefined but similarly sensitive species would be expected. Mortality in very tolerant species of fish, including fathead minnows, does not seem likely. Additional fish mortality due to oxygen depletion could occur in bodies of water with dense populations of aquatic vegetation that are sensitive to picloram.

4.4.3.2. Amphibians (Aquatic-Phase)

As discussed in 4.3.3.2, no dose-response assessment for amphibians is developed. Consequently, no quantitative risk characterization can be derived. Based on a marginal data set involving bioassays of one species of fish and two species of amphibians using a herbicide formulation containing picloram and perhaps 2,4-D as well, no remarkable differences in sensitivity between fish and amphibians are apparent (Johnson 1976,1978). While this information is marginal, it is generally supportive of the approach taken in U.S. EPA/OPPTS (2004, p. 32) in which data on freshwater fish are used as surrogates for aquatic-phase amphibians.

4.4.3.4. Aquatic Invertebrates

Except for the upper bound HQ for sensitive species of aquatic invertebrates following an accidental spill (HQ=8), HQs for aquatic invertebrates are below the level of concern. A limitation in this risk characterization is that a dose-response assessment is not developed for longer-term exposures in potentially sensitive species of aquatic invertebrates (Section 4.3.3.3.2). For presumably tolerant species of aquatic invertebrates, the upper bound longer-term HQ is 0.001—i.e., below the level of concern by a factor of 1000. While longer effects in potentially sensitive species of aquatic invertebrates cannot be characterized directly, the very low HQ for tolerant species does not suggest a substantial basis for concern in potentially sensitive species.

4.4.3.4. Aquatic Plants

4.4.3.4.1. Algae

In the event of an accidental spill, the HQs for sensitive species of algae exceed the level of concern across the range of estimated exposures —i.e., HQs = 66 (4 to 790). In the event of an accidental spill, substantial mortality would be expected at the central estimates and upper bounds of exposures and some mortality could be expected at the lower bounds of exposures.

Based on expected concentrations in surface water, the only exceedance involves the upper bound HQ for acute exposures (HQ=8) at an application rate of 1 lb a.e./acre. At lower and more typical application rates of 0.25 lb a.e./acre, the HQ would only modestly exceed a level of concern (HQ=2). The HQ of 8 is associated with a concentration of picloram in water of 0.18 mg a.e./L (Table 14). As discussed in Section 4.3.3.4.1, the LOAEC for sensitive species of algae is 0.023 mg a.e./L and the EC_{50} is 0.93 mg a.e./L. Thus, at the HQ of 8, effects on algae might be detectable if careful examinations of algal populations were made; however, substantial mortality in algal species (i.e., readily observable effects) would probably not be apparent.

The upper bound estimates of longer-term concentrations of picloram in surface water at an application rate of 1 lb a.e./acre yield an HQ of 0.4 for sensitive species of algae.

No risks to tolerant species of algae are apparent, including exposures associated with an accidental spill.

4.4.3.4.2. Macrophytes

As discussed in Section 4.3.3.4.2, differences in the sensitivity of aquatic macrophytes to picloram cannot be characterized. Only one directly useful study is available, a bioassay of Tordon K in duckweed (*Lemna gibba*) by Kirk et al. (1994). In the absence of any additional

useful information, the conservative assumption is made that duckweed is a tolerant rather than sensitive species. Nonetheless, it is equally plausible that duckweed could be a sensitive species.

Thus, while the Worksheet G03 gives HQs for tolerant but not sensitive species, this approach is taken simply to accommodate the standard structure of EXCEL workbooks used in Forest Service risk assessments. The most reasonable verbal interpretation, however, is that risks can be characterized for duckweed, at least in one species of duckweed, but not for other aquatic macrophytes.

Based on this interpretation, risks to duckweed are marginal. In the event of an accidental spill, the upper bound HQ is only marginally above the level of concern (HQ=1.5). This HQ is associated with a concentration of picloram in water of about 18 mg a.e./L. As summarized in Table 25, the EC_{50} for duckweed is 47.8 mg a.e./L, above the peak concentration by a factor about 2.5. It is unclear that the HQ of 1.5 would be associated with substantial or even detectable adverse effects.

Based on expected environmental concentrations, the upper bound peak HQ (0.01) for duckweed is below the level of concern by a factor of 100 and the upper bound longer-term HQ (0.0008) for duckweed is below the level of concern by a factor of 1250. Given these HQs, no adverse effects on duckweed are anticipated.

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.

ClrRev	**Cleared reviews at http://www.epa.gov/pesticides/foia/reviews.htm.**
E-Docket	**Selected documents (out of a total of 456) from www.regulations.gov.**
MCS	**Papers on Multiple Chemical Sensitivity**
MRID03	**Registrant studies from 2003 RA.**
MRID11	**Registrant studies received for 2011 RA.**
PeerRev	**Additional information after peer review.**
RA 2003	**Summary from 2003 Forest Service risk assessment**
RA 2003r	**2003 Forest Service risk assessment, reordered**
Sec	**Studies taken from secondary sources.**
Set00	**Preliminary scoping and related risk assessments.**
Set01	**TOXLINE update.**
Set02	**ECOTOX.**
Set03	**Anion transport and sundry additional citations.**
Set04	**Hexachlorobenzene in vegetation.**
Std	**Standard references used in most Forest Service risk assessments.**

Note: Standard reference books that are copyrighted are not on the peer review CD.

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Table 1: Picloram Physical and Chemical Properties

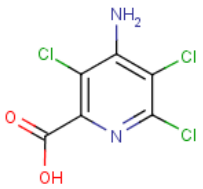
Item	Value	Reference
	Identifiers	
Common name:	Picloram	Tomlin 2004aa
CAS Name	4-amino-3,5,6-trichloro-2-pyridinecarboxylic acid	Tomlin 2004aa
IUPAC Name	4-amino-3,5,6-trichloropyridine-2-carboxylic acid; 4-amino-3,5,6-trichloropicolinic acid	Tomlin 2004a
CAS No.	Form (Abbrev): Acid — 1918-02-1; Potassium salt — 2545-60-0	Tomlin 2004a, NLM 2011a
Molecular formula	$C_6H_3C_{l3}N_2O_2$	Tomlin 2004a
Smiles Notation	`Nc1c(CL)c(CL)nc(C(=O)(O))c1CL`	U.S. EPA/OPP 2011
Structure		NLM 2011a
	Chemical Properties	
Henry's Law Constant	3.3×10^{-10} atm m^3/mole [$3.3x10^{-5}$ Pa m^3/mole]	Mabury and Crosby 1996
	4.7×10^{-5} Pa m^3/mole	Health Canada 2007
	3.4×10^{-5} Pa m^3/mole	Suntio et al. 1988
Hydrolysis half-life	stable	U.S. EPA/OPP 1995a
Kow	79.4 [log Kow = 1.9], protonated form	Tomlin 2004a; Washburn 2002; Health Canada 2007
	1.8 (pH not specified)	Bidlack 1980
	0.89 [pH 5-9] [log Kow=-0.05]	USDA/ARS 1995
Molecular weight	Form: Acid — 241.5; Potassium salt — 279.6	Tomlin 2004a
a.i. to a.e. conversion	Form (Abbrev): Potassium salt — Factor 0.8637. a.i. to a.e. calculated as MW of acid ÷ MW of salt.	See entry for molecular weight.
Melting point	Decomposes before melting.	Tomlin 2004a
	218-219°C	Suntio et al. 1988
pKa	2.3 (22°C)	Tomlin 2004a, Baker 1989c; Health Canada 2007
	3.6	Budavari et al. 1989
	1.9	USDA/ARS 1995
Specific gravity	0.895	Tomlin 2004a
Thermal decomposition	190°C	Tomlin 2004a
Vapor pressure	8 $x10^{-11}$ mPa (25 °C)	Tomlin 2004a
	6.16×10^{-7} mm Hg (35°C)	Budavari et al. 1989
	6.0×10^{-10} mm Hg (25°C)	Baker 1989c
Water solubility	560 mg/L (pH 3, 20 °C)	Tomlin 2004a
	430 mg/L (acid, pH 2.5)	USDA/ARS 1995

Table 1: Picloram Physical and Chemical Properties

Item	Value	Reference
	430 mg/L (25 °C)	Health Canada 2007
	200,000 mg/L (salt)	Knisel and Davis 2000
	430,000 mg/L (K salt)	Neary et al. 1993
	7.2 mg/L (technical in distilled water)	Washburn 2002
	Environmental Fate Properties	
Bioconcentration factor	3.1 L/kg wet wt. [Log BCF=0.5]	U.S. EPA/OPPTS 2011
	Bluegills, whole fish: <0.17	U.S. EPA/OPP 1994b
Foliar washoff fraction	0.6	Knisel and Davis 2000
Foliar half-life	8 days	Knisel and Davis 2000
Foliar half-life	7-8.3 days (grass)	Willis and McDowell 1987
Foliar half-life	32.9 days (crown vegetation) 23.2 days (browse vegetation) 26 days (litter)	Newton et al. 1990
Foliar residue half-life	5.78 and 10.73 (rape plant)	Zhao et al. 2011
$K_{d(ads)}$	0.07 to 0.98	U.S. EPA/OPP 1994b
Koc	16	Knisel and Davis 2000
	16 (2.2 to 92.9)	Havens et al. 2001
	29 (7-48)	USDA/ARS 1995
	Soil / %OM / Koc Silt loam / 2.9 / 23 (14-33) / / 45.3(9-82) Sandy loam / 3.3 / 47(22-71) / / 29.9(23.7-36.1) Different estimates for each soil based on measured or optimized porosity.	Close et al. 1998
	138 (optimized)	Dann et al. 2006
Soil half-life (NOS)	90 days	Knisel and Davis 2000
Soil dissipation half-life	3.45 and 7.11 days	Zhao et al. 2011
Soil half-life, aerobic	90 (24 to 272) days	Havens et al. 2001
	18 to 300 days	USDA/ARS 1995
	167 to 513 days	U.S. EPA/OPP 1994b
Soil half-life, anaerobic	stable	U.S. EPA/OPP 1994b
Soil Field dissipation half-life, terrestrial	131 days	Micheal and Neary 1993
	108 (31 to 206) days	USDA/ARS 1995
	203 (160-246) days [Silt Loam] 244 (181-299) days [Sandy Loam]	Close et al. 1998
	CA: 1.6 lb/acre 278 days (bare ground) 135 days (short grass) NC: 2 lb/acre 108 days (bare ground) 104 days (short grass) Montana: 256 ±37 days SC: 1.08 lb/acre, forest site 123 ±13 days (bare ground) 34 ±18 days (litter cover) WA: forest site 5.3 days (bare ground, bi-exponential) 97 days (bare ground, first-order) 4.7 days (litter cover, bi-exponential) 21.4 days (litter cover, first-order)	U.S. EPA/OPP 1994b
Water, anaerobic metabolic half-times	stable	U.S. EPA/OPP 1994b

Table 1: Picloram Physical and Chemical Properties		
Item	**Value**	**Reference**
Water, photodegradation	2.6 days (25°C), surface water with degradation via photolysis	Woodburn et al. 1989; U.S. EPA/OPP 1994b
Water, field dissipation half-time	14 [0.048 day^{-1}]	Scifres et al. 1989

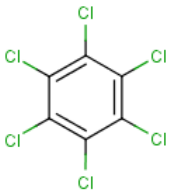
Table 2: Hexachlorobenzene Physical and Chemical Properties		
Item	**Value**	**Reference**
	Identifiers	
Common name:	Hexachlorobenzene	NLM 2011a
Synonyms:	Benzene, 1,2,3,4,5,6-hexachloro-	NLM 2011a
CAS No.	118-74-1	NLM 2011a
Molecular formula	C_6Cl_6	NLM 2011a
Smiles Notation	c1(c(c(c(Cl)c(c1Cl)Cl)Cl)Cl)Cl	NLM 2011a
Structure		NLM 2011a
	Chemical Properties	
Boiling point	325 °C	NLM 2011a
Henry's Law Constant	0.0017 atm-m^3/mole	NLM 2011a
	$5.8x10^{-4}$ atm-m^3/mole	ATSDR 2002
	$3.3x10^{-10}$ atm-m^3/mole	Mabury and Crosby 1996
Kow	≈537,000 [log Kow = 5.73]	NLM 2011a; ATSDR 2002
	≈1,510,000 [log Kow = 6.18]	U.S. EPA/OPP 1998a
Molecular weight	284.784 g/mole	NLM 2011a
Melting point	231.8 °C	NLM 2011a
Specific gravity	2.044	ATSDR 2002, Table 4-2
Vapor pressure	$1.8x10^{-5}$ mm Hg	NLM 2011a
	$1.09x10^{-5}$ mm Hg	ATSDR 2002
Water solubility	0.0035 to 0.006 mg/L	U.S. EPA/OPP 1998a
	0.0051 mg/L	Knisel and Davis 2000
	0.005815 to 0.006 mg/L	ATSDR 2002
	Environmental Fate Properties	
Bioconcentration	2,000 to 20,000	ATSDR 2002
Koc	3,890 [Log Koc: 3.59] 166,000 [Log Koc: 5.22] 1,200,000 [Log Koc: 6.08]	U.S. EPA/OPP 1998a, Table 3; ATSDR 2002
	50,000	Knisel and Davis 2000
Soil half-life	3 to 6 years (subsurface)	U.S. EPA/OPP 1998a
	7.1 days (soil surface, volatilization)	Beall (1976)
Vegetation half-life	Highly volatile (assume 1 day in risk assessment)	ATSDR 2002
Water, dissipation half-life	2.7 to 5.7 years (surface water) 5.3 to 11.4 years (ground water)	EPA/OPP 1998a, Table 3; ATSDR 2002

Table 3: Forest Service Use by Region for 2004

Region	Acres	Pounds	Average lbs/acre	Proportion of Total Acres	Proportion of Total Pounds
R1 (Northern)	28167.50	7509.27	0.27	0.428	0.402
R2 (Rocky Mountain)	17506.38	7188.22	0.41	0.266	0.385
R3 (Southwestern)	0	0	N/A	0	0
R4 (Intermountain)	15482.87	3358.87	0.22	0.235	0.180
R5 (Pacific Southwest)	0	0	N/A	0	0
R6 (Pacific Northwest)	4510.19	517.37	0.11	0.068	0.028
R8 (Southern)	190	95.0	0.50	0.003	0.005
R9 (Eastern)	0	0	N/A	0	0
R10 (Alaska)	0	0	N/A	0	0
Total	65856.94	18668.73	0.28		

Table 4: Forest Service Use by Management Objective for 2004

Objective	Pounds	Acres	Average lbs/acre	Acres, Proportion of Total	Pounds, Proportion of Total
Noxious Weed Control	14,602.62	57,159.14	0.26	0.868	0.782
Agricultural Weed Control	3,799.22	8,346.33	0.46	0.127	0.204
Right-of-Way Management	266.90	351.55	0.76	0.005	0.014
Total:	18,668.73	65,856.94	0.28		

Table 5: Summary of Subchronic and Chronic Toxicity Studies in Mammals

Species, Sex	Duration (Days)	Endpoint [a]	Dose (mg a.e./kg bw/d)[b]		Reference
			NOAEL	LOAEL	
Mice	730	Slight increase in kidney weights (7% relative). No histopathology.	500	1,000	Stott et al. 1992
Rats	14	No toxicologically significant effects on liver or kidney.	≈575		Hayes et al. 1986
	90	Acceleration of normal renal and hepatic lesions. [Mortality at doses of about 580 mg/kg bw.]	≈60	≈185	
Rats M&F	91	Liver, increased weight, no histopathology.	50	150	Gorzinski et al. 1982
Rats, Males		Increase kidney weight, no pathology	150	300	
Rats	730	Liver pathology (altered staining properties) but no liver necrosis. **Basis for chronic RfD.**	**20**	60	Landry et al. 1986
Dogs	9	Decreased food consumption and body weight.	200	400	Dow Chemical 1980
	≈180	Increase in liver weights (males only). No pathology.	7	35	Barna-Lloyd et al. 1982
	365	Increase in liver weights (both sexes). No pathology.	35	175	MRID 40834301 in U.S. EPA/OPP 1995a and 1994a

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

Table 6: Summary of Exposure Assessments in HHRA

		Agent		
	Attachment No:	1	2	
Scenario	**Person**	Picloram	Hexachloro-benzene	Worksheet
WORKERS				
General Exposure	**Worker**	■	■	C01a-c
Accidental Exposures				
Contaminated gloves, 1 minute	**Worker**	■		C02a
Contaminated gloves, 1 hour	**Worker**	■		C02b
Spill, hands, 1 hour	**Worker**	■		C03a
Spill, lower legs, 1 hour	**Worker**	■		C03b
GENERAL PUBLIC				
Accidental Acute Exposures				
Direct Spray of Child, whole body	**Child**	■		D01a
Direct Spray of Woman, feet and lower legs	**Female**	■		D01b
Water consumption (spill)	**Child**	■		D05
Fish consumption (spill)	**Male**	■		D08a
Fish consumption (spill)	**SP**	■		D08b
Non-Accidental Acute Exposures				
Vegetation Contact, shorts and T-shirt	**Female**	■		D02
Contaminated Fruit	**Female**	■		D03a
Contaminated Vegetation	**Female**	■		D03b
Swimming, one hour	**Female**	■		D11
Water consumption	**Child**	■		D06
Fish consumption	**Male**	■		D09c
Fish consumption	**SP**	■		D09d
Chronic/Longer Term Exposures				
Contaminated Fruit	**Female**	■	■	D04a
Contaminated Vegetation	**Female**	■	■	D04b
Water consumption	**Male**	■	■	D07
Fish consumption	**Male**	■	■	D09a
Fish consumption	**SP**	■	■	D09b

See Section 3.2 for discussion

Table 7: Worker Exposure Rates for Standard Terrestrial Application Methods

Worker Group	Central	Lower	Upper
Absorbed Dose Rates	**mg/kg bw/day per lb applied**		
Directed foliar	0.003	0.0003	0.01
Broadcast foliar	0.0002	0.00001	0.0009
Aerial	0.00003	0.000001	0.0001
Treatment Rate	**Acres Treated per Day**		
Directed foliar	4.4	1.5	8.0
Broadcast foliar	112	66	168
Aerial	490	240	800

See Section 3.2.2.1 for discussion.

Table 8: Site Characteristics and Parameters Used in Gleams-Driver Modeling

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

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

GLEAMS Crop Cover Parameters[3]	Description	Value
ICROP	Trees, hardwood + conifer	71
CRPHTX	Maximum height in feet.	20
BEGGRO	Julian day for starting growth	32
ENDGRO	Julian day for ending growth	334

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

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

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

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

Table 9: Precipitation, Temperature and Classifications for Standard Test Sites

Location	Precipitation	Temperature	Average Annual Rainfall (inches)	Average Annual Temperature (◦F)
HI, Hilo	Wet	Warm	126.06	73.68
WA, Quillayute [1]	Wet	Temperate	95.01	49.14
NH, Mt. Washington[2]	Wet	Cool	98.49	27.12
FL, Key West	Average	Warm	37.68	77.81
IL, Springfield	Average	Temperate	34.09	52.79
MI, Sault Ste. Marie	Average	Cool	32.94	40.07
AR, Yuma Test Station	Dry	Warm	3.83	73.58
CA, Bishop	Dry	Temperate	5.34	56.02
AK, Barrow	Dry	Cool	4.49	11.81

[1] Based on composite estimation in WEPP using a latitude of 47.94 N and a longitude of -124.54 W. See SERA (2007b) for details.

[2] This site yielded the maximum concentration of picloram in surface water. See text for discussion.

Table 10: Picloram - Chemical parameters used in Gleams-Driver modeling

Parameter	Values	Note/Reference
Halftimes (days)		
Aquatic Sediment	2000	Note 1
Foliar	8 (6 to 23)	Note 2
Soil	90 (18 to 513)	Note 3
Water	2.6 to 15	Note 4
Soil $K_{o/c}$, mL/g	16 (2.2 to 92.9)	Note 5
Sediment K_d, mL/g	0.07 to 0.98	Note 6
Water Solubility, mg/L	200,000	Knisel and Davis 2000
Foliar wash-off fraction	0.6	Knisel and Davis 2000
Fraction applied to foliage	0.5	Note 7
Depth of Soil Incorporation	1 cm	Note 7
Irrigation after application	none	Note 7

Note 1	Aquatic sediment halftimes not encountered. Value of 2000 days based on halftimes for picloram in deep soil layers (Close et al. 1999, Table 5, p. 70).
Note 2	Central value from Knisel and Davis (2000). Lower bound from the 5.78 day half-life given by Zhao et al. (2011), rounded to integer. Upper bound from 23.2 day half-life for browse vegetation from Newton et al. (1990) rounded to nearest integer. Modeled with triangular distribution.
Note 3	Central estimate from Knisel and Davis (2000) and Havens et al. 2001. Lower bound from USDA/ARS (1995). Upper bound from U.S. EPA/OPP 1994b). Modeled with triangular distribution.
Note 4	The lower bound is from Woodburn et al. (1989), also cited by EPA/OPP (1994b) reflecting degradation via photolysis. The upper bound is from Scifres et al. (1989). Modeled using uniform distribution.
Note 5	Central estimate and range from Havens et al. (2001). Central estimate of 16 also reported by Knisel and Davis (200). These values are consistent with and encompass the Koc's reported by Close et al. 1998. Modeled using triangular distribution.
Note 6	From U.S. EPA/OPP 1994b. Modeled using uniform distribution.
Note 7	Standard assumptions used in all Forest Service risk assessments for foliar applications.

Note: The database for Gleams-Driver includes only central estimates for the above parameters. The uniform and triangular distributions used in the simulations discussed in this risk assessment were implemented using the Full Run feature in Gleams-Driver.

Table 11: Hexachlorobenzene - Chemical used in Gleams-Driver modeling

Parameter	Values	Note/Reference
Halftimes (days)		
Aquatic Sediment	2190 days	Note 1
Foliar	3 days	Note 2
Soil	Top 1 inch: 80 days Deeper Soil Layers: 1095 to 2190 days	Note 3
Water	986 to 2080 days	Note 4
Soil $K_{o/c}$, mL/g	50,000 (3,890 to 1,200,000)	Note 5
Sediment K_d, mL/g	850 (66 to 20,000)	Note 6
Water Solubility, mg/L	0.0051	Knisel and Davis 2000
Foliar wash-off fraction	0.5	Note 2
Fraction applied to foliage	0.5	Note 7
Depth of Soil Incorporation	1 cm	Note 7
Irrigation after application	none	Note 7

Note 1	ATSDR (2002) gives reported halftimes for hexachlorobenzene in soil ranging from 3 to 6 years. For aquatic sediment, the upper range is used – i.e., 3 years × 365days/year = 2190 days.
Note 2	Foliar half-life based on residues in grass from Beall (1976). See Section 3.2.3.4.3.1 for discussion. No data on foliar washoff fraction. A central estimate of 0.5 is used by default.
Note 3	1 Inch: 14 days based on study by Beall (1976) for upper 2 cm (≈0.8 inch) soil depth for grass covered soil. Rapid dissipation probably due to volatilization. Deeper Soil Layers: ATSDR (2002) reported halftimes for hexachlorobenzene in soil ranging from 3 years (1095 days) to 6 years (2190 days). Modeled with a uniform distribution.
Note 4	ATSDR (2002) gives reported halftimes for hexachlorobenzene in surface water ranging from 2.7 years [≈986 days] to 5.7 years [≈2080 days]. This range is modeled with a uniform distribution. This does not consider the rapid dissipation of hexachlorobenzene from water. These values do not consider the rapid volatilization of hexachlorobenzene from surface water. See Section 3.2.3.4.3.2.2 for discussion
Note 5	The reported values for Koc are highly variable. The central estimate is taken from Knisel and Davis (2000) and the bounds are taken from U.S. EPA/OPP (1998a, Table 3). Modeled with a triangular distribution.
Note 6	Calculated as Kd = Ko/c × OC using the Ko/c values from Note 5. Given the substantial variability in the Ko/c values, an average OC of 0.017 is used. All estimates of Kd are rounded to 2 significant figures.
Note 7	Standard assumptions used in all Forest Service risk assessments for foliar applications.

Note: The database for Gleams-Driver includes only central estimates for the above parameters. The uniform and triangular distributions used in the simulations discussed in this risk assessment were implemented using the Full Run feature in Gleams-Driver.

Table 12: Picloram, Summary of modeled and monitored concentrations in surface water

Scenario	Concentrations (ppb or µg/L)	
	Peak	**Long-Term Average**
MODELING FOR THIS RISK ASSESSMENT (1 lb a.e./acre)		
Direct Spray and Spray Drift		
Pond, Direct Spray (Section 3.2.3.4.2) [a]	112	N/A
Pond, drift at 25 feet (Section 3.2.3.4.2) [a]	≈ 1 to 25	N/A
Stream, Direct Spray (Section 3.2.3.4.2) [a]	91	N/A
Stream, drift at 25 feet (Section 3.2.3.4.2) [a]	≈ 0.8 to 20	N/A
Gleams-Driver		
Ground Broadcast Applications, 1 lb a.e./acre		
Pond (Section 3.2.3.4.4) [b]	8.8 (0 to 134)	1.1 (0 -13)
Stream (Section 3.2.3.4.4) [c]	14 (0 - 178)	0.6 (0 - 7)
Other Modeling		
U.S. EPA (1995a),[d]	21.35	
Monitoring [f]		
Defined applications (ppb per lb a.e./acre)		
Davis and Ingebo 1973, 10.4 kg/ha (9.3 lb/acre), pellet applications, post-storm event	40	
Michael and Neary 1993		
Aerial application at 5.6 kg a.i./ha (5 lb a.i./acre)		
During Application (drift)	79	
Post-application (probably from runoff)	14 to 43	
Ground broadcast application at 5.0 kg a.i./ha (4.5 lb a.i./acre)	2	
Watson et al. (1989), 0.28 kg a.e./ha (about 0.25 lb/acre) or 1.12 kg a.e./ha (1 lb/acre)	N.D. (<0.5)	
Not associated with defined applications		
USGS Stream Monitoring (Gilliom et al. 2007), Appendix 7		0.01 (max)

[a] Section 3.2.3.4.2 discusses expected concentrations in terms of the unit application rate of 1.0 lb a.e./acre. The values for direct spray and drift are taken from Worksheet B04c (pond) and Worksheet B04d (stream).
[b] See Appendix 7, Tables 7 and 8, for more detailed site-specific summary of pond modeling.
[c] See Appendix 7, Tables 5 and 6, for more detailed site-specific summary of stream modeling.
[d] U.S. EPA/OPP 1995a, p. 75. Modeling (not discussed in detail) for potassium picloram at 2 lb a.i./acre for a 6 foot deep pond. Values in table above are normalized for a.e. and an application rate of 1 lb a.e./acre.

See Section 3.2.3.4.3.2.1 for discussion.

Table 13: HCB, Summary of modeled and monitored concentrations in surface water

Scenario	Concentrations (ppb or µg/L)	
	Peak	**Long-Term Average**
MODELING FOR THIS RISK ASSESSMENT (0.1 lb/acre)		
Gleams-Driver		
Ground Broadcast Applications, 0.1 lb/acre		
Pond (Section 3.2.3.4.4) [a]	0.39 (0 to 5.1)	0.032 (0 -0.4)
Stream (Section 3.2.3.4.4) [b]	0.99 (0 – 13.5)	0.046 (0 – 0.5)
Normalized to 1 lb/acre		
Pond (Section 3.2.3.4.4) [a]	3.9 (0 to 51)	0.32 (0 - 4)
Stream (Section 3.2.3.4.4) [b]	9.9 (0 - 135)	0.46 (0 - 5)
Other Modeling		
U.S. EPA (1998a),[d]		0.01 EEC
Monitoring [f]		
ATSDR (2002)		0.0903 (max)
U.S. EPA/OPP 1998a, summary of STORET (Table 5, p. 13)		0.1 (max lake)
		0.026 (max stream)

[a] See Appendix 8, Tables 7 and 8, for more detailed site-specific summary of pond modeling.
[b] See Appendix 8, Tables 5 and 6, for more detailed site-specific summary of stream modeling.
[c] U.S. EPA/OPP 1998a. Generic assessment for several species. No specific exposure modeling for picloram or other pesticides.

See Section 3.2.3.4.3.2.2 for discussion.

Table 14: Water Contamination Rates used in this risk assessment

	Water contamination rate in mg/L per lb/acre applied [1]	
Picloram	**Peak**	**Longer-term**
Central	0.011	0.00085
Lower	0.001	0.00009
Upper	0.18	0.01
Hexachlorobenzene	**Peak**	**Longer-term[2]**
Central	**N/A**	0.00039
Lower		0.00004
Upper		0.005

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

[2] The concentrations of hexachlorobenzene in water are substantially overestimated because volatilization is not considered quantitatively. See Sections 3.2.3.4.3.2.2 and 3.2.3.4.6 for discussion.

Sec Section 3.2.3.4.6 for discussion.

Table 15: Estimated residues in food items as ppm per lb applied

Food Item	Concentration in Food Item (ppm per lb/acre)		
	Central [a]	Lower [b]	Upper [a]
Rates adopted from Fletcher et al. 1997			
Short grass	85	30	240
Tall grass	36	12	110
Broadleaf/forage plants and small insects	45	15	135
Fruits, pods, seeds, and large insects	7	3.2	15

[a] U.S. EPA/EFED 2001, p. 44 as adopted from Fletcher et al. (1997).
[b] Central values × (Central Value ÷ Upper Value).

Table 16: Toxicity values used in human health risk assessment

Duration	Derivation of RfD	Reference	Comment
Picloram, Acute – single exposure			
NOAEL Dose	200 mg/kg bw/day	Dow Chemical 1980	No acute RfD has been derived for picloram by U.S. EPA/OPP. A surrogate acute RfD can be based on the 10-day health advisory from the U.S. EPA's Office of Water.
LOAEL Dose	400 mg/kg bw/day		
LOAEL Endpoint(s)	Decrease body weight		
Species	Beagle dogs		
Uncertainty Factor	100	U.S. EPA/OW 1992	
Surrogate Acute RfD	2 mg/kg bw/day		
Picloram, Chronic – lifetime exposure			
NOAEL Dose	20 mg/kg bw/day	Landry et al. 1986, MRID 00155940	See Section 3.3.3.
LOAEL Dose	60 mg/kg bw/day		
Species	Rats		
LOAEL Endpoint(s)	Staining properties of liver cells		
Uncertainty Factor	100	U.S. EPA/OPP 1994a, 1995a	
RfD	0.2 mg/kg bw/day		
Hexachlorobenzene, Cancer Potency			
Cancer Potency Factor	1.02 $(mg/kg\ bw/day)^{-1}$	U.S. EPA/OPP 1998b, 1999	See Section 3.3.6.
Species	Rats		
Risk Level	1 in 1-million		
Dose	0.00000098 mg/kg bw/day		

Table 17: Risk Characterization for Workers

Application Rate = 1 lb a.e. picloram/acre
HCB in picloram = 3 ppm

Scenario	Receptor	Hazard Quotients		
		Central	Lower	Upper
Picloram: Accidental/Incidental Exposures				
Contaminated Gloves, 1 min.	Worker	2E-05	3E-06	3E-04
Contaminated Gloves, 1 hour	Worker	1E-03	2E-04	2E-02
Spill on Hands, 1 hour	Worker	1E-05	2E-06	8E-05
Spill on lower legs, 1 hour	Worker	2E-05	4E-06	2E-04
Picloram: General Exposures (Systemic Toxicity)				
Backpack Applications:		7E-02	2E-03	0.4
Ground Broadcast Applications:		0.1	3E-03	0.8
Aerial Applications:		7E-02	1E-03	0.4
Hexachlorobenzene: General Exposures (Carcinogenicity) [1]				
Backpack Applications:		4E-02	1E-03	0.2
Ground Broadcast Applications:		0.1	2E-03	0.5
Aerial Applications:		5E-02	7E-04	0.2

[1] The HQs for carcinogenicity are calculated as the exposure divided by the dose associated with a risk of 1 in 1-million.

Source: Worksheets E02 in Attachment 1 (Picloram) and Attachment 2 (Hexachlorobenzene)
See Section 3.4.2 for discussion.

Table 18: Risk Characterization for General Public

Scenario	Receptor	Hazard Quotients		
		Central	Lower	Upper
Picloram: Accidental Acute Exposures (dose in mg/kg/event)				
Direct Spray of Child	Child	1E-03	7E-05	2E-02
Direct Spray of Woman	Female	1E-04	7E-06	2E-03
Water consumption (spill)	Child	6E-02	2E-03	**1.0**
Fish consumption (spill)	Adult Male	2E-03	1E-04	2E-02
Fish consumption (spill)	Subsistence	8E-03	5E-04	1E-01
Picloram: Non-Accidental Acute Exposures				
Vegetation Contact	Female	2E-04	4E-05	5E-04
Contaminated Fruit	Female	6E-03	3E-03	9E-02
Contaminated Vegetation	Female	8E-02	6E-03	0.7
Swimming, one hour	Female	4E-07	4E-08	3E-06
Water consumption	Child	2E-03	2E-04	1E-02
Fish consumption	Male	6E-05	1E-05	2E-04
Fish consumption	Subsistence	3E-04	6E-05	1E-03
Picloram: Systemic Toxicity from Longer Term Exposures				
Contaminated Fruit	Female	8E-03	3E-03	0.3
Contaminated Vegetation	Female	0.1	5E-03	**2**
Water consumption	Male	1E-04	9E-06	2E-03
Fish consumption	Male	6E-07	6E-08	7E-06
Fish consumption	Subsistence	5E-06	5E-07	6E-05
Hexachlorobenzene: Carcinogenicity from Lifetime Exposures				
Contaminated Fruit	Female	4E-05	2E-05	6E-04
Contaminated Vegetation	Female	5E-04	4E-05	4E-03
Contaminated Tuber	Female	2E-02	1E-02	0.1
Water consumption	Male	3E-05	2E-06	5E-04
Fish consumption	Male	3E-03	3E-04	4E-02
Fish consumption	Subsistence	3E-02	3E-03	0.4

Source: Worksheets E04 in Attachment 1 (Picloram) and Attachment 2 (Hexachlorobenzene)
See Section 3.4.3 for discussion.

Table 19: Vegetative Vigor Assays in Monocots and Dicots

Species	EC_{25} (g a.e./ha)
Monocots (Schwab 1996)	
Wheat	29.4
Barley	57.9
Onion	113.1
Corn	253.1
Monocots (Weseloh and Stockdale 1989)	
Wheat	310
Barley	>560
Onion	>560
Corn	>560
Dicots (Schwab 1996)	
Sunflower	0.081
Pinto bean	0.083
Tomato	0.17
Soybean	0.27
Cucumber	1.02
Alfalfa	1.42
Rape	1.84
Radish	36.3
Dicots (Weseloh and Stockdale 1989)	
Soybean	0.4
Tomato	0.97
Dry bean	1.1
Sunflower	6.9
Radish	>70
Oilseed rape	>70

See Figure 7 for illustration of data and Appendix 3, Table A3-1 for details.
See Section 4.1.2.5.1 for discussion.

Table 20: Seedling Emergence Assays in Monocots and Dicots

Species	EC_{25} (g a.e./ha)
Monocots, Schwab 1995	
Wheat	136
Onion	736
Barley	>1120
Corn	>1120
Monocots, Weseloh and Stockdale 1989	
Wheat	23.5
Barley	36.9
Onion	55.3
Corn	>560
Dicots, Schwab 1995	
Pinto bean	6.34
Tomato	7.54
Soybean	23
Sunflower	>560
Rape	>1120
Radish	>1120
Dicots, Weseloh and Stockdale 1989	
Soybean	0.014
Dry bean	0.1
Tomato	0.58
Sunflower	1.5
Oilseed rape	20.6
Radish	33.7

See Figure 9 for illustration of data and Appendix 3, Table A3-2 for details.
See Section 4.1.2.5.2 for discussion.

Table 21: Summary of 96-hour LC_{50}s in Fish

Species/Group	96-hour LC_{50}	Reference	Modifier
Bluegills	14.5	Batchelder 1974	Acid
	20.7	Alexander and Batchelder 1965	Tordon, 26.7°C
	21.9	Mayes and Oliver 1986	Acid
	23	Johnson and Finley 1980	Acid, 22°C
	23.2	Johnson and Finley 1980	K-salt, 18°C
	41.7	Mayes and Dill 1984	Acid
	51.4	Mayes and Dill 1984	K-salt
Geometric Mean	**25.8**		
Channel catfish	5.8	Mayer and Ellersieck 1986	Yolk sac fry
	6.3	Johnson and Finley 1980	18 °C
	6.8	Mayer and Ellersieck 1986	Swim up fry
	11	Alexander and Batchelder 1965	
	15.5	Johnson and Finley 1980	22 °C
	16	Mayer and Ellersieck 1986	Advanced fry
Geometric Mean	**9.4**		
Fathead minnow	52	Mayes and Dill 1984	acid
	75	Mayes and Dill 1985	K-salt
Geometric Mean	**62.4**		
Cutthroat trout	1.5	Johnson and Finley 1980	10°C
	3.45	Woodward 1976	Hard water
	3.45	Woodward 1976	Very hard water
	3.7	Woodward 1976	Soft water
	3.9	Woodward 1982	
	4.1	Woodward 1976	15°C
	4.15	Woodward 1976	pH 8.5
	4.5	Woodward 1982	
	4.7	Woodward 1976	pH 7.5
	4.8	Johnson and Finley 1980	12°C
	4.8	Mayer and Ellersieck 1986	Aged solution
	5	Woodward 1976	10°C
	5.8	Mayer and Ellersieck 1986	Fresh solution
	6.5	Woodward 1976	5°C
	8.6	Woodward 1976	pH 6.5
Geometric Mean	**4.3**		
Lake Trout	1.55	Woodward 1976	Hard
	2.05	Woodward 1976	pH 8.5
	2.1	Woodward 1976	Very hard
continued on next page	2.15	Woodward 1976	Soft
	2.35	Woodward 1976	15°C

Table 21: Summary of 96-hour LC_{50}s in Fish

Species/Group	96-hour LC_{50}	Reference	Modifier
Lake Trout	2.7	Woodward 1976	pH 7.5
(continued)	3.6	Woodward 1976	5°C
	4.25	Woodward 1976	10°C
	4.3	Johnson and Finley 1980	10°C
	4.95	Woodward 1976	pH 6.5
Geometric Mean	**2.8**		
Rainbow Trout	5.5	Batchelder 1974	Acid
	8	Mayer and Ellersieck 1986	Yolk sac fry
	8	Mayer and Ellersieck 1986	Swim up fry
	11	Mayer and Ellersieck 1986	Advanced fry
	11.2	Alexander and Batchelder 1965	
	12.5	Johnson and Finley 1980	Acid
	18	Mayes and Dill 1984	Acid
	18	Mayes and Dill 1984	K-salt
	22.3	Fogels and Sprague 1977	Tordon 22K
	41	Fairchild et al. 2007	K-salt
Geometric Mean	**12.3**		
Bull Trout	16	Fairchild et al. 2007	K-salt
Flagfish	22.6	Fogels and Sprague 1977	Tordon 22K
Sheepshead minnow [1]	>27.2 NOAEC	Boeri et al. 1995b	Tordon 22K

[1] Marine/Estuarine

See Appendix 4 (Table A4-1) for details of data.
See Figures 11 and 12 for illustration of data.
See Section 4.1.3.1.1 for discussion.

Table 22: Summary of Acute and Chronic Toxicity Values in Fish

Species	96-hour LC_{50} (mg a.e./L)	Chronic NOAEC (mg a.e./L)	Chronic Duration (days)	Reference for Chronic Study	Acute-to-Chronic Ratio
Lake trout	2.8	<0.035[1]	60	Woodward 1976	>80.0
Rainbow trout	13.2	1.18	30	Fairchild et al. 2009	11.2
Rainbow trout	13.2	0.55	60	Mayes et al. 1984	24.0
Bull Trout	24.0	0.6	30	Fairchild et al. 2009	40.0
Fathead minnow	62.4	7.19	32	Weinberg et al. 1996	8.7

[1] The concentration of 0.035 mg a.e./L is an LOAEC.

See Appendix 4 (Table A4-3) for details of data.
See Section 4.1.3.1.2 for discussion.

Table 23: Amphibians, Acute Toxicity Values from Johnson (1976)

Species	LC_{50}s
Tadpoles (*Adelotus brevis*) 1- to 2-weeks-old	24-hour TL_{50} = 143 ppm 48-hour TL_{50} = 123 ppm 96-hour TL_{50} = 95 ppm
Tadpoles (*Adelotus brevis*), 4-weeks-old, 20/concentration	24-hour TL_{50} = 210 ppm 48-hour TL_{50} = 182 ppm 96-hour TL_{50} = 154 ppm
Tadpoles (*Limnodynastes peroni*), 1- to 2-weeks old	24-hour TL_{50} = 120 ppm 48-hour TL_{50} = 116 ppm 96-hour TL_{50} = 105 ppm
Mosquito fish (*Gambusia affinis*) [1]	24-hour TL50 = 133 ppm 48-hour TL50 = 125 ppm 96-hour TL50 = 120 ppm

[1] From Johnson (1978)

NOTE: Agent used in bioassays contained picloram but may have also contained 2,4-D. The units in which the LC_{50}s are reported – i.e., a.e., a.i., or formulation – is not clear.

See Section 4.1.3.2 for discussion.

Table 24: Toxicity to Aquatic Invertebrates

ACUTE EXPOSURES				
Organism	**Modifier**	**EC_{50}/LC_{50} (mg a.e./L)**		**Reference**
		48-Hours	**96-Hours**	
Daphnia magna[2]	Acid	68.3		Gersich et al. 1984
	Acid [1]	48		Mayes and Dill 1984
	Potassium salt [1]	79		Mayes and Dill 1984
	Potassium salt	173		McCarty 1977
Daphnia similis	Tordon 24K [4]	12		Perina and Pedrolli 1996
Eastern oyster, larvae [3]	Tordon 10K pellets	>100		Heitmuller 1975a
	Tordon 22K	>3.9 < 6.9		Heitmuller 1975b
Fiddler crab	Tordon 10K pellets		>100	Heitmuller 1975a
	Tordon 22K		>215	Heitmuller 1975b
Pink shrimp	Tordon 10K pellets		123	Heitmuller 1975a
	Tordon 22K		26.9	Heitmuller 1975b
Scud (*Gammarus lacustris*)	Acid	48	27	Sanders 1969
Scud (*Gammarus pseudolimnaeus*)	Acid	123	56	Boeri et al. 2002b
Stonefly (*Pteronarcys californica*)	Acid	90	48	Sanders and Cope 1968
Stonefly, (*Pteronarcella* sp)	Acid		>10	Johnson and Finley 1980
LONGER-TERM EXPOSURES (picloram acid only)				
Organism	**Exposure**	**Effect**		**Reference**
Daphnia magna	0, 7.6, 11.8, 18.1, 29.6, or 49.6 mg/L mg a.e./L for 21 days	NOAEC: 11.8 mg a.e./L based on decreases in survival, body weight, brood size, and number of offspring/adult at 18.1 mg a.e/L.		Gersich et al. 1984
Daphnia magna	0, 3.56, 6.79, 13.5,25.9, and 50.3 mg/L for 21 days	NOAEC: 6.79 mg a.e./L based on significant decrease in number of surviving young per female at 13.5 mg a.e./L.		Boeri et al. 2002a

[1] Based on 95% confidence intervals (Appendix 5, Table A5-1), LC_{50} for potassium salt is significantly greater than the LC_{50} for the acid.
[2] Endpoint: immobility.
[3] Endpoint: failure to develop normally to the straight-hinge stage within 48 hours.
[4] Tordon 24K is an Argentinean formulation produced by Dow AgroSciences, Argentina, that contains 24% picloram a.e..

Note: Low LC_{50}s reported by Johnson and Finley (1980) for *Gammarus fasciatus* and a *Pteronarcys* species are excluded from analysis. These LC_{50}s appear to be reporting errors. See Section 4.1.3.3.1 for discussion.

See Appendix 5 for additional details.
See Section 4.1.3.3 for discussion.

Table 25: Toxicity to Aquatic Plants

Species	Modifier	Duration	EC_{50} (mg a.e./L)	Reference
Algae				
Anabaena flos aquae	Tordon K	5 days	142	Boeri et al. 1994b
Chlorella vulgaris	Acid	4 days	≈100	Garten and Frank 1984
Chlorella vulgaris	Acid	14 days	>160	Baarschers et al. 1988
Chlorella pyrenoidosa	Acid	14 days	>160	Baarschers et al. 1988
Navicula pelliculosa	Tordon K	5 days	0.97	Boeri et al. 1994c
Selenastrum capricornutum	Acid	4 days	≈100	Garten and Frank 1984
Selenastrum capricornutum	K-salt (formulation?)	5 days	78.3	Hughes 1990
Selenastrum capricornutum	Tordon 22K (units not clear)	14 days	44.8	Turbak et al. 1986
Selenastrum capricornutum	Form not clear, flask assay	4 days	21.7	St Laurent et al. 1992
Selenastrum capricornutum	Form not clear, plate assay	4 days	22.7	St Laurent et al. 1992
Skeletonema costatum	Tordon K	5 day	3.4	Boeri et al. 1994d
Macrophytes				
Lemna gibba	Tordon K	14 days	47.8	Kirk et al. 1994

Note: Macrophyte studies by Nishiuchi (1974) and Forsyth et al. (1997) are not included in above table. See Section 4.1.3.4 for discussion.

See Appendix 6 for additional details of studies.
See Section 4.1.3.4 for discussion.

Table 26: Terrestrial Nontarget Animals Used in Ecological Risk Assessment

Animal	Representative Species	W[4]	Food Consumption[5]	Water Consumption	Other
MAMMALS[1]					
Small mammal	Mice	20	$2.514\ W^{0.507}$ [Eq 3-48]	$0.099\ W^{0.9}$ [Eq 3-17]	
Larger mammal	Squirrels	400	$2.514\ W^{0.507}$ [Eq 3-48]		
Canid	Fox	5,000	$0.6167\ W^{0.862}$ [Eq 3-47]		
Large Herbivorous Mammal	Deer	70,000	$1.518\ W^{0.73}$ [Eq 3-46]		
Large Carnivorous Mammal	Bear	70,000	$0.6167\ W^{0.862}$ [Eq 3-47]		
BIRDS[2]					
Small bird	Passerines	10	$2.123\ W^{0.749}$ [Eq 3-36]	$0.059\ W^{0.67}$ [Eq 3-17]	
Predatory bird	Owls	640	$1.146\ W^{0.749}$ [Eq 3-37]		
Piscivorous bird	Herons	2,400	$1.916\ W^{0.704}$ [Eq 3-38]		
Large herbivorous bird	Geese	4,000	$1.146\ W^{0.749}$ [Eq 3-37]		
INVERTEBRATES[3]					
Honey bee	*Apis mellifera*	0.000116	≈2 (1.2 to 4)[6]	Not used	SA[7]: 1.42 cm^2
Herbivorous Insects	Various	Not used	1.3 (0.6 to 2.2)	Not used	

[1] Sources: Reid 2006; U.S. EPA/ORD 1993.
[2] Sources: Sibley 2000; Dunning 1993; U.S. EPA/ORD 1993.
[3] Sources: Humphrey and Dykes 2008; Reichle et al. 1973; Winston 1987
[4] Body weight in grams.
[5] For vertebrates, based on allometric relationships estimating field metabolic rates in kcal/day for rodents (omnivores), herbivores, and non-herbivores. For mammals and birds, the estimates are based on Nagy (1987) as adapted by U.S. EPA/ORD (1993). The equation numbers refer to U.S. EPA/ORD (1993). See the following table for estimates of caloric content of food items. For herbivorous insects, consumption estimates are based on fractions of body weight (g food consumed/g bw) from the references in Note 3.
[6] For honeybees, food consumption based on activity and caloric requirements. Used only when estimates of concentrations in nectar and/or pollen can be made, which is not the case in the current risk assessment.
[7] Based on the algorithms suggested by Humphrey and Dykes (2008) for a bee with a body length of 1.44 cm.

See data on food commodities in following table.
See Sections 4.2.2 and 4.2.3.2 for discussion.

Table 27: Diets: Metabolizable Energy of Various Food Commodities

Food Item	Animal Group	Caloric Value [1] (kcal/g dw)	Water Content [2]	Comment/Source(s)
Fruit	Mammals	1.1	0.77	See Footnote 3
	Birds	1.1	0.77	See Footnote 4
Fish	Mammals	4.47	0.70	Water content from Ali et al. (2005)
	Birds	3.87	0.70	
Insects	Mammals	4.47	0.70	Water contents from Chapman (, p. 491). Typical ranges of 60-80%.
	Birds	4.30	0.70	
Vegetation (NOS)	Mammals	2.26	0.85	
	Birds	2.0	0.85	See Footnote 5

[1] Metabolizable energy. Unless otherwise specified, the values are taken from U.S. EPA/ORD (1993), Table 3-1, p. 3-5 as adopted from Nagy 1987.

[2] From U.S. EPA/ORD (1993), Table 4-2, p. 4-14 unless otherwise specified.

[3] Based on a gross caloric value of 2.2 kcal/g dw (U.S. EPA/ORD 1993, Table 4-2). An assimilation factor for mammals eating fruit not identified. Use estimate for birds (see below).

[4] Based on a gross caloric value of 2.2 kcal/g dw (U.S. EPA/ORD 1993, Table 4-2) and an assimilation factor for the consumption of fruit by birds of 51% [2.2 kcal/g dw x 0.51 ≈ 1.1 kcal/g dw]

[5] Based on a gross caloric value of 4.2 kcal/g dw for dicot leaves (U.S. EPA/ORD 1993, Table 4-2) and an assimilation factor for the consumption leaves by birds of 47% [4.2 kcal/g dw x 0.47 = 1.974 kcal/g dw]

See Sections 4.2.2.3 for discussion.

Table 28: Toxicity Values Used in Ecological Risk Assessment

Group/Duration	Organism	Endpoint	Toxicity Value (a.e.)	Reference
Terrestrial Animals				
Acute				
Mammals (All)		NOAEL (Dogs)	200 mg/kg bw	Section 4.3.2.1.
Birds		Acute gavage NOAEL (mallards)	1600 mg/kg bw	Section 4.3.2.2.1
Herbivorous Insects (oral)		Oral NOAEL (honeybees)	860 mg/kg bw	Section 4.3.2.4.1
Honey Bee (contact)		Contact NOAEL	270 mg/kg bw	Section 4.3.2.4.2
Longer-term				
Mammals (All)		NOAEL (Rats)	20 mg/kg bw/day	Section 4.3.2.1
Bird		NOAEL (Quail)	65 mg/kg bw/day	Section 4.3.2.2.2
Terrestrial Plants				
Soil	Sensitive	NOAEL (dicot)	0.00021 lb/acre	Section 4.3.2.5.2
	Tolerant	NOAEL (monocot)	0.43 lb/acre	Section 4.3.2.5.2
Foliar	Sensitive	NOAEL (dicots)	0.000026 lb/acre	Section 4.3.2.5.1
	Tolerant	NOAEL (monocot)	0.05 lb/acre	Section 4.3.2.5.1
Aquatic Animals				
Acute				
Amphibians	Sensitive	No toxicity data	N/A	Section 4.3.3.2
	Tolerant	No toxicity data	N/A	
Fish	Sensitive	Adjusted NOAEC	0.19 mg/L	Section 4.3.3.1
	Tolerant	Use chronic NOAEC	7.2 mg/L	
Invertebrates	Sensitive	NOAEC, oyster larvae	2.15 mg/L	Section 4.3.3.3
	Tolerant	NOAEC, fiddler crab	215 mg/L	Section 4.3.3.3
Longer-term				
Amphibians	Sensitive	No toxicity data	N/A	Section 4.3.3.2
	Tolerant	No toxicity data	N/A	
Fish	Sensitive	Chronic LOAEC ÷ 10	0.0035 mg/L	Section 4.3.3.1
	Tolerant	Chronic NOAEC	7.2 mg/L	Section 4.3.3.1
Invertebrates	Sensitive	See Section 4.4.3.4.	N/A	Section 4.3.3.3
	Tolerant	Chronic NOAEC, daphnids	6.8 mg/L	Section 4.3.3.3
Aquatic Plants				
Algae	Sensitive	LOAEC ÷ 10	0.023 mg/L	Section 4.3.3.4
	Tolerant	NOAEC	94 mg/L	Section 4.3.3.4
Macrophytes	Sensitive	No toxicity data	N/A	Section 4.3.3.4
	Tolerant	NOAEC, duckweed	12. 2 mg/L	Section 4.3.3.4

Table 29: Comparison of NOAECs in Terrestrial Plants

Assay Type	Plant Group	Species	NOAEL (g a.e./ha)		Ratio A/B
			A) Weseloh and Stockdale 1989	B) Schwab (1995, 1996)[1]	
Vegetative Vigor	Monocots	Barley	280	30.2	9.27
		Corn	560	60.5	9.26
		Onion	280	30.2	9.27
		Wheat	70	<7.56	>9.26
	Dicots	Rape	17.5	0.47	37.2
		Soybean	0.125	0.12	1.04
		Sunflower	1.1	0.029	37.9
		Tomato	0.25	0.029	8.62
Seedling Emergence	Monocots	Barley	17.5	60.4	0.29
		Corn	280	484	0.58
		Onion	35.0	121	0.29
		Wheat	8.8	30.2	0.29
	Dicots	Rape	8.8	7.6	1.16
		Soybean	<0.031	7.6	<0.0041
		Sunflower	0.5	7.6	0.0658
		Tomato	0.25	3.8	0.0658

[1] Schwab (1996) for vegetative vigor and Schwab (1995) for seedling emergence.

See Appendix 3 for additional details and Figure 13 for illustration.
See Section 4.3.2.5 for discussion.

Table 30: Selected HQs for Mammals and Birds

Application Rate:	1	lb a.e./acre			
Scenario	Receptor	Hazard Quotients			Toxicity Value
		Central	Lower	Upper	
Non-Accidental Acute Exposures					
Contaminated Fruit (Lowest Residue Rate)					
	Small mammal (20g)	8E-02	1E-02	0.3	**200**
	Larger Mammal (400g)	2E-02	2E-03	7E-02	**200**
	Large Mammal (70g)	1E-02	1E-03	4E-02	**200**
	Small bird (10g)	2E-02	3E-03	8E-02	**1600**
	Large Bird (4 kg)	2E-03	3E-04	9E-03	**1600**
Contaminated Vegetation (Short Grass - Highest Residue Rate)					
	Small mammal (20g)	0.7	8E-02	**3**	**200**
	Larger Mammal (400g)	0.2	2E-02	0.8	**200**
	Large Mammal	9E-02	1E-02	0.4	**200**
	Small bird (10g)	0.2	2E-02	**1.1**	**1600**
	Large Bird (4 kg)	3E-02	3E-03	0.1	**1600**
Chronic/Longer Term Exposures					
Contaminated Fruit (Lowest Residue Rate)					
	Small mammal (20g)	0.1	1E-02	1.0	**20**
	Larger Mammal (400g)	2E-02	2E-03	0.2	**20**
	Large Mammal (70g)	1E-02	1E-03	0.1	**20**
	Small bird (10g)	3E-02	3E-03	0.3	**135**
	Large Bird (4 kg)	4E-03	4E-04	4E-02	**135**
Contaminated Vegetation (Short Grass - Highest Residue Rate)					
	Small mammal (20g)	0.9	7E-02	**12**	**20**
	Larger Mammal (400g)	0.2	2E-02	**3**	**20**
	Large Mammal (70g)	0.1	1E-02	**1.5**	**20**
	Small bird (10g)	0.7	6E-02	**9**	**65**
	Large Bird (4 kg)	8E-02	6E-03	**1.0**	**65**

Source: Worksheet G02 of Attachment 1, EXCEL workbook for picloram.
See Section 4.4.2.1 (Mammals) and Section 4.4.2.2 (Birds) for discussion.

Table 31: Direct Spray and Spray Drift HQs for Terrestrial Plants

Distance Downwind (feet)	Application Method			
	Aerial	High Boom Ground Broadcast	Low Boom Ground Broadcast	Backpack
	Hazard Quotients for Sensitive Species			
0	**38,462**	**38,462**	**38,462**	**38,462**
25	**8,577**	**4,000**	**1,346**	**320**
50	**6,577**	**1,923**	**681**	**167**
100	**3,765**	**954**	**365**	**93**
300	**1,200**	**290**	**135**	**36**
500	**738**	**150**	**80**	**22**
900	**477**	**64**	**42**	**12**
	Hazard Quotients for Tolerant Species			
0	**20**	**20**	**20**	**20**
25	**4**	**2**	0.7	0.2
50	**3**	1.0	0.4	9E-02
100	**2.0**	0.5	0.2	5E-02
300	0.6	0.2	7E-02	2E-02
500	0.4	8E-02	4E-02	1E-02
900	0.2	3E-02	2E-02	6E-03

Source: Worksheet G05 of Attachment 1, EXCEL workbook for picloram.
See Section 4.4.2.5 for discussion.

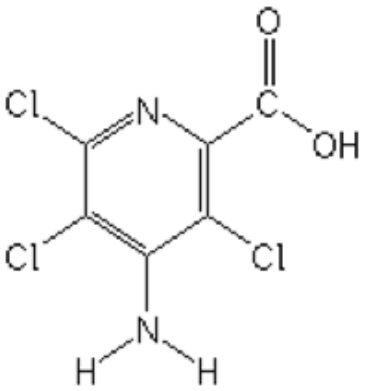
Table 32: HQs for Aquatic Organisms

Application Rate: 1 lb a.e./acre

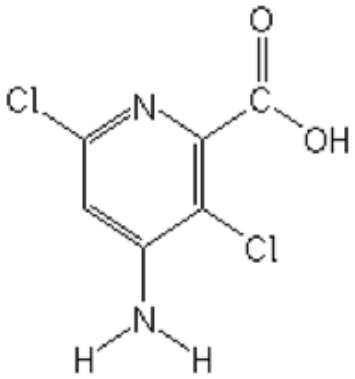
Exposures	Concentrations (mg/L)				
	Scenario	Central	Lower	Upper	Worksheet
	Accidental Spill	1.514	0.09084	18.168	B04b
	Peak EEC	0.011	0.001	0.18	B04a
	Chronic	0.00085	0.00009	0.01	B04a

Receptor	Type	Hazard Quotients			Toxicity Value	Toxicity Endpoint
		Central	Lower	Upper		
Accidental Acute Exposures						
Fish	Sensitive	**8**	0.5	**96**	**0.19**	NOEAC*
	Tolerant	0.2	1E-02	**3**	**7.2**	NOAEC
Amphibian	Sensitive	No toxicity data.			N/A	
	Tolerant	No toxicity data.			N/A	
Invertebrate	Sensitive	0.7	4E-02	**8**	**2.15**	NOAEC
	Tolerant	7E-03	4E-04	8E-02	**214**	NOAEC
Macrophyte	Sensitive	No toxicity data.			N/A	
	Tolerant	0.1	7E-03	**1.5**	**12.2**	NOAEC
Algae	Sensitive	**66**	**4**	**790**	**0.023**	NOAEC*
	Tolerant	2E-02	1E-03	0.2	**94**	NOAEC
Non-Accidental Acute Exposures						
Fish	Sensitive	6E-02	5E-03	0.9	**0.19**	NOEAC*
	Tolerant	2E-03	1E-04	3E-02	**7.2**	NOAEC
Amphibian	Sensitive	No toxicity data.			N/A	
	Tolerant	No toxicity data.			N/A	
Invertebrate	Sensitive	5E-03	5E-04	8E-02	**2.15**	NOAEC
	Tolerant	5E-05	5E-06	8E-04	**214**	NOAEC
Macrophyte	Sensitive	No toxicity data.			N/A	
	Tolerant	9E-04	8E-05	1E-02	**12.2**	NOAEC
Algae	Sensitive	0.5	4E-02	**8**	**0.023**	NOAEC*
	Tolerant	1E-04	1E-05	2E-03	**94**	NOAEC
Chronic/Longer Term Exposures						
Fish	Sensitive	0.2	3E-02	**3**	**0.0035**	NOAEC*
	Tolerant	1E-04	1E-05	1E-03	**7.2**	NOAEC
Amphibian	Sensitive	No toxicity data.			N/A	
	Tolerant	No toxicity data.			N/A	
Invertebrate	Sensitive	No toxicity data.			N/A	
	Tolerant	7E-05	8E-06	8E-04	**11.8**	NOAEC
Macrophyte	Sensitive	No toxicity data.			N/A	
	Tolerant	7E-05	7E-06	8E-04	**12.2**	NOAEC
Algae	Sensitive	4E-02	4E-03	0.4	**0.023**	NOAEC*
	Tolerant	9E-06	1E-06	1E-04	**94**	NOAEC

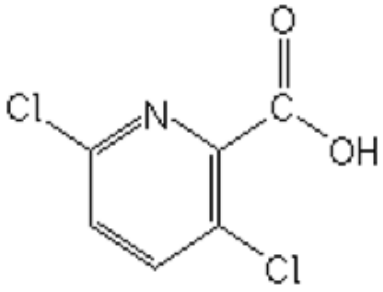
Source: Worksheet G03 of Attachment 1, EXCEL workbook for picloram.
See Section 4.4.3 for discussion.



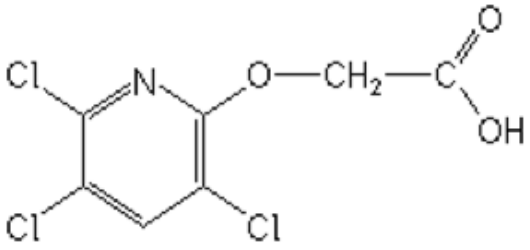
Picloram



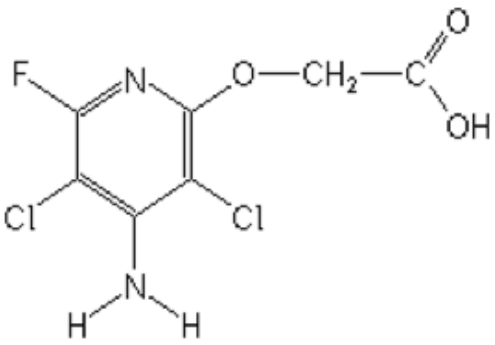
Aminopyralid



Clopyralid



Triclopyr



Fluroxypyr

Figure 1: Chemical Structure of Picloram and Related Compounds

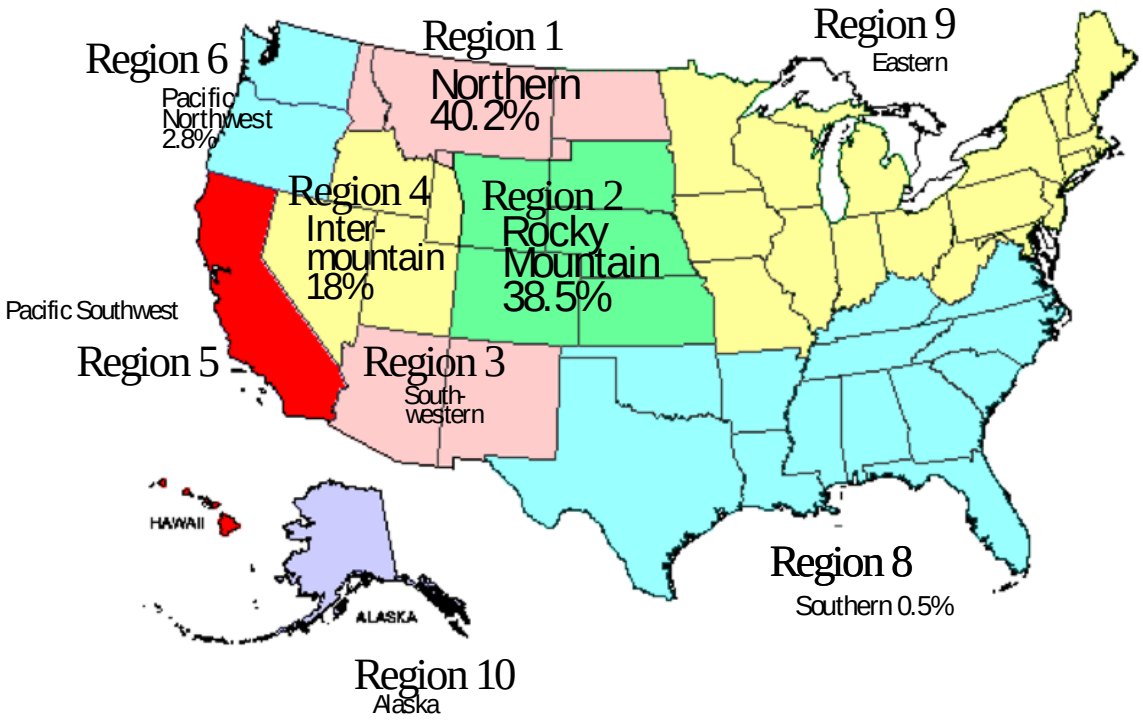
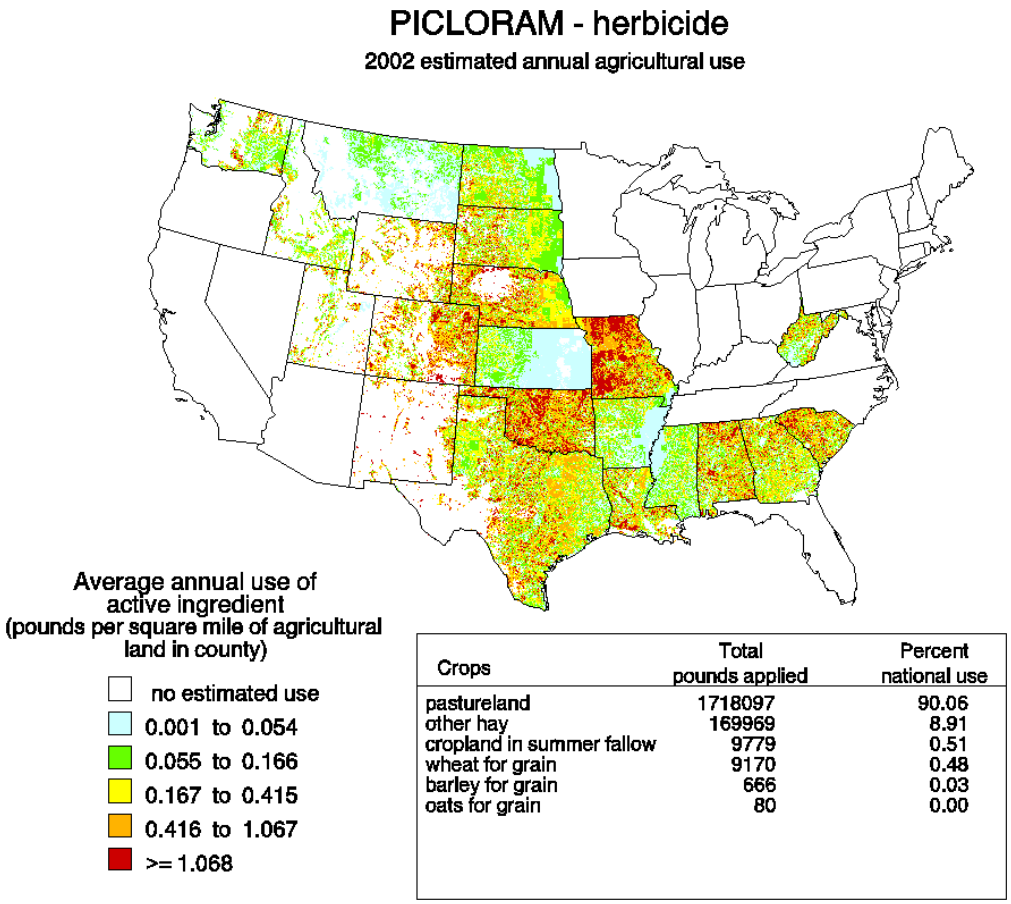


Figure 2: Triclopyr Use by Forest Service Region for 2004

See Table 3 for additional details.
See Section 2.5 for discussion.



Crops	Total pounds applied	Percent national use
pastureland	1718097	90.06
other hay	169969	8.91
cropland in summer fallow	9779	0.51
wheat for grain	9170	0.48
barley for grain	666	0.03
oats for grain	80	0.00

Figure 3: Agricultural Use of Picloram in 2002

Source: USGS 2003a

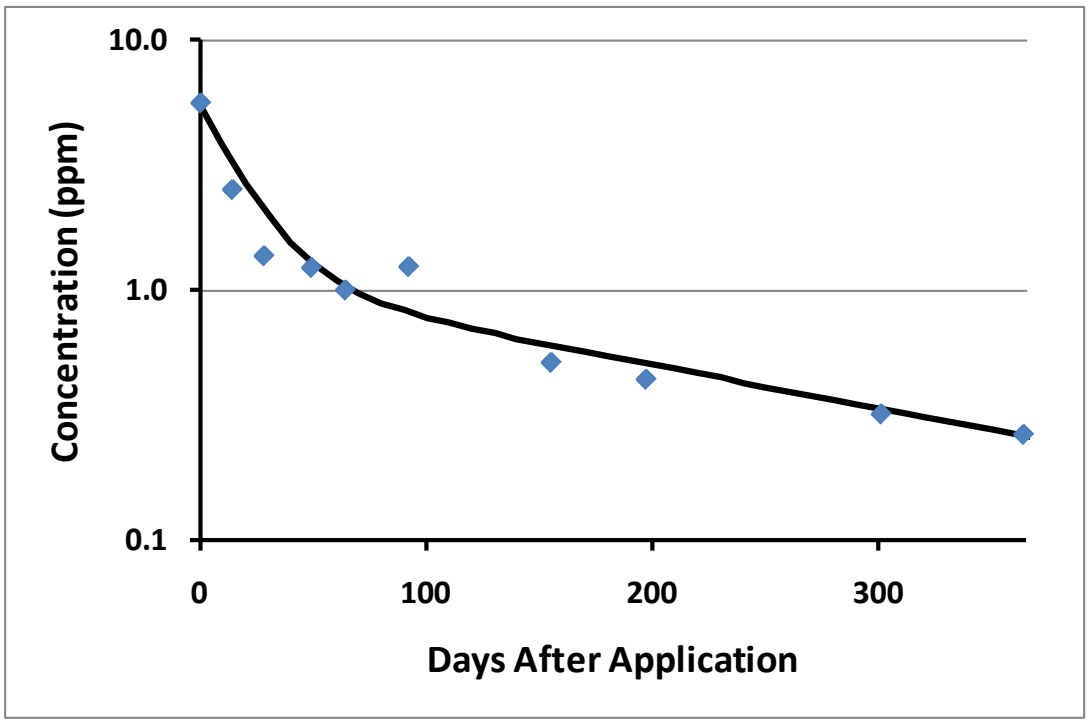


Figure 4: Dissipation of Hexachlorobenzene from Soil Surface (0 to 2 cm)

Data from Beall (1976), Table 1, p. 369
See Section 3.2.3.4.3.1 for discussion.

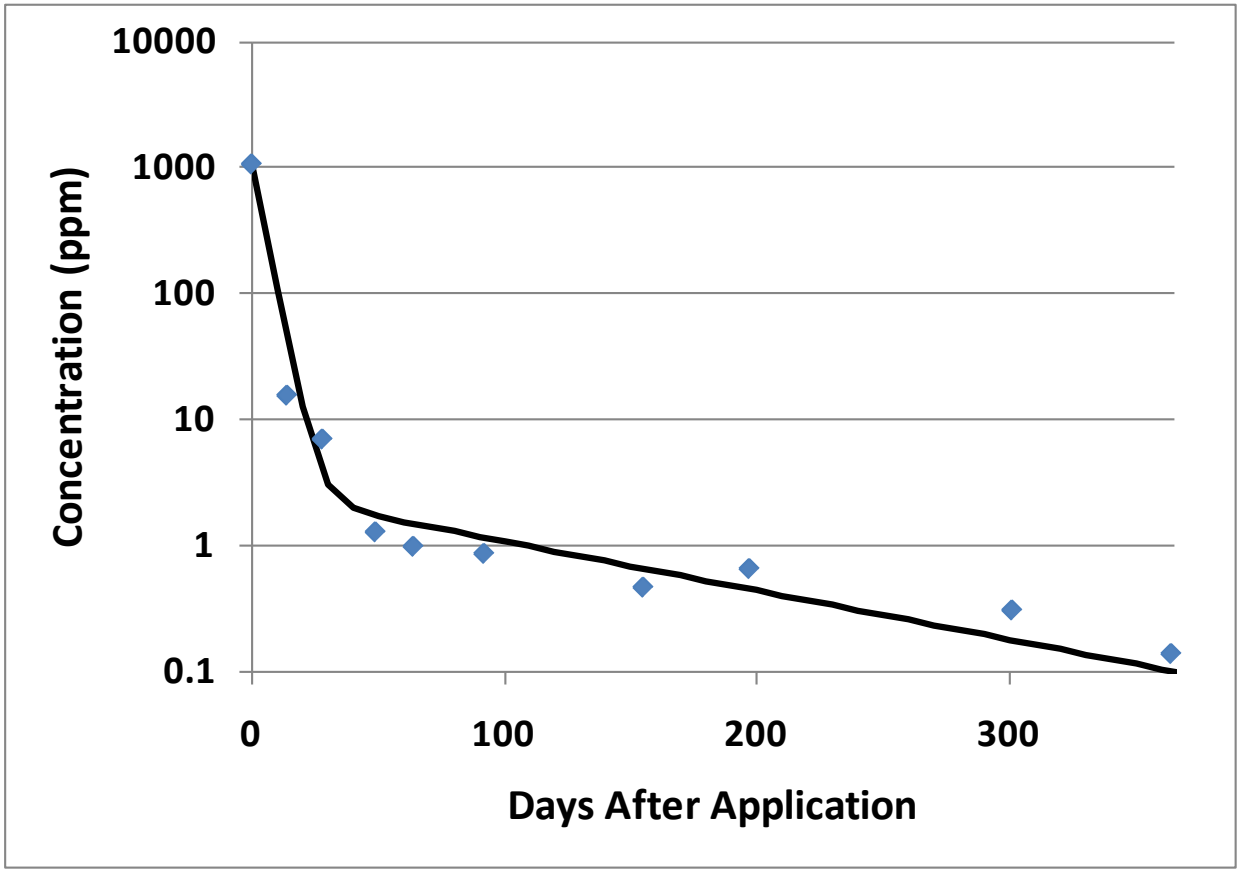


Figure 5: Dissipation of Hexachlorobenzene from Grass

Data from Beall (1976), Table 1, p. 369
See Section 3.2.3.4.3.1 for discussion.

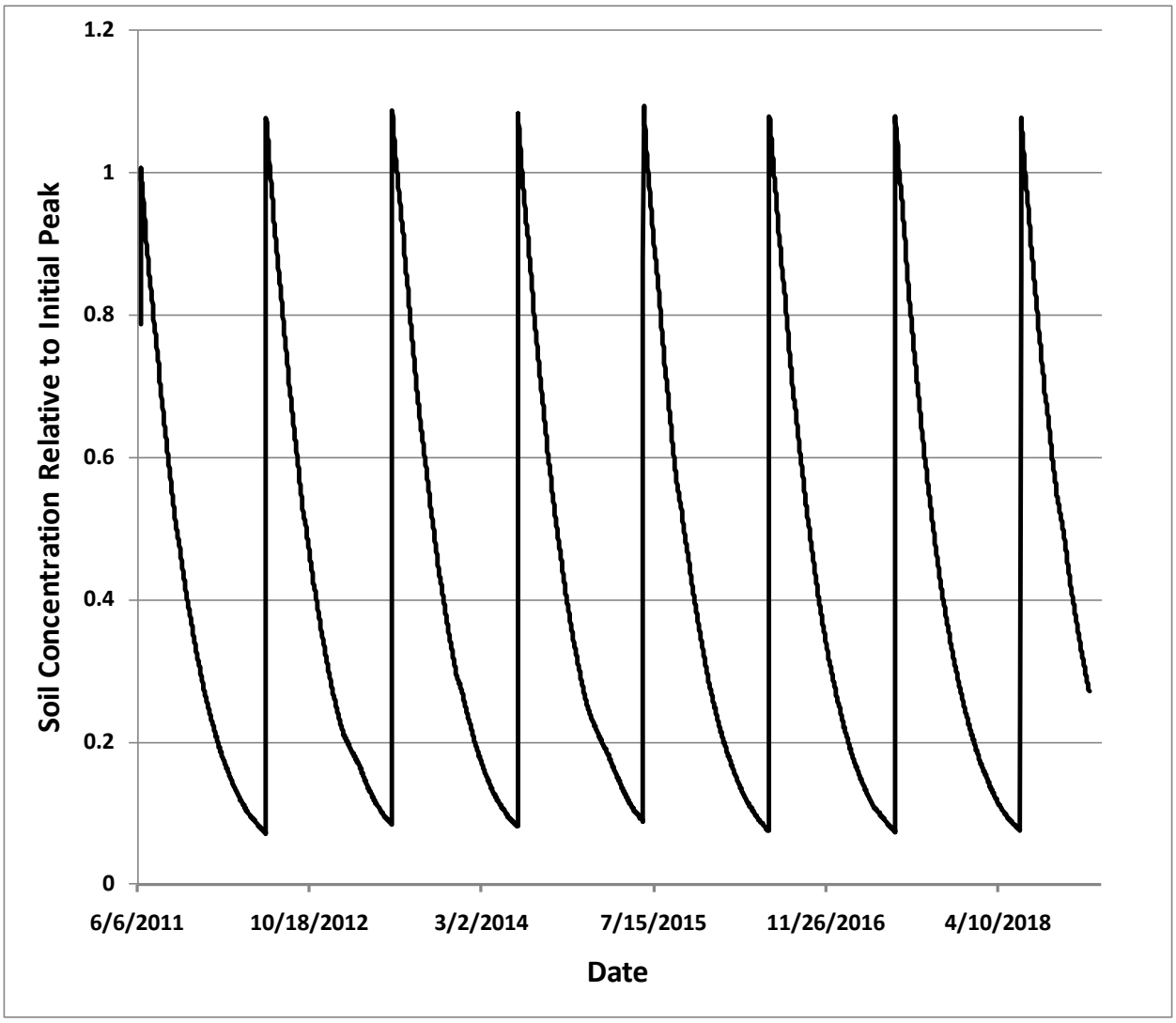


Figure 6: Concentration of Hexachlorobenzene in Soil After Multiple Applications

See Section 3.2.3.6.2 for discussion.

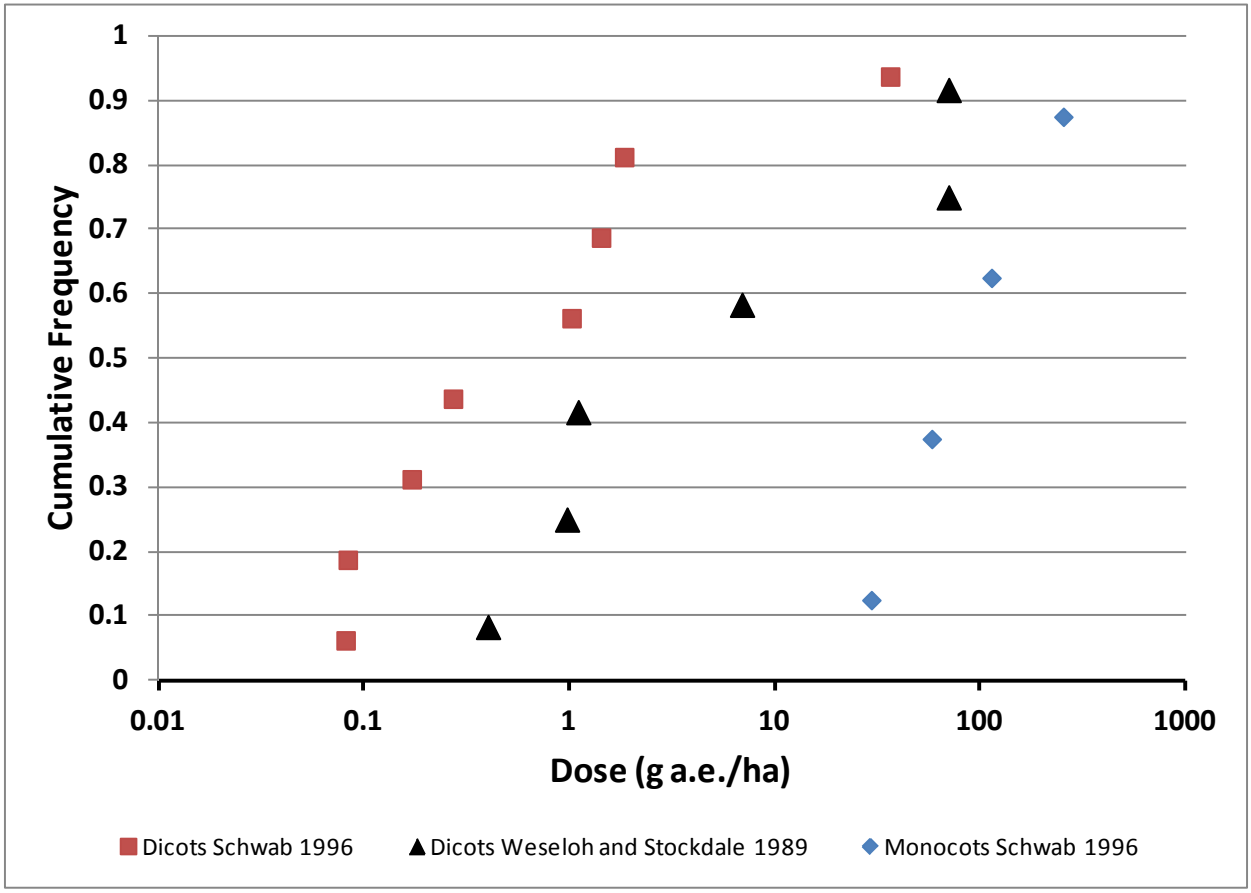


Figure 7: Summary of Vegetative Vigor EC_{25}s in Dicots and Monocots

Note: Data from monocots in the study by Weseloh and Stockdale (1989) are not included in Figure 7 because all but one EC_{25} from Weseloh and Stockdale (1989) are reported simply as >560 g a.e./ha. See Section 4.1.2.5.1 for discussion.

See Table 19 for data and Appendix 3, Table A3-1 for details.
See Section 4.1.2.5.1 for discussion.

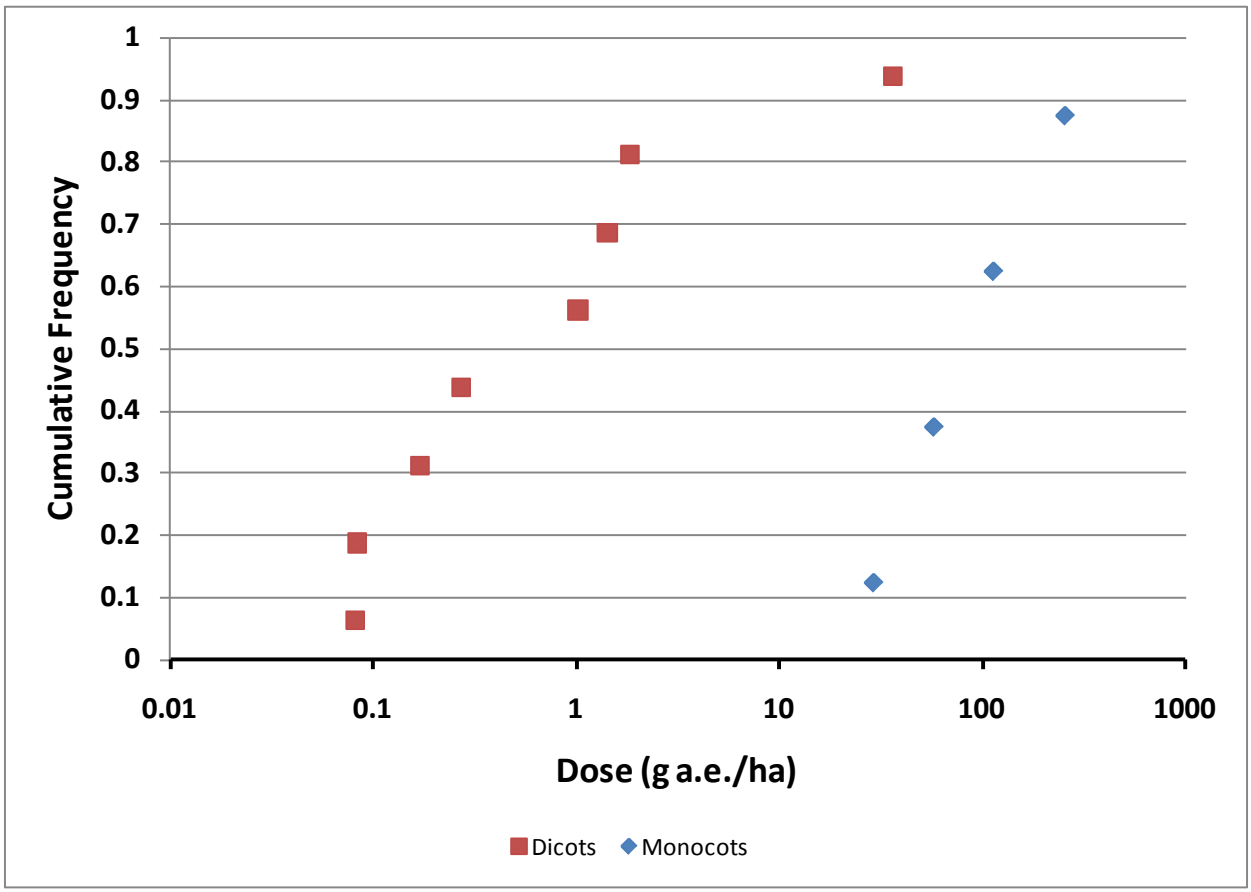


Figure 8: Summary of Vegetative Vigor EC_{25}s in Dicots and Monocots from Schwab (1996)

See Table 19 for data and Appendix 3, Table A3-1 for details.
See Section 4.1.2.5 for discussion.

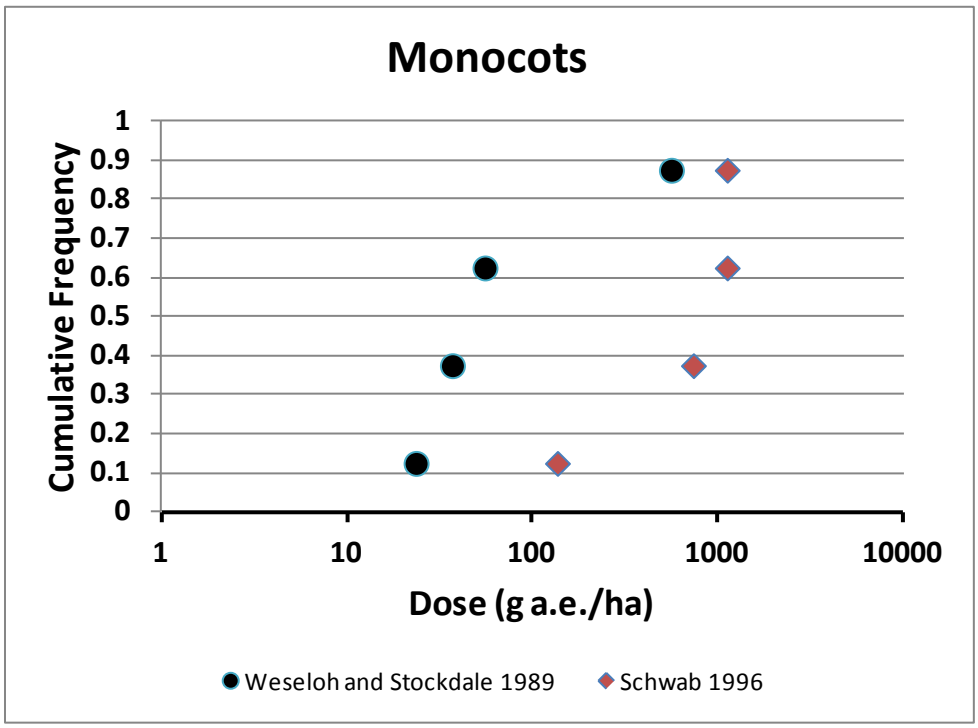


Figure 9: Summary of Seedling Emergence EC_{25}s in Monocots

NOTE: The EC_{25}s plotted as 560 and 1120 g a.e./ha are indefinite EC_{25}s of >560 and >1120 g a.e./ha. See Table 20 for details and Section 4.1.2.5.2 for discussion.

See Table 20 for data and Appendix 3, Table A3-2 for details.
See Section 4.1.2.5.2 for discussion.

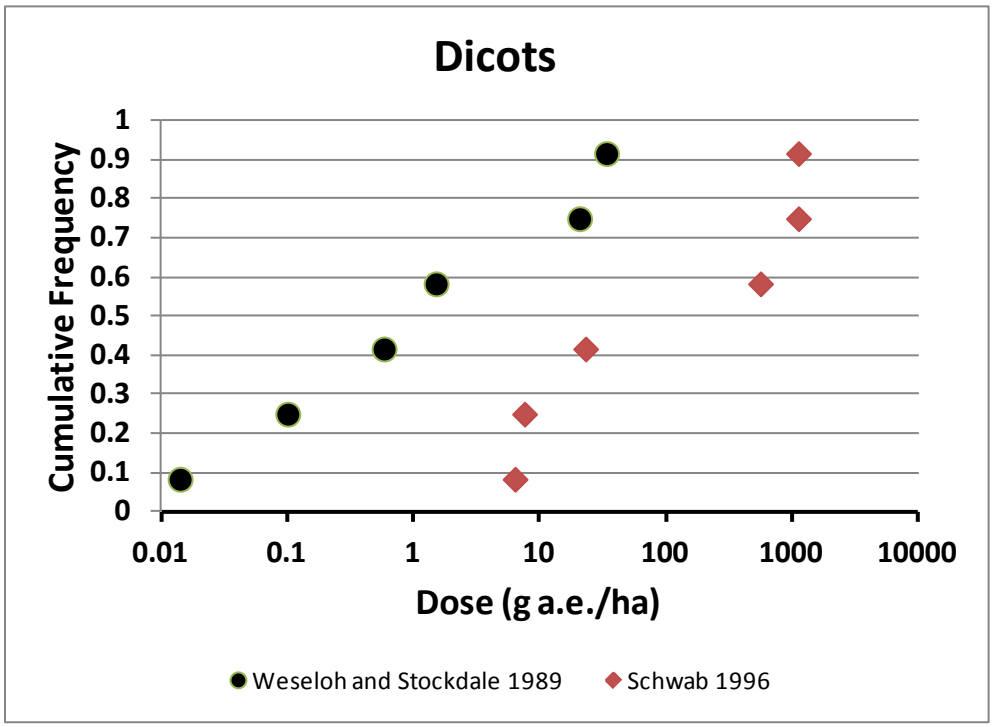


Figure 10: Summary of Seedling Emergence EC25s in Dicots

See Tables 19 and 20 for data and Appendix 3, Tables A3-1 and A3-2 for details.
See Section 4.1.2.5.2 for discussion.

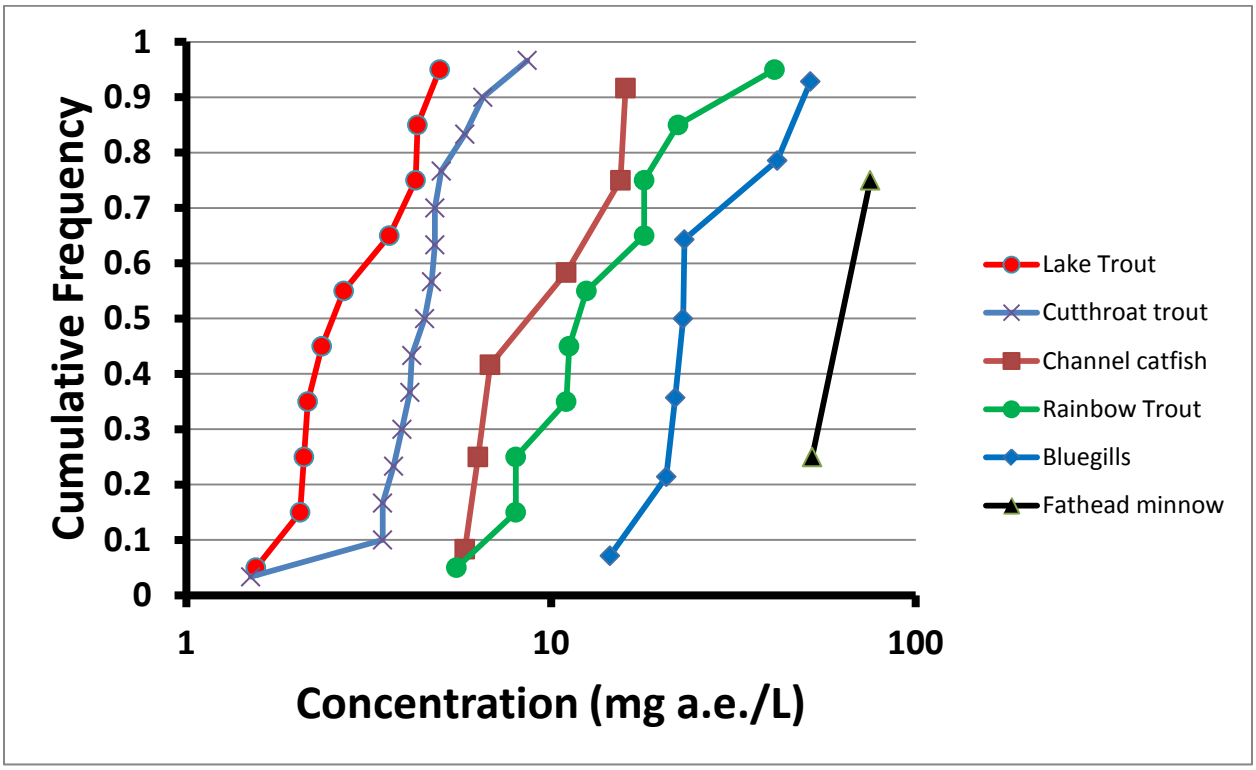


Figure 11: Distribution of 96-hour LC_{50}s in Various Species of Fish

See Table 21 for summary of plotted data.
See Section 4.1.3.1.1 for discussion.

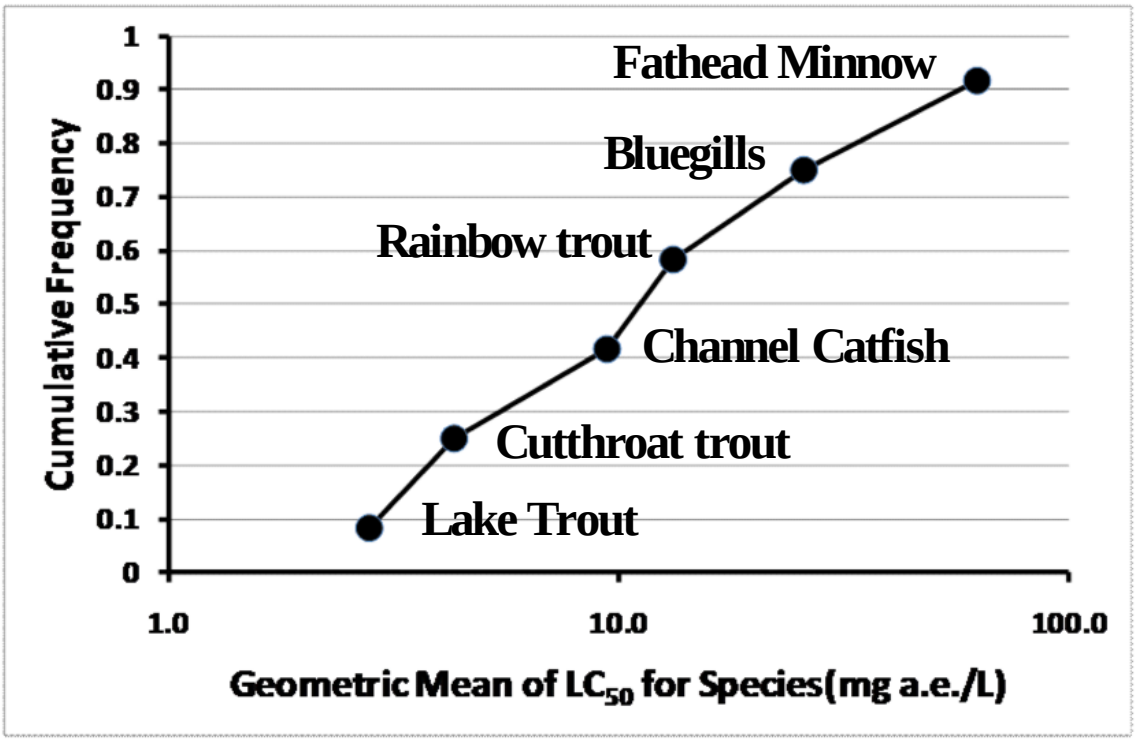


Figure 12: Species Sensitivity Distributions for Fish Based on 96-hour LC_{50}s in

See Table 21 for a summary of the plotted data and Figure 11 for details of distributions for individual species.
See Section 4.1.3.1.1 for discussion.

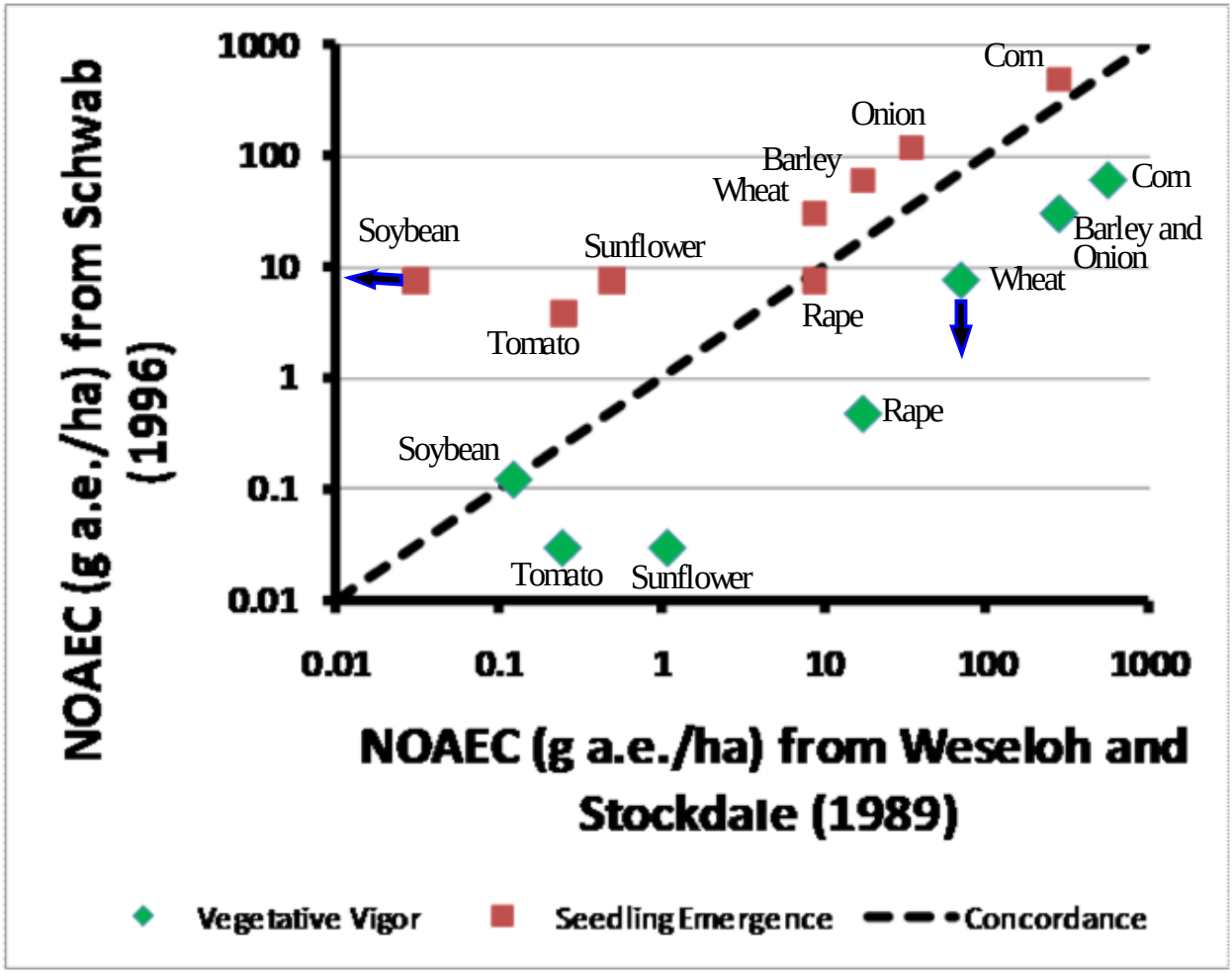


Figure 13: Comparison of NOAECs in Terrestrial Plants

Note: The arrows adjacent to the points for soybean seedling emergence and wheat vegetative vigor denote NOAECs that are expressed as less than values – i.e., the plotted values are LOAECs rather than NOAECs.

See Table 28 for data.
Sec Section 4.3.2.5 for discussion.

Appendix 1: Toxicity to Mammals

A1 Table 1: Acute Oral/Gavage Toxicity

Species	Exposure	Response	Reference
Rats, Fischer 344, males and females, 8- to 9-weeks-old, 5/sex	Technical picloram (94.1% picloram by weight) Single gavage doses: 5000 mg/kg (5 rats/sex) Due to mortality in females given 5000 mg/kg, two additional groups of females were treated with 500 or 2500 mg/kg. Vehicle = corn oil.	LD_{50} >5000 mg a.e./kg (males) LD_{50} = 4012 mg a.e./kg (females) (95% CI = 3091-6654) At 5000 mg/kg dose level, two males and four females died within 24 hours after treatment. Clinical observations of these rats included diarrhea, lethargy, lacrimation, and tonic-clonic convulsions. At necropsy, the rats that died had nonspecific terminal changes. All females dosed with 500 or 2500 mg/kg survived the treatment in good health.	Jeffrey 1987a MRID 40479413

A1 Table 1: Acute Oral/Gavage Toxicity			
Species	**Exposure**	**Response**	**Reference**
Rats, Charles River CD, males (mean body weight of 192 g) and females (mean body weight of 164 g), 5 rats/sex/group	Technical grade potassium salt of picloram as an aqueous solution containing 37.3% potassium picloram (***solutions used without neutralization***). Test solution pH: 11.3. Single gavage doses (males): 0, 500, 600, 700, 750, 800, 840, 1100, or 1200 mg/kg Single gavage doses (females): 0, 600, 700, 750, 800, or 850 mg/kg All doses appear to be expressed as mg a.i..kg bw.	Active ingredient Males: LD_{50} = 954 mg a.i./kg (95% CI = 812-1120 mg/kg) Females: LD_{50} = 686 a.i. mg/kg (95% CI = 599-786 mg/kg) *Acid equivalents* Males: LD_{50} = 823 mg a.e./kg Females: LD_{50} = 592 a.e. mg/kg Mortality occurred within about 1 to 12 hours in all animals that died. All animals that dies evidenced intermittent convulsions which were not seen in any animals that survived. Gross pathology revealed a dose-dependent discoloration of the lungs and adrenals of both sexes, which was most pronounced during the first 24-hours post treatment and barely discernable at the end of the 14-day observation period. No indication of damage to the stomach.	Hayes et al. 1986
Rats, Fischer 344, males and females, 8- to 9-weeks-old, 5/sex	Tordon K+ salt liquor (determined to be 38.8% picloram potassium salt). Single gavage dose of 5000 mg test material/kg bw (undiluted). The pH of the test material is not specified in the study. Due to mortality in females given 5000 mg/kg, two additional groups of females were treated with 500 or 2500 mg/kg as a 25% (v/v) aqueous solution.	Males: LD_{50} >5000 mg/kg [≈1940 mg a.i./kg bw or 1,676 mg a.e./kg bw] Females: LD_{50} = 3536 mg/kg or 1,372 mg a.i./kg bw or 1,185 mg a.e./kg bw. At 5000 mg/kg dose, all females and one male died within 4 hours after treatment. All surviving rats appeared to be in good health and had gained weight by study termination. Rats that died within 4 hours after treatment had nonspecific terminal changes consisting of facial soiling and visceral congestion. In addition, 4/5 females that did not survive treatment had focal hyperemia (excess blood) of the stomach.	Jeffrey et al. 1987b MRID 40479401

Appendix 1: Toxicity to Mammals *(continued)*

A1 Table 1: Acute Oral/Gavage Toxicity

Species	Exposure	Response	Reference
Rats, Fischer 344, 9-weeks-old, 5/sex	Tordon 22K Weed Killer (20.36 ±0.08% picloram a.e.) Single gavage dose of 5000 mg undiluted test material/kg bw. Equivalent to a dose of about 1153 mg a.e./kg bw. Working Note: This formulation is very similar if not identical to the formulations considered in the current risk assessment. See Section 3.1.4 for discussion.	No mortality; all rats appeared to be in good health throughout the study and observation period. All rats gained weight steadily throughout the observation period and were at normal limits at necropsy. LD_{50} >5000 mg formulation/kg (males and females) or >1153 mg a.e./kg bw.	Jeffrey et al. 1987c MRID 40677401
Various (see column 3)	Details of the test compound(s) are not specified. See Section 3.1.4 for discussion.	**Species** / **Oral LD_{50} (mg/kg bw)** Rats: 8,200 Rabbit: 2,000 Guinea pig: 3,000 Sheep: >1,000 Mouse: 2,000 to 4,000 Cow: >750	HSDB 2011 Sassman et al. 1984 U.S. EPA/OW 1992 [1]

[1] Toxicity data cited to Dow Chemical 1983.

A1 Table 2: Subchronic and Chronic Oral Toxicity			
Species	**Exposure**	**Response**	**Reference**
Subchronic oral			
Rats, CDF Fischer 344, 6-weeks-old, 15/sex/dose group	Technical grade picloram (92% a.i.) Nominal concentrations: 0, 15, 50, 150, 300, or 500 mg/kg bw in the diet for 13 weeks.	Adverse effects limited primarily to the liver of males and females, with a dose-dependent increase in absolute and relative liver weights observed at dose levels of 150, 300, or 500 mg/kg bw. Males treated with 300 or 500 mg/kg bw had increased absolute and relative kidney weights not associated with histopathological changes. NOEL = 50 mg/kg/day for both sexes.	Gorzinski et al. 1982 MRID 00110537
Rats, Charles River CD, males and females (weighing between 127 and 165 g), 10 rats/sex/group	Technical grade potassium salt of picloram as an aqueous solution containing 37.3% potassium picloram added to deionized water (solutions adjusted to pH 7.0 w/HCL) Intended dosage: 0, 60, 190, or 600 mg picloram/kg/day in drinking water for 14 consecutive days. Actual dosage: 53±6, 140±30, or 578±113 mg/kg/day (males) and 51±5, 155±32, or 572±109 mg/kg/day (females)	No treatment-related mortality or significant effects on body weight; no treatment related adverse effects on hematology, or urinalysis. Adverse effects included decreases in SGPT and SGOT at the high dose in males and females, and caecal enlargement and lung discoloration observed at necropsy.	Hayes et al. 1986

A1 Table 2: Subchronic and Chronic Oral Toxicity			
Species	**Exposure**	**Response**	**Reference**
Rats, Charles River CD, males (mean body weight of 102 g) and females (mean body weight of 92 g), 20 rats/sex/group, except in high dose group which consisted of 10/rats/sex/group	Technical grade potassium salt of picloram as an aqueous solution containing 37.3% potassium picloram added to deionized water (solutions adjusted to pH 7.0 w/HCL) Intended dosage: 0, 60, 190, 600 or 1070 mg picloram/kg/day in drinking water for 14 consecutive days. Actual dosage: 0, 58±2, 181±5, 570±20, or 1009±50 mg/kg/day (males) and 0, 61±2, 193±4, 590±15or 1060±80 mg/kg/day (females)	Dose-dependent mortality: **Males**: ***4/20*** at 570 mg/kg ***9/10*** at 1009 mg/kg **Females**: ***2/20*** at 590 mg/kg ***7/10*** at 1060 mg/kg Treatment appeared to exacerbate renal and hepatic lesions: at levels up to 1070 mg/kg mild lesions in the kidney of treated rats, especially in males at 600 mg/kg, were noted. Also noted were an increased incidence of mononuclear liver foci in male rats that received 190 and 600 mg/kg and an increased severity of mononuclear liver foci in females that received 600 mg/kg. There were no other consistent biologically significant treatment-related effects.	Hayes et al. 1986
Dogs	Picloram at 200, 400, and 800 mg/kg bw/day for 9 days	NOAEL: 200 mg/kg bw/day LOAEL: 400 mg/kg bw/day based on decreased food consumption and body weight. Working Note: Identified only as a Dow palatability study conducted in 1981, TXT:K-38323(24), EPA Accession No. 247156.	Dow Chemical 1980. As summarized in U.S. EPA/ODW 1987 and U.S. EPA/OW 1992.

A1 Table 2: Subchronic and Chronic Oral Toxicity			
Species	**Exposure**	**Response**	**Reference**
Chronic Oral			
Beagles, male and female, approx 16- to 18-wks-old, mean bw: 8.22-8.42 kg (males), mean bw: 7.73-7.79 kg (females), 6/sex/group	Technical grade picloram (91.2% pure) in diet for 6 months. Nominal doses of 0, 7, 35, or 175 mg/kg bw/day for 6 months. Working Note: See Table 7 of study for food consumption data	NOEL = 7 mg/kg bw/day No effects observed in females at 35 mg/kg bw/day or in males or females at 7 mg/kg bw/day At 35 mg/kg bw/day, adverse effects included increased absolute and relative liver weight in males only. At 175 mg/kg bw/day, adverse effects included decreased body weight, body weight gain, food consumption, and ALT (SPGT): increased AP, absolute and relative liver weight in both males and females. Study concludes that liver is the primary target organ.	Barna-Lloyd et al. 1982 MRID 00110534 Working Note: Cleared review available on Peer Review CD. Full study available for risk assessment but is not on peer review CD. DER indicates a report date of 1988. This appears to be an error.
Beagle dogs	Nominal doses of 0, 7, 35, or 175 mg/kg bw/day for 1 year.	NOAEL: 35 mg/kg bw/day LOAEL: 175 mg/kg bw/day based on increases in relative and absolute liver weight.	MRID 40834301 as summarized in U.S. EPA/OPP 1995a and 1994a
Fischer 344 Rats	2 Years Dietary exposures equivalent to 20, 60, and 200 mg/kg bw/day.	No overt signs of toxicity. At two higher doses, a statistically significant increase in liver pathology (altered staining properties of centrilobular hepatocytes). No indication of liver necrosis. NOAEL: 20 mg/kg *bw*/day LOAEL: 60 mg/kg bw/day **Working Note: This is the basis of the chronic RfD.**	Landry et al. 1986 MRID 00155940
Mice, 50/sex/dose	2 Years 0, 100, 500, or 1,000 mg/kg/day	No signs of toxicity. Slight but statistically significant increase at 24 months in kidney weights (6% absolute and 7% relative) in males at 1000 mg/kg bw/day but no histological lesions in kidney. [See Table 2 of DER] U.S. EPA/OPP 1994a NOAEL: 500 mg/kg bw/day	Stott et al. 1992 MRID 42619301

A1 Table 3: Reproductive and Developmental Studies			
Species	**Exposure**	**Response**	**Reference**[1]
Reproduction			
CD Rats, 30 males and 30 females per dose group.	Two generation reproduction study. Dietary exposures picloram acid adjusted to yield doses of 0, 20, 200 or 1000 mg a.e./kg/day. F_0 and F_1 mated after 10 weeks.	Summarized in U.S. EPA/OPP 1995a: *parental LOEL is 1000 mg/kg/day based on histopathological lesions in the kidney of males of both generations and some females. In males of both generations, blood in the urine, decreased urine specific gravity, increased absolute and relative kidney weight, and increased body weight gain was observed at the high dose. The parental LOEL is 1000 mg/kg/day and the NOEL is 200 mg/kg/day. The reproductive LOEL was not identified and the NOEL is 1000 mg/kg/day.* Above summary is consistent with DER. Note that all doses are mg a.e./kg bw – i.e., picloram acid is the test material.	Breslin et al. 1991, MRID 42078701
Developmental			
New Zealand White rabbits, artificially inseminated, approx. 3.5-4.5 kg, 25/dose group	Picloram potassium salt (undiluted aqueous solution characterized as 37.3% a.e.) Oral administration (by gastric intubation) of 40, 200, or 400 mg a.i./kg/day on days 6 through 18 of gestation. Controls given vehicle: distilled water. Working Note: Doses in column 3 are expressed as a.i., the units reported in the study. The doses are equivalent to about 0, 34.5, 173, or 345 mg a.e./kg bw. The units discussed in the body of the risk assessment are a.e.	Maternal toxicity: No consistent treatment-related effects on general appearance or demeanor noted during the study. At 400 mg/kg/day, rabbits lost weight on gestation days 6 through 8, but gained weight on the successive days, and total weight gain during gestation was comparable to controls. Also, at this dose level, there was a slight, but not statistically significant increase in absolute and relative liver weights. At 200 mg/kg/day, rabbits lost weight on gestation days 6 through 8 but showed consistent weight gain during the remainder of the experimental period. No other effects on body weight or organ (liver or kidney) weights were observed among treated rabbits. Several rabbits in the treatment groups died (largely due to pneumonia) during the course of the study, and the deaths were not considered to be treatment related. Embryo- or fetotoxicity: No adverse effects on pregnancy rate, implantations resorbed, pre-implantation loss, sex ratio, or fetal body measurements observed among treated rabbits. Fetal observations: Low incidences of some malformations, including severe forelimb flexure, omphalocele and hemivertebra with fused ribs observed among litters of treated	John et al. 1984 MRID 00138703

A1 Table 3: Reproductive and Developmental Studies			
Species	**Exposure**	**Response**	**Reference**[1]
		rabbits, but there was no indication of a dose-related fetotoxic response. All of the malformations were observed historically among control groups of rabbits in the laboratory, and the sporadic cases of these malformations in the treated groups were not considered to be indicative of teratogenicity.	
Rats, CD (Sprague-Dawley derived), females, mean weight of 214 g (170-276 g), 30 mated females/dose group	Potassium (K) salt of picloram, aqueous solution, (34.7% a.i.). Dose levels: 0, 100, 500, or 1000 mg/kg/day by gastric intubation on days 6-15 of gestation Vehicle: distilled, deionized water.	No mortality in control or treated groups. Pregnancy rates: 100 mg/kg/day (96.7%) 29/30 500 mg/kg/day (96.7%) 29/30 1000 mg/kg/day (93.3%) (28/30) A dose-related increase in the incidence of excessive salivation, significant only at 1000 mg/kg bw. Decreased maternal food consumption and body weight at 1000 mg/kg bw/day. Results indicate that aqueous solution of test substance administered by gastric intubation on days 6 through 15 of gestation was not embryotoxic, fetotoxic, or teratogenic. Developmental NOAEL = 1000 mg/kg be/day. Maternal NOAEL = 500 mg/kg bw/day.	Schroeder 1990 MRID 41382502 Working Note: The EPA has a Cleared Review for Schroeder 1990 for MRID 41382504. This is for the TIPA salt of picloram and is not the study summarized in this appendix.

A1 Table 3: Reproductive and Developmental Studies			
Species	**Exposure**	**Response**	**Reference**[1]
Rats, Sprague-Dawley, adult females, averaging 238 g, 35/dose group	Picloram acid Daily single gavage doses of 0, 500, 750 or 1000 mg picloram/kg/ day on days 6-15 of gestation. Vehicle: corn oil.	**Maternal Toxicity**: 500 mg/kg/day resulted in no overt signs of toxicity. At 750 and 1000 mg/kg/day, rats developed hyperesthesia and diarrhea after 1-4 days and 10 maternal deaths occurred (three at 750 mg/kg/day and seven at 1000 mg/kg/day) between days 7 and 15 of gestation. Autopsy of dams in the 1000 mg/kg/day group revealed enlarged adrenals and gastric erosions, considered to be stress related. In surviving dams, no effects on maternal weight gain, litter size, resorptions rate, or other reproductive parameters were observed at any dose level. **Developmental Toxicity**: No fetal mortality. A transient increased incidence of unossified fifth sternebrae observed in fetuses from treated groups was considered to be a non-specific retardation of fetal growth. Investigators conclude that *subtoxic and even of maternally toxic doses of picloram during organogenesis produces neither teratogenesis nor adverse effects on neonatal development in the Sprague-Dawley rat.*	Thompson et al. 1972 EPA review is in Dykstra 1980.

A1 Table 4: Acute and Subchronic Dermal Toxicity			
Species	**Exposure**	**Response**	**Reference**
ACUTE			
New Zealand white rabbits, weighing 2.9-3.1kg, 5/sex	Technical picloram, granular solid (94.1% picloram by weight). Fur-free backs of rabbits treated with 2000 mg test material/kg bw, held in contact with skin by a gauze dressing and non-irritating tape. Trunks of animals wrapped in plastic, secured with rubber bands. 5 mL of distilled water was placed under the wrap to ensure sufficient skin contact. After 24 hours, the skin was washed with mild soap and water, rinsed thoroughly and dried with a soft towel. Rabbits were fitted with a plastic collar to prevent ingestion of any residual test material that remained after washing.	No mortality and no significant effects on body weights; all rabbits gained weight by study termination. No treatment-related effects observed in any of the rabbits. Gross observation of a single enlarged kidney in one of the female rabbits was considered and incidental finding unrelated to treatment. LD_{50} >2000 mg/kg (males and females). Based on these results, the acute dermal toxicity of Picloram Acid (Picloram Technical) was categorized as low.	Jeffrey et al. 1987e MRID 40479414
New Zealand white rabbits, weighing 2.2-2.4 kg, 5/sex	Tordon K+ salt liquor (determined to be 38.8% picloram potassium salt). Fur-free backs of rabbits treated with 2000 mg undiluted test material/kg bw, held in contact with skin by a gauze dressing and non-irritating tape. Trunks of animals wrapped in plastic, secured with rubber bands. After 24-hour exposure, wrappings removed and observations for any irritation at the application site were recorded. Rabbits were fitted with a plastic collar to prevent ingestion of any residual test material.	No mortality and no systemic signs of toxicity observed. Day 1 after treatment, some of the rabbits had erythema, edema, and small pinpoint blisters at the application site. Although rabbits were near or slightly below their pretreatment weights on Day 1 after treatment, all males and females gained weight by study termination. At necropsy (2 weeks after treatment) all rabbits were within normal limits. LD_{50} >2000 mg/kg (males and females).	Jeffrey et al. 1987d MRID 40479402

A1 Table 4: Acute and Subchronic Dermal Toxicity			
Species	**Exposure**	**Response**	**Reference**
New Zealand white rabbits, 2.164 – 2.475 kg at start, 5 males and 5 females	Tordon 22K (24.1% picloram potassium salt as a.i. or 20.8% a.e.) Single, 24-hour dermal exposure to 5000 mg neat Tordon 22K/kg bw applied to shaved trunk by impregnated gauze patch (10x14 cm), which was held in place by elastic jacket. Treated area represented approx. 10% of the surface area of each rabbit.	No mortality among treated rabbits. Fecal soiling observed in one male from 6 ½ hours through day 2 of testing. Erythema (seven rabbits) and edema (one rabbit) immediately after removal of test material. No effects observed on body weight during 2-week observation period. No treatment-related observations made at necropsy. One male rabbit had a testicle that was decreased in size. LD_{50} >5000 mg/kg (limit dose).	Gilbert 1996c MRID 43959603
New Zealand white rabbits, weighing 2.8-3.1 kg, 5/sex.	Tordon 22K Weed Killer (20.36 ±0.08% picloram a.e.) Fur-free backs of rabbits treated with 2000 mg undiluted test material/kg bw, held in contact with skin by a gauze dressing and non-irritating tape. Trunks of animals wrapped in plastic, secured with rubber bands. After 24-hour exposure, wrappings removed and observations for any irritation at the application site were recorded. Rabbits were fitted with a plastic collar to prevent ingestion of any residual test material.	No mortality and no systemic signs of toxicity observed throughout the study. All rabbits showed signs of erythema at the application site at 1-day post treatment. One male had non-treatment related kidney lesions consistent with a spontaneous disease process. 24-hour LD_{50} >2000 mg/kg Based on these results, the acute dermal toxicity of TORDON 22K Weed Killer was categorized as low.	Jeffrey et al. 1987a MRID 40677402

A1 Table 4: Acute and Subchronic Dermal Toxicity			
Species	**Exposure**	**Response**	**Reference**
SUBCHRONIC			
New Zealand white rabbits, male and female, approx. 5 months, 5/sex/dose	21 days Distilled water, 75.3, 252, or 753 mg/kg/day aqueous solution of picloram-K+ (0, 65, 217, or 650 mg/kg/day a.e.) at rate of 1.7 mL/kg bw/day . All animals received a total of 15 applications to shaved back during the 21-day interval – i.e., once per day excluding weekends.	No clinical signs of toxicity. Erythema observed in males and females at all dose levels. Edema observed in males at 251 and 753 mg/kg/day and in females at 753 mg/kg/day. No skin irritation observed in controls. NOEC (systemic toxicity) = 753 mg/kg bw/day for males and females.	Atkin et al. 1990 MRID 41384901

A1 Table 5: Acute Inhalation Studies			
Species	**Exposure**	**Response**	**Reference**
Rats, Fischer 344, males (mean body weight: 172.2 g at start) and females (mean body weight: 130.6 g at start), 5/sex	Technical grade picloram acid (94.1% by weight). 4-hour whole body exposure to time-weighted concentration of 35.1 mg/m^3 (0.0351 mg/L), the highest practically attainable concentration. Mass median aerodynamic diameter of the aerosol/dust was 7.96 µ and the average geometric standard deviation of the particle size distribution was 3.59.	No treatment-related mortality; one female had reddish, porphyrin stains around the nares, but appeared normal by day 2. Body weights increased throughout 2-week observation period. Gross pathological examination revealed that one female had a distended ovarian bursa, which was considered incidental to exposure.	Streeter et al. 1987a MRID 40479415
Rats, Fischer 344, males (mean body weight: 216.9 g at start) and females (mean body weight: 131.9 g at start), 5/sex	Tordon K salt liquor (picloram potassium salt, 38.8% ±0.5) 4-hour whole body exposure to a time-weighted concentration of 1.63 mg/L, the highest attainable concentration. Average mass median aerodynamic diameter of the aerosol was 4.12 µ and the average geometric standard deviation of the particle size distribution was 1.95.	No treatment-related mortality; all treated animals had fur wetted by test material, wet muzzles, and urine staining in the perineum for a few days following exposure. Mean body weights of males decreased initially after exposure then increased during the remainder of the study; mean body weights of females increased throughout the observation period. No abnormal changes were observed during complete gross pathological examination of each treated animal, two weeks after exposure.	Streeter et al. 1987b MRID 40479403
Rats, Fischer 344, males and females, approx 11-weeks-old, 5/sex/group	Tordon 22K Weed Killer (containing 24.1% picloram potassium salt as a.i.) Nose-only, single 4-hour exposure to time-weighted average concentration of 8.11 mg Tordon 22K Weed Killer/L respirable test atmosphere with a mean MMAD of ≤4 µm.	No mortality during exposure period or 2-week post-exposure observation period. All rats appeared normal during and after exposure throughout the 2-week observation period. Mean body weight loss was 3% (males) and 2% (females) on day following exposure to test material; however, by day 8, mean body weights of males and females exceeded pre-exposure values. No treatment-related observations were noted at animal necropsy. LC_{50} >8.11 mg/L (with particle size distribution MMAD of 1.74 microns.	McGuirk and Cieszlak 1996, MRID 43959605

A1 Table 5: Acute Inhalation Studies			
Species	**Exposure**	**Response**	**Reference**
Rats, Fischer 344, males (mean body weight:259.7 g at start) and females (mean body weight: 154.1 g at start), 5/sex	Tordon 22K Weed Killer (picloram potassium salt, 20.4±0.1) acid equivalent. 4-hour whole body exposure to a time-weighted concentration of 0.65 mg/L, the highest attainable concentration. Average mass median aerodynamic diameter of the aerosol was 4.80 µ and the average geometric standard deviation of the particle size distribution was 1.58. A nominal concentration of 18.3 mg/L was calculated based on the amount of test material and the total air passed through the chamber during exposure.	No treatment-related mortality; after exposure, animals were urine and prophyrin stained; however, most were normal by day 2. Mean body weights of males decreased slightly after exposure then increased throughout the remainder of the observation period. Mean body weights of females decreased slightly after exposure and then again after day 4, but increased thereafter. Gross pathological examination 2 weeks after exposure indicated that all treated animals were within normal limits.	Streeter et al. 1988 MRID 40677403

A1 Table 6: Skin Irritation Studies			
Species	**Exposure**	**Response**	**Reference**
New Zealand white rabbits, 4 males and 2 females, 2.9-3.2 kg	Technical picloram, granular solid (94.1% picloram by weight). 0.5 g aliquot test material under gauze patch applied to clipped backs of rabbits and held in place with non-irritating tape. Gauze patch moistened with 0.5 mL water and covered with flannel bandage for 4 hours. After treatment, animals' backs were wiped with damp towel to remove residual test material. Treated sites were graded for erythema and edema at 30 minutes, and 24, 48, and 72 hours after patch removal.	No signs of dermal irritation observed at any time post application.	Jeffrey 1987c MRID 40479417
New Zealand white rabbits, 5 males and 1 female, weighing 3.1-3.3 kg	Tordon K+ salt liquor (determined to be 38.8% picloram potassium salt). 0.5 mL aliquot test material under gauze patch applied to clipped backs of rabbits and held in place with non-irritating tape. Gauze patch moistened with 0.5 mL water and covered with flannel bandage for 4 hours. After treatment, animals' backs were wiped with damp towel to remove residual test material. Treated sites were graded for erythema and edema at 30 minutes, and 24, 48, and 72 hours after patch removal.	No signs of dermal irritation were observed at any time after treatment. Tordon K+ Salt Liquor was not irritating to the skin of rabbits.	Jeffrey 1987f MRID 40479405

A1 Table 6: Skin Irritation Studies			
Species	**Exposure**	**Response**	**Reference**
Albino rabbits (NOS), 2 animals	Tordon 22K Weed Killer (24.9% potassium picloram, 21.5 % a.e.), 0.5 ml of formulation applied to abraded and unabraded sites, covered. Observations at 48 and 72 hours.	Initial erythema and edema along the abrasions but effect at 72 hours after treatment. No irritation of unabraded skin.	Teeters 1973 Working Note: This study (EPA Cleared Review) has not been identified in U.S. EPA/OPP 1994a or 1995a (RED and HED Science Chapter.

A1 Table 7: Skin Sensitization Studies			
Species	**Exposure**	**Response**	**Reference**
Guinea pigs, Hartley albino, males, approx. 6-weeks-old, 270-325 g, n=10	Technical picloram, granular solid (94.1% picloram by weight) Positive controls (n=10): three applications of dipropylene glycol monomethyl ether during induction phase. Induction phase: three applications of granular test material. Challenge phase: 2 weeks after last induction application, all groups were challenged with either the test material or 10% dipropylene glycol monomethyl ether (positive controls).	Positive controls: 7/10 animals had slight erythema at the application site. None of the animals challenged with test material showed any signs of sensitization. Conclusion: picloram acid (picloram technical) not considered a potential skin sensitizer.	Jeffrey 1987b MRID 40479418
Guinea pigs, Hartley albino, males, approx. 6-weeks-old, 406-481 g at study start, n=10	Tordon 22K (20.6% a.e.) 3-week induction phase: Single application of 0.4 mL aliquot of 75% solution of Tordon 22K in distilled water to left shaved side for 6 hours. Application site was washed with tap water. Challenge phase: Approx. 2 weeks after induction phase, single 0.4 mL aliquot of 75% solution of Tordon 22K in distilled water (highest non-irritating dose) applied to right side in same manner as in the induction phase for 6 hours. Additionally, five naïve guinea pigs were treated with single 0.4 aliquot of a 50% solution of Tordon 22K in distilled water for 6 hours. Application sites observed and graded approx. 24 and 48 hours after the challenge application.	Challenge application caused slight erythema at test site in 8/10 animals, and very slight erythema in the remaining two animals; none of the naïve animals showed evidence of irritation, following 48 hours. All animals appeared to be in good health and gained weight during the study. Conclusion: Tordon 22K caused delayed contact hypersensitivity in guinea pigs.	Haut and Bell 1997 MRID 44389101

A1 Table 8: Eye Irritation Studies			
Species	**Exposure**	**Response**	**Reference**
New Zealand white rabbits, 4 males and 2 females, weighing 1.7-2.3 kg	Technical picloram, granular solid (94.1% picloram by weight). 0.1 g aliquot test material instilled once into conjunctival sac of the right eye of each rabbit. Untreated left eyes served as controls. Eyes of all rabbits remained unwashed. Both eyes of each rabbit were examined with penlight at 1, 24, 48, and 72 hours and also at 7 days post instillation for conjunctival redness and chemosis, discharge, corneal opacity and reddening of the iris.	Slight to moderate discomfort observed in the rabbits upon instillation of the test material. Post treatment examination of the conjunctivae showed slight to marked redness, slight to moderate chemosis, and slight to marked discharge in the treated eye. Reddening of the iris was observed in all rabbits. One rabbit had some scattered or diffuse areas of corneal opacity; however, no signs of corneal opacity were observed at any time in the remaining five animals. All signs of ocular irritation were resolved by 7 days post-treatment.	Jeffrey 1987d MRID 40479416.

A1 Table 8: Eye Irritation Studies			
Species	**Exposure**	**Response**	**Reference**
New Zealand white rabbits, adults, 4 males and 2 females, weighing 2.4-3.5 kg	Tordon K+ salt liquor (determined to be 38.8% picloram potassium salt). 0.1 mL aliquot test material instilled once into conjunctival sac of the right eye of each rabbit. Untreated left eyes served as controls. Eyes of all rabbits remained unwashed. Both eyes of each rabbit were examined with penlight at 1, 24, 48, and 72 hours and also at 7 and 14 days post instillation for conjunctival redness and chemosis, discharge, corneal opacity and reddening of the iris.	Moderate discomfort observed in one animal immediately post-treatment, led to right eye of the remaining rabbits to be anesthetized prior to instillation of the test material. Examination of the conjunctivae post-treatment showed slight to moderate redness and slight to moderate chemosis. In addition, the treated eyes had a slight to marked amount of discharge and reddening of the iris. One rabbit had scattered or diffuse areas of corneal opacity which were resolved within 72 hours after treatment. All signs of eye irritation were absent by 72 hours after treatment in four rabbits, by 7 days after treatment in one rabbit and by 14 days after treatment in the remaining rabbit.	Jeffrey 1987e MRID 40479404
Albino rabbits (NOS), n=6	Tordon 22K formulation (24.9% potassium picloram, 21.5 % a.e.) 0.1 ml of the product placed in the conjunctival sac of left eye. No washing of eyes after treatment.	Mild iritis in 3/6 rabbits at 24 hours. Mild conjunctivitis in 3/6 rabbits at 72 hours. No effects at 96 hours.	Teeters 1973 Working Note: This study (EPA Cleared Review) has not been identified in U.S. EPA/OPP 1994a or 1995a (RED and HED Science Chapter.

Appendix 2: Toxicity to Birds

A2 Table 1: Acute Oral/Gavage Toxicity to Birds

Species	Exposure	Response	Reference[1]
Mallard duck (*Anas platyrhynchos*), mature males and females, 10/dose group	Picloram acid, technical (93.8%) Nominal concentrations: 0, 398, 631, 1000, 1590, or 2510 mg a.i./kg of body weight by intubation (single oral dose). All dosages adjusted to 100% a.i. Vehicle: corn oil	Control group: no mortality; all birds normal in appearance and behavior throughout study Treated groups: no mortality at any dose level. NOEL = 398 mg a.e./kg, based on signs of toxicity, including lethargy, marked loss of coordination, and lower limb weakness. LD_{50} >2510 mg a.e./kg (HDT)	Beavers 1983 MRID 00157173
Mallard duck (*Anas platyrhynchos*), approx 17-wks-old, 846-1282 g, 5 males and 5 females/group	Technical picloram potassium salt (38.6 ± 0.16% a.e.) Single oral dose (gavage) Nominal concentrations: 0, 292, 486, 810, 1350, or 2250 mg picloram potassium salt/kg bw by gavage. All dosages adjusted to 100% a.i. Vehicle: distilled water	Control group: no mortality; all birds normal in appearance and behavior throughout study. No apparent treatment-related effects on body weight or feed consumption. NOEL = 2250 mg a.i./kg (HDT) equivalent to ≈1943 mg a.e./kg bw LD_{50} >2250 mg a.i./kg (HDT)	Beavers 1985 MRID 00157174
Mallard duck (*Anas platyrhynchos*), females, 3- to 4-months old	Technical grade picloram (90.5% purity) by gelatin capsule	LD_{50} >2000 mg/kg Signs of toxicity included regurgitation	Tucker and Crabtree 1970
Mallard duck (*Anas platyrhynchos*), females, 7-months-old	Tordon 22K formulation suspended in corn oil.	LD_{50} >2000 mg/kg Signs of toxicity included regurgitation	Tucker and Crabtree 1970
Pheasants (*Phasianus colchicus*), female, 3- to 4-months old	Technical grade picloram (90.5% purity) by gelatin capsule	LD_{50} >2000 mg/kg Signs of toxicity included mild ataxia and fasciculation	Tucker and Crabtree 1970
Chicken (NOS)	No details provided	LD_{50}: 6000 mg/kg bw	HSDB 2011

A2 Table 2: Acute Dietary Toxicity to Birds

Species	Exposure	Response	Reference[1]
Mallard ducking (*wild type*), *Anas platyrhynchos*. 10 animals/per dose group. 50 animals in control group.	Tordon (technical Tordon acid dried; purity 79.3%) dietary concentrations of 100, 300, 400, 500, 600, 700, 900, or 1000 ppm for 5 days. Average Day 5 body weight of about 130 g. No relationship to exposure levels (Study table on p. 4). Average Day 1 to Day 5 food consumption about 32 g (Study table on p. 4) for a food consumption rate of about 0.25 kg food/kg bw. The agent used in this study – i.e., technical Tordon acid dried – is not clear.	Mortality 0-8 days: 100 ppm – 0/10 300 ppm – 2/10 500 ppm – 0/10 1000 ppm – 1/10 3000 ppm – 1/10 5000 ppm – 1/10 7000 ppm – 1/10 10000 ppm – 0/10 Total mortality in exposed birds: 6/80. Mortality in control: 0/50. The p-value using the Fisher Exact Test is marginal (p=0.05039). No dose-response relationship. No signs of toxicity in any organisms. LD_{50} =56,711 ppm. Given the low mortality, the calculated LC_{50} has little meaning. All doses appear to be essentially NOAELs. Based on food consumption, 10,000 ppm corresponds to 2,500 mg/kg bw/day.	Stevenson 1965c MRID 00075781 Not cited in U.S. EPA/OPP 1994b, 1995a
Bobwhite quail (*Colinus virginianus*), 10-days-old, 10/group	Picloram potassium salt (38.6% picloram a.e.) Nominal concentrations: 562, 1000, 1780, 3160 or 5620 ppm a.i. in the diet for 5 days, followed by 3-day observation period. Vehicle: corn oil (2% concentration) All dietary concentrations adjusted to 100% a.i. Day 5 body weights: ≈30 g (Study Table 4). Day 0-5 food consumption: 10 g (Study Table 5). Food consumption factor about 0.33 kg food/kg bw.	No mortality in controls or treated bird. Sublethal effects All control birds normal in appearance and behavior throughout study. Treated groups: one bird at 100 ppm had toe picking lesions (form of aggression) beginning on morning of day 5 until study termination. All other treated birds were normal in appearance and behavior throughout the study. No treatment-related effects on body weight or feed consumption, relative to controls. LC_{50} >5620 ppm. NOEC = 5620 ppm a.i. or ≈4850 ppm a.e. Based on food consumption, NOAEL ≈ 1600 mg a.e./kg bw.	Beavers 1986 MRID 00164727

Appendix 2: Toxicity to Birds *(continued)*

A2 Table 2: Acute Dietary Toxicity to Birds			
Species	**Exposure**	**Response**	**Reference[1]**
Bobwhite quail *(Colinus virginianus)*, 10-days-old, 10/concentration	Three unspecified *ad libitum* dietary concentrations of picloram for 5 days, followed by 3 days of untreated diet.	LC_{50} >5000 ppm No signs of toxicity at 5000 ppm	Heath et al. 1972; Hill et al. 1975
Japanese quail *(Coturnix coturnix japonica)* 7-days-old, 14/concentration	Three unspecified *ad libitum* dietary concentrations of picloram for 5 days, followed by 3 days of untreated diet.	LC_{50} >5000 ppm	Heath et al. 1972; Hill et al. 1975
Ring-necked pheasant *(Phasianus colchicus)* 10-days-old, 8/concentration	Three unspecified *ad libitum* dietary concentrations of picloram for 5 days, followed by 3 days of untreated diet.	LC_{50} >5000 ppm	Heath et al. 1972; Hill et al. 1975
Mallard duck *(Anas platyrhynchos)* 10-days-old, 10/concentration	Three unspecified *ad libitum* dietary concentrations of picloram for 5 days, followed by 3 days of untreated diet.	LC_{50} >5000 ppm	Heath et al. 1972; Hill et al. 1975
Japanese quail *(Coturnix japonica)* 7-days-old, 14/concentration	Technical grade picloram acid (90.5% a.i.), alternate name, Tordon. Three dietary concentrations ranging from 1250 to 5000 ppm diluted in corn oil in diet for 5 days.	No overt signs of toxicity. LC_{50} >5000 ppm	Hill and Camardese 1986

A2 Table 3: Reproductive and Subchronic Toxicity to Birds			
Species	**Exposure**	**Response**	**Reference**[1]
Reproduction			
Fertile mallard eggs, day 3 of development, 30 eggs/treatment group	Tordon K concentrations based on lbs a.i./100 gallons/acre (kg/935 L/ha). 30-second immersion	LC_{50} = Reported as 100 lbs/acre at 100 gallons/acre. This corresponds to ≈200,000 mg/L [100 lb = 45360 g / 100 gal = 378.5 L = 198.841 g/L = 198,841 mg/L]. Working Note: At 1 lb/acre and 5 gal/acre, the maximum field concentration anticipated is 24,000 mg/L. Adverse effects included reduced growth by Day 18 after doses greater than or equal to the 200,000 mg/L.	Hoffman and Albers 1984
Hens and cockerels (*Gallus domesticus*) from fertile eggs sprayed with 10x recommended dosage of Tordon 22K either prior to incubation or after 4 and 18days	Two incubation studies were performed with the eggs of the hens and cockerels from the originally 10x dosage-contaminated eggs. The first evaluated reproductive success as a function of parental treatments while the second involved an egg retreatment with spray contamination restricted to the pre-incubation period.	In general, there was no definitive evidence that picloram had any adverse effects on domestic fowl reproduction through one generation and into the second. Working Note: The exposures are not well-characterized in this study. The U.S. EPA/OPP (1994b) appears to summarize this study with a reported application rate of 11.2 kg/ha (≈10 lb/acre).	Somers et al. 1978
Japanese quail *(Coturnix coturnix japonica)*, 8 weeks old at start of study. 50 per dose group at start of study.	Dietary exposures to 0, 100, 500, and 1000 ppm for 3 generations (P, F_0, and F_1).	Working Note: Outcome of study is not clearly detailed. **U.S. EPA/DER:** *Information given in this report are insufficient to allow for evaluation of the results. The major inadequacies are (1) failure to identify the test material adequately; (2) failure to describe statistical procedures and to report the results of statistical analysis; and (3) failure to describe the method used to formulate test diets.*	Stevenson 1965a,b Working Note: This study is not cited or discussed in U.S. EPA/OPP (1994b) or U.S. EPA/OPP (1995a).

A2 Table 3: Reproductive and Subchronic Toxicity to Birds			
Species	**Exposure**	**Response**	**Reference**[1]
Northern Bobwhite (*Colinus virginianus*), 20 birds per sex per dose group (including controls).	Picloram acid at dietary concentrations of 0, 375, 750, and 1500 ppm for 23 weeks to adult birds. Offspring fed control diet for 14-days post-hatch. Mean food consumption during test: 19 g. Mean body weights at week 8: ≈ 212 g. Approximate food consumption: 0.09 kg food/kg bw. Dietary concentrations correspond to doses of about 33.75, 67,5, and 135 mg/kg bw. Note: European Union (2007) estimated somewhat different doses: 31.4, 65, and 127.5 mg/kg bw/day.	Incidental morality not related to concentration: 1/40, 1/40, 4/20 and 4/20 at 0, 375, 750, and 1500 ppm. **Adult Toxicity and Reproduction** No signs of toxicity in adults and no effect on reproductive parameters. Adult and reproductive NOAEL: 1500 ppm. **Offspring Toxicity** Survival and Weight loss: **See Appendix 10 for details and discussion.**	Mach 2002

Appendix 3: Toxicity to Terrestrial Plants

A3 Table 1: Vegetative Vigor

Form	Species	Exposure	Response	Reference [1]
Monocots				
Tordon K (25.2% a.i.)	barley *(Hordeum* sp.*)*	Doses: 0.0085, 0.017, 0.034, 0.068, 0.14, 0.27, 0.55, 1.10, 2.19, 4.38, 8.75, 17.5, 35, 70, 140, 280, 560, or 1120 g a.i./ha	**Phytotoxicity**: NOEC = 35 g a.i./ha EC_{25} = 67 g a.i./ha EC_{50} = 192 g a.i./ha **Shoot Length**: NOEC = 17.5 g a.i./ha EC_{25} = 118 g a.i./ha EC_{50} = 289 g a.i./ha **Shoot Weight**: NOEC = 70 g a.i./ha EC_{25} = 136 g a.i./ha EC_{50} = 266 g a.i./ha	Schwab 1996 MRID 44156701
Tordon K (25.2% a.i.)	corn *(Zea mays)*	Doses: 0.0085, 0.017, 0.034, 0.068, 0.14, 0.27, 0.55, 1.10, 2.19, 4.38, 8.75, 17.5, 35, 70, 140, 280, 560, or 1120 g a.i./ha	**Phytotoxicity**: NOEC = 70 g a.i./ha EC_{25} = 293 g a.i./ha EC_{50} = 525 g a.i./ha **Shoot Length**: NOEC = 140 g a.i./ha EC_{25} = 324 g a.i./ha EC_{50} = 649 g a.i./ha **Shoot Weight**: NOEC =140 g a.i./ha EC_{25} = 428 g a.i./ha EC_{50} = 731 g a.i./ha	Schwab 1996 MRID 44156701
Tordon K (25.2% a.i.)	wheat *(Triticum aestivum)*	Doses: 0.0085, 0.017, 0.034, 0.068, 0.14, 0.27, 0.55, 1.10, 2.19, 4.38, 8.75, 17.5, 35, 70, 140, 280, 560, or 1120 g a.i./ha	**Phytotoxicity**: NOEC <8.75 g a.i./ha EC_{25} = 34 g a.i./ha EC_{50} = 159 g a.i./ha **Shoot Length**: NOEC =17.5 g a.i./ha EC_{25} = 60 g a.i./ha EC_{50} = 165 g a.i./ha **Shoot Weight**: NOEC =35 g a.i./ha EC_{25} = 70 g a.i./ha EC_{50} = 149 g a.i./ha	Schwab 1996 MRID 44156701

A3 Table 1: Vegetative Vigor				
Form	**Species**	**Exposure**	**Response**	**Reference [1]**
Tordon K (25.2% a.i.)	onion *(Allium cepa)*	Doses: 0.0085, 0.017, 0.034, 0.068, 0.14, 0.27, 0.55, 1.10, 2.19, 4.38, 8.75, 17.5, 35, 70, 140, 280, 560, or 1120 g a.i./ha	**Phytotoxicity**: NOEC = 35 g a.i./ha EC_{25} = 131 g a.i./ha EC_{50} = 310 g a.i./ha **Shoot Length**: NOEC = 280 g a.i./ha EC_{25} = 433 g a.i./ha EC_{50} = 971 g a.i./ha **Shoot Weight**: NOEC = 70 g a.i./ha EC_{25} = 58 g a.i./ha EC_{50} = 177 g a.i./ha	Schwab 1996 MRID 44156701
Potassium salt of picloram (K-salt) containing 0.2885% picloram	Field corn, *Zea mays*	Doses: 0.0, 17.5, 35, 70, 140, 280, or 560 g a.e./ha (foliage application)	55 days after treatment: NOEL = 560 g a.e./ha EC_{25} >560 g a.e./ha EC_{50} >560 g a.e./ha	Weseloh and Stockdale 1989 MRID 41296501
Potassium salt of picloram (K-salt) containing 0.2885% picloram	Spring wheat, *Triticum aestivum*	Doses: 0.0, 17.5, 35, 70, 140, 280, or 560 g a.e./ha (foliage application)	42 days after treatment: NOEL = 70 g a.e./ha EC_{25} = 310 g a.e./ha EC_{50} >560 g a.e./ha	Weseloh and Stockdale 1989 MRID 41296501
Potassium salt of picloram (K-salt) containing 0.2885% picloram	Onion, *Allium cepa*	Doses: 0.0, 17.5, 35, 70, 140, 280, or 560 g a.e./ha (foliage application)	36 days after treatment: NOEL = 280 g a.e./ha EC_{25} >560 g a.e./ha EC_{50} >560 g a.e./ha	Weseloh and Stockdale 1989 MRID 41296501
Potassium salt of picloram (K-salt) containing 0.2885% picloram	Spring barley, *Hordeum vulgare*	Doses: 0.0, 17.5, 35, 70, 140, 280, or 560 g a.e./ha (foliage application)	55 days after treatment: NOEL = 280 g a.e./ha EC_{25} >560 g a.e./ha EC_{50} >560 g a.e./ha	Weseloh and Stockdale 1989 MRID 41296501
Working Note: Data from Weseloh and Stockdale (1989) yield values that are much higher than and inconsistent with those of Schwab (1996). See Section 4.1.2.5 for discussion.				
Dicots				
Tordon K (24.1% a.i.)	Radish (*Rhaphanus sativus*)	Doses: 1.25 to 320 g a.e./ha	Shoot length: EC_{25}: >320 g a.e./ha EC_{50}: >320 g a.e./ha NOAEL: >320 g a.e./ha Shoot Weight: EC_{25}: 327 g a.e./ha EC_{50}: 518 g a.e./ha NOAEL: 160 g a.e./ha	Schwab 1994 MRID 43276601
Tordon K (24.1% a.i.)	Rape (*Brassica oleracea*)	Doses: 1.25 to 320 g a.e./ha	Shoot length: EC_{25}: >320 g a.e./ha EC_{50}: >320 g a.e./ha NOAEL: 80 g a.e./ha Shoot Weight: EC_{25}: 230 g a.e./ha EC_{50}: 343 g a.e./ha NOAEL: 160 g a.e./ha	Schwab 1994 MRID 43276601

A3 Table 1: Vegetative Vigor				
Form	**Species**	**Exposure**	**Response**	**Reference [1]**
Tordon K (25.2% a.i.)	alfalfa *(Medicago sativa)*	Doses: 0.0085, 0.017, 0.034, 0.068, 0.14, 0.27, 0.55, 1.10, 2.19, 4.38, 8.75, 17.5, 35, 70, 140, 280, 560, or 1120 g a.i./ha	**Phytotoxicity**: NOEC = 0.27 g a.i./ha EC_{25} = 1.65 g a.i./ha EC_{50} = 7.21 g a.i./ha **Shoot Length**: NOEC = 4.38 g a.i./ha EC_{25} = 7.09 g a.i./ha EC_{50} = 14.7 g a.i./ha **Shoot Weight**: NOEC = 1.10 g a.i./ha EC_{25} = 1.15 g a.i./ha EC_{50} = 3.43 g a.i./ha	Schwab 1996 MRID 44156701
Tordon K (25.2% a.i.)	cucumber *(Cucumis sativus)*	Doses: 0.0085, 0.017, 0.034, 0.068, 0.14, 0.27, 0.55, 1.10, 2.19, 4.38, 8.75, 17.5, 35, 70, 140, 280, 560, or 1120 g a.i./ha	**Phytotoxicity**: NOEC = 0.55 g a.i./ha EC_{25} = 1.18 g a.i./ha EC_{50} = 2.49 g a.i./ha **Shoot Length**: NOEC =1.10 g a.i./ha EC_{25} = 2.48 g a.i./ha EC_{50} = 5.04 g a.i./ha **Shoot Weight**: NOEC =4.38 g a.i./ha EC_{25} = 6.80 g a.i./ha EC_{50} = 8.65 g a.i./ha	Schwab 1996 MRID 44156701
Tordon K (25.2% a.i.)	pinto bean *(Phaseolus vulgaris)*	Doses: 0.0085, 0.017, 0.034, 0.068, 0.14, 0.27, 0.55, 1.10, 2.19, 4.38, 8.75, 17.5, 35, 70, 140, 280, 560, or 1120 g a.i./ha	**Phytotoxicity**: NOEC = 0.068 g a.i./ha EC_{25} = 0.097g a.i./ha EC_{50} = 0.48 g a.i./ha **Shoot Length**: NOEC =0.27 g a.i./ha EC_{25} = 0.97 g a.i./ha EC_{50} = 2.99 g a.i./ha **Shoot Weight**: NOEC = 0.55 g a.i./ha EC_{25} = 0.72 g a.i./ha EC_{50} = 1.75 g a.i./ha	Schwab 1996 MRID 44156701

A3 Table 1: Vegetative Vigor				
Form	**Species**	**Exposure**	**Response**	**Reference [1]**
Tordon K (25.2% a.i.)	radish *(Raphanus sativus)*	Doses: 0.0085, 0.017, 0.034, 0.068, 0.14, 0.27, 0.55, 1.10, 2.19, 4.38, 8.75, 17.5, 35, 70, 140, 280, 560, or 1120 g a.i./ha	**Phytotoxicity**: NOEC = 8.75 g a.i./ha EC_{25} = 42 g a.i./ha EC_{50} = 112 g a.i./ha **Shoot Length**: NOEC = 140 g a.i./ha EC_{25} >280 g a.i./ha EC_{50} >280 g a.i./ha **Shoot Weight**: NOEC =140 g a.i./ha EC_{25} >280 g a.i./ha EC_{50} >280 g a.i./ha	Schwab 1996 MRID 44156701
Tordon K (25.2% a.i.)	rape *(Brassica napus)*	Doses: 0.0085, 0.017, 0.034, 0.068, 0.14, 0.27, 0.55, 1.10, 2.19, 4.38, 8.75, 17.5, 35, 70, 140, 280, 560, or 1120 g a.i./ha	**Phytotoxicity**: NOEC = 0.55 g a.i./ha EC_{25} = 2.13 g a.i./ha EC_{50} = 12.1 g a.i./ha **Shoot Length**: NOEC =140 g a.i./ha EC_{25} = 217 g a.i./ha EC_{50} >280 g a.i./ha **Shoot Weight**: NOEC = 70 g a.i./ha EC_{25} = 160 g a.i./ha EC_{50} >280 g a.i./ha	Schwab 1996 MRID 44156701
Tordon K (25.2% a.i.)	soybean *(Glycine max)*	Doses: 0.0085, 0.017, 0.034, 0.068, 0.14, 0.27, 0.55, 1.10, 2.19, 4.38, 8.75, 17.5, 35, 70, 140, 280, 560, or 1120 g a.i./ha	**Phytotoxicity**: NOEC = 0.14 g a.i./ha EC_{25} = 0.31 g a.i./ha EC_{50} = 1.37 g a.i./ha **Shoot Length**: NOEC = 1.10 g a.i./ha EC_{25} = 5.03 g a.i./ha EC_{50} = 9.89 g a.i./ha **Shoot Weight**: NOEC = 0.27 g a.i./ha EC_{25} = 0.98 g a.i./ha EC_{50} = 3.10 g a.i./ha	Schwab 1996 MRID 44156701

A3 Table 1: Vegetative Vigor				
Form	**Species**	**Exposure**	**Response**	**Reference [1]**
Tordon K (25.2% a.i.)	sunflower *(Helianthus annus)*	Doses: 0.0085, 0.017, 0.034, 0.068, 0.14, 0.27, 0.55, 1.10, 2.19, 4.38, 8.75, 17.5, 35, 70, 140, 280, 560, or 1120 g a.i./ha	**Phytotoxicity**: NOEC = 0.034 g a.i./ha EC_{25} = 0.094 g a.i./ha EC_{50} = 0.86 g a.i./ha **Shoot Length**: NOEC = 0.27 g a.i./ha EC_{25} = 0.55 g a.i./ha EC_{50} = 2.30 g a.i./ha **Shoot Weight**: NOEC = 0.27 g a.i./ha EC_{25} = 0.67 g a.i./ha EC_{50} = 3.19 g a.i./ha	Schwab 1996 MRID 44156701
Tordon K (25.2% a.i.)	Tomato *(Lycopersicon esculentum)*	Doses: 0.0085, 0.017, 0.034, 0.068, 0.14, 0.27, 0.55, 1.10, 2.19, 4.38, 8.75, 17.5, 35, 70, 140, 280, 560, or 1120 g a.i./ha	**Phytotoxicity**: NOEC = 0.034 g a.i./ha EC_{25} = 0.20 g a.i./ha EC_{50} = 0.80 g a.i./ha **Shoot Length**: NOEC = 1.10 g a.i./ha EC_{25} = 2.53 g a.i./ha EC_{50} = 4.40 g a.i./ha **Shoot Weight**: NOEC = 0.27 g a.i./ha EC_{25} = 0.93 g a.i./ha EC_{50} = 1.65 g a.i./ha	Schwab 1996 MRID 44156701
Potassium salt of picloram (K-salt) containing 0.2885% picloram	Soybean, *Glycine max*	0.0, 0.125, 0.25, 0.5, 1.1, 2.2, 4.4, or 8.8 g a.e./ha (foliage application)	55 days after treatment: NOEL = 0.125 g a.e./ha EC_{25} = 0.40 g a.e./ha EC_{50} = 1.4 g a.e./ha	Weseloh and Stockdale 1989 MRID 41296501
Potassium salt of picloram (K-salt) containing 0.2885% picloram	Dry bean, *Phaseolus vulgaris vulgaris*	0.0, 0.125, 0.25, 0.5, 1.1, 2.2, 4.4, or 8.8 g a.e./ha (foliage application)	42 days after treatment: NOEL = 0.25 g a.e./ha EC_{25} = 1.1 g a.e./ha EC_{50} = 2.5 g a.e./ha	Weseloh and Stockdale 1989 MRID 41296501
Potassium salt of picloram (K-salt) containing 0.2885% picloram	Radish, *Raphanus sativus*	0.0, 1.1, 2.2, 4.4, 8.8, 17.5, 35, or 70 g a.e./ha (foliage application)	21 days after treatment: NOEL = 35 g a.e./ha EC_{25} >70 g a.e./ha EC_{50} >70 g a.e./ha	Weseloh and Stockdale 1989 MRID 41296501
Potassium salt of picloram (K-salt) containing 0.2885% picloram	Tomato, *Lycopericum esculentum*	0.0, 0.125, 0.25, 0.5, 1.1, 2.2, 4.4, or 8.8 g a.e./ha (foliage application)	42 days after treatment: NOEL = 0.25 g a.e./ha EC_{25} = 0.97 g a.e./ha EC_{50} = 2.5 g a.e./ha	Weseloh and Stockdale 1989 MRID 41296501
Potassium salt of picloram (K-salt) containing 0.2885% picloram	Sunflower, *Helianthus annus*	0.0, 0.125, 0.25, 0.5, 1.1, 2.2, 4.4, or 8.8 g a.e./ha (foliage application)	36 days after treatment: NOEL = 1.1 g a.e./ha EC_{25} = 6.9 g a.e./ha EC_{50} = 15.8 g a.e./ha	Weseloh and Stockdale 1989 MRID 41296501

A3 Table 1: Vegetative Vigor

Form	Species	Exposure	Response	Reference [1]
Potassium salt of picloram (K-salt) containing 0.2885% picloram	Oilseed rape, *Brassica napus napus*	0.0, 1.1, 2.2, 4.4, 8.8, 17.5, 35, or 70 g a.e./ha (foliage application)	42 days after treatment: NOEL = 17.5 g a.e./ha EC_{25} >70 g a.e./ha EC_{50} >70 g a.e./ha	Weseloh and Stockdale 1989 MRID 41296501

Working Note: Data from Weseloh and Stockdale (1989) yield values that are modestly higher than those of Schwab (1996). See Section 4.1.2.5 for discussion.

A3 Table 2: Seedling Emergence				
Form	**Species**	**Exposure**	**Response**	**Reference [1]**
Monocots				
Tordon K (24.1% a.i.)	Barley *(Hordeum* sp.*)*	Doses: 1.3 to 80 g a.e./ha	$EC_{25:}$ 6.8 g a.e./ha EC_{50}: 16 g a.e./ha NOAEL: 2.5 g a.e./ha	Schwab 1994 MRID 43276601
Tordon K (24.1% a.i.)	barley *(Hordeum)*	Doses: 0.0085, 0.017, 0.034, 0.068, 0.14, 0.27, 0.55, 1.10, 2.19, 4.38, 8.75, 17.5, 35, 70, 140, 280, 560, or 1120 g a.i./ha	**Emergence Phytotoxicity**: NOEC = 70 g a.i./ha EC_{25} >1120 g a.i./ha EC_{50} >1120 g a.i./ha **Percent Emergence**: NOEC >1120 g a.i./ha EC_{25} >1120 g a.i./ha EC_{50} >1120 g a.i./ha **Emergence Shoot Length**: NOEC >1120 g a.i./ha EC_{25} >1120 g a.i./ha EC_{50} >1120 g a.i./ha **Emergence Shoot Weight**: NOEC = 560 g a.i./ha EC_{25} >1120 g a.i./ha EC_{50} >1120 g a.i./ha	Schwab 1995 MRID 43959505
Tordon K (24.1% a.i.)	corn *(Zea mays)*	Doses: 0.0085, 0.017, 0.034, 0.068, 0.14, 0.27, 0.55, 1.10, 2.19, 4.38, 8.75, 17.5, 35, 70, 140, 280, 560, or 1120 g a.i./ha	**Emergence Phytotoxicity**: NOEC = 560 g a.i./ha EC_{25} >1120 g a.i./ha EC_{50} >1120 g a.i./ha **Percent Emergence**: NOEC >1120 g a.i./ha EC_{25} >1120 g a.i./ha EC_{50} >1120 g a.i./ha **Emergence Shoot Length**: NOEC >1120 g a.i./ha EC_{25} >1120 g a.i./ha EC_{50} >1120 g a.i./ha **Emergence Shoot Weight**: NOEC = 560 g a.i./ha EC_{25} >1120 g a.i./ha EC_{50} >1120 g a.i./ha	Schwab 1995 MRID 43959505

A3 Table 2: Seedling Emergence

Form	Species	Exposure	Response	Reference [1]
Tordon K (24.1% a.i.)	wheat *(Triticum aestivum)*	Doses: 0.0085, 0.017, 0.034, 0.068, 0.14, 0.27, 0.55, 1.10, 2.19, 4.38, 8.75, 17.5, 35, 70, 140, 280, 560, or 1120 g a.i./ha	**Emergence Phytotoxicity**: NOEC = 35 g a.i./ha EC_{25} = 136 g a.i./ha EC_{50} = 640 g a.i./ha **Percent Emergence**: NOEC >1120 g a.i./ha EC_{25} >1120 g a.i./ha EC_{50} >1120 g a.i./ha **Emergence Shoot Length**: NOEC >1120 g a.i./ha EC_{25} >1120 g a.i./ha EC_{50} >1120 g a.i./ha **Emergence Shoot Weight**: NOEC >1120 g a.i./ha EC_{25} >1120 g a.i./ha EC_{50} >1120 g a.i./ha	Schwab 1995 MRID 43959505
Tordon K (24.1% a.i.)	onion *(Allium cepa)*	Doses: 0.0085, 0.017, 0.034, 0.068, 0.14, 0.27, 0.55, 1.10, 2.19, 4.38, 8.75, 17.5, 35, 70, 140, 280, 560, or 1120 g a.i./ha	**Emergence Phytotoxicity**: NOEC = 140 g a.i./ha EC_{25} = 736 g a.i./ha EC_{50} >1120 g a.i./ha **Percent Emergence**: NOEC = 560 g a.i./ha EC_{25} >1120 g a.i./ha EC_{50} >1120 g a.i./ha **Emergence Shoot Length**: NOEC = 560 g a.i./ha EC_{25} = 627 g a.i./ha EC_{50} = 1104 g a.i./ha **Emergence Shoot Weight**: NOEC = 280 g a.i./ha EC_{25} = 403 g a.i./ha EC_{50} = 719 g a.i./ha	Schwab 1995 MRID 43959505
Potassium salt of picloram (K-salt) containing 0.2885% picloram	Field corn, *Zea mays*	0.0, 17.5, 35, 70, 140, 280, or 560 g a.e./ha (in soil)	34 days after treatment: NOEL = 280 g a.e./ha EC_{25} >560 g a.e./ha EC_{50} >560 g a.e./ha	Weseloh and Stockdale 1989 MRID 41296501
Potassium salt of picloram (K-salt) containing 0.2885% picloram	Spring wheat, *Triticum aestivum*	0.0, 1.1, 2.2, 4.4, 8.8, 17.5, 35, or 70 g a.e./ha (in soil)	34 days after treatment: NOEL = 8.8 g a.e./ha EC_{25} = 23.5 g a.e./ha EC_{50} = 38.0 g a.e./ha	Weseloh and Stockdale 1989 MRID 41296501
Potassium salt of picloram (K-salt) containing 0.2885% picloram	Onion, *Allium cepa*	0.0, 1.1, 2.2, 4.4, 8.8, 17.5, 35, or 70 g a.e./ha (in soil)	34 days after treatment: NOEL = 35.0 g a.e./ha EC_{25} = 55.3 g a.e./ha EC_{50} = 83.9 g a.e./ha	Weseloh and Stockdale 1989 MRID 41296501

A3 Table 2: Seedling Emergence				
Form	**Species**	**Exposure**	**Response**	**Reference [1]**
Potassium salt of picloram (K-salt) containing 0.2885% picloram	Spring barley, *Hordeum vulgare*	0.0, 1.1, 2.2, 4.4, 8.8, 17.5, 35, or 70 g a.e./ha (in soil)	34 days after treatment: NOEL = 17.5 g a.e./ha EC_{25} = 36.9 g a.e./ha EC_{50} = 53.1 g a.e./ha	Weseloh and Stockdale 1989 MRID 41296501
Dicots				
Tordon K (24.1% a.i.)	Rape *(Brassica oleracea)*	Doses: 1.3 to 80 g a.e./ha	$EC_{25:}$ 1.5 g a.e./ha EC_{50}: 5.4 g a.e./ha NOAEL: <1.5 g a.e./ha	Schwab 1994 MRID 43276601
Tordon K (24.1% a.i.)	Pinto bean *(Phaseolus vulgaris)*	Doses: 0.0196 to 2.5 g a.e./ha	Percent Emergence NOAEL: >2.5 g a.e./ha Shoot length NOAEL: 0.0782 g a.e./ha Shoot weight NOAEL: >2.5 g a.e./ha	Schwab 1994 MRID 43276601
Tordon K (24.1% a.i.)	Soybean *(Glycine max*)	Doses: 0.0791 to 40.2 g a.e./ha	Percent Emergence NOAEL: >40.2 g a.e./ha Shoot length NOAEL: 20.2 g a.e./ha Shoot weight NOAEL: 20.2 g a.e./ha	Schwab 1994 MRID 43276601
Tordon K (24.1% a.i.)	pinto bean *(Phaseolus vulgaris)* Working Note: most sensitive for emergence phytotoxicity, percent emergence, emergence shoot length, and emergence shoot weight	Doses: 0.0085, 0.017, 0.034, 0.068, 0.14, 0.27, 0.55, 1.10, 2.19, 4.38, 8.75, 17.5, 35, 70, 140, 280, 560, or 1120 g a.i./ha	**Emergence Phytotoxicity**: NOEC = 0.27 g a.i./ha EC_{25} = 7.40 g a.i./ha EC_{50} = 20.3 g a.i./ha **Percent Emergence**: NOEC = 35 g a.i./ha EC_{25} = 6.34 g a.i./ha EC_{50} = 70 g a.i./ha **Emergence Shoot Length**: NOEC = 8.75 g a.i./ha EC_{25} = 24 g a.i./ha EC_{50} = 48 g a.i./ha **Emergence Shoot Weight**: NOEC = 0.55 g a.i./ha EC_{25} = 3.15 g a.i./ha EC_{50} = 16 g a.i./ha	Schwab 1995 MRID 43959505

A3 Table 2: Seedling Emergence				
Form	**Species**	**Exposure**	**Response**	**Reference [1]**
Tordon K (24.1% a.i.)	radish *(Raphanus sativus)*	Doses: 0.0085, 0.017, 0.034, 0.068, 0.14, 0.27, 0.55, 1.10, 2.19, 4.38, 8.75, 17.5, 35, 70, 140, 280, 560, or 1120 g a.i./ha	**Emergence Phytotoxicity**: NOEC = 70 g a.i./ha EC_{25} = 44 g a.i./ha EC_{50} = 167 g a.i./ha **Percent Emergence**: NOEC >1120 g a.i./ha EC_{25} >1120 g a.i./ha EC_{50} >1120 g a.i./ha **Emergence Shoot Length**: NOEC >1120 g a.i./ha EC_{25} >1120 g a.i./ha EC_{50} >1120 g a.i./ha **Emergence Shoot Weight**: NOEC = 560 g a.i./ha EC_{25} = 1042 g a.i./ha EC_{50} >1120 g a.i./ha	Schwab 1995 MRID 43959505
Tordon K (24.1% a.i.)	rape *(Brassica napus)*	Doses: 0.0085, 0.017, 0.034, 0.068, 0.14, 0.27, 0.55, 1.10, 2.19, 4.38, 8.75, 17.5, 35, 70, 140, 280, 560, or 1120 g a.i./ha	**Emergence Phytotoxicity**: NOEC = 8.75 g a.i./ha EC_{25} = 184 g a.i./ha EC_{50} = 1083 g a.i./ha **Percent Emergence**: NOEC >1120 g a.i./ha EC_{25} >1120 g a.i./ha EC_{50} >1120 g a.i./ha **Emergence Shoot Length**: NOEC >1120 g a.i./ha EC_{25} >1120 g a.i./ha EC_{50} >1120 g a.i./ha **Emergence Shoot Weight**: NOEC = 140 g a.i./ha EC_{25} = 411 g a.i./ha EC_{50} >1120 g a.i./ha	Schwab 1995 MRID 43959505

A3 Table 2: Seedling Emergence				
Form	**Species**	**Exposure**	**Response**	**Reference [1]**
Tordon K (24.1% a.i.)	soybean *(Glycine max)*	Doses: 0.0085, 0.017, 0.034, 0.068, 0.14, 0.27, 0.55, 1.10, 2.19, 4.38, 8.75, 17.5, 35, 70, 140, 280, 560, or 1120 g a.i./ha	**Emergence Phytotoxicity**: NOEC = 8.75 g a.i./ha EC_{25} = 23.0 g a.i./ha EC_{50} = 46 g a.i./ha **Percent Emergence**: NOEC = 35 g a.i./ha EC_{25} = 27 g a.i./ha EC_{50} = 381 g a.i./ha **Emergence Shoot Length**: NOEC = 35 g a.i./ha EC_{25} = 47 g a.i./ha EC_{50} = 74 g a.i./ha **Emergence Shoot Weight**: NOEC = 17.5 g a.i./ha EC_{25} = 39 g a.i./ha EC_{50} = 64 g a.i./ha	Schwab 1995 MRID 43959505
Tordon K (24.1% a.i.)	sunflower *(Helianthus annus)*	Doses: 0.0085, 0.017, 0.034, 0.068, 0.14, 0.27, 0.55, 1.10, 2.19, 4.38, 8.75, 17.5, 35, 70, 140, 280, 560, or 1120 g a.i./ha	**Emergence Phytotoxicity**: NOEC = 8.75 g a.i./ha EC_{25} = 25.3 g a.i./ha EC_{50} = 137 g a.i./ha **Percent Emergence**: NOEC = 280 g a.i./ha EC_{25} >560 g a.i./ha EC_{50} >560 g a.i./ha **Emergence Shoot Length**: NOEC = 280 g a.i./ha EC_{25} >560 g a.i./ha EC_{50} >560 g a.i./ha **Emergence Shoot Weight**: NOEC = 280 g a.i./ha EC_{25} >560 g a.i./ha EC_{50} >560 g a.i./ha	Schwab 1995 MRID 43959505

A3 Table 2: Seedling Emergence				
Form	**Species**	**Exposure**	**Response**	**Reference [1]**
Tordon K (24.1% a.i.)	Tomato *(Lycopersicon esculentum)*	Doses: 0.0085, 0.017, 0.034, 0.068, 0.14, 0.27, 0.55, 1.10, 2.19, 4.38, 8.75, 17.5, 35, 70, 140, 280, 560, or 1120 g a.i./ha	**Emergence Phytotoxicity**: NOEC = 4.38 g a.i./ha EC_{25} = 7.54 g a.i./ha EC_{50} = 23.7 g a.i./ha **Percent Emergence**: NOEC = 140 g a.i./ha EC_{25} = 25 g a.i./ha EC_{50} = 445 g a.i./ha **Emergence Shoot Length**: NOEC = 140 g a.i./ha EC_{25} = 194 g a.i./ha EC_{50} = 282 g a.i./ha **Emergence Shoot Weight**: NOEC = 35 g a.i./ha EC_{25} = 31 g a.i./ha EC_{50} = 59 g a.i./ha	Schwab 1995 MRID 43959505
Potassium salt of picloram (K-salt) containing 0.2885% picloram	Soybean, *Glycine max*	0.0, 0.031, 0.063, 0.125, 0.25, 0.5, 1.1, or 2.2 g a.e./ha (in soil)	35 days after treatment: NOEL <0.031 g a.e./ha EC_{25} = 0.014 g a.e./ha EC_{50} = 0.05 g a.e./ha	Weseloh and Stockdale 1989 MRID 41296501
Potassium salt of picloram (K-salt) containing 0.2885% picloram	Dry bean, *Phaseolus vulgaris vulgaris*	0.0, 0.031, 0.063, 0.125, 0.25, 0.5, 1.1, or 2.2 g a.e./ha (in soil)	34 days after treatment: NOEL <0.031 g a.e./ha EC_{25} = 0.10 g a.e./ha EC_{50} = 0.27 g a.e./ha	Weseloh and Stockdale 1989 MRID 41296501
Potassium salt of picloram (K-salt) containing 0.2885% picloram	Radish, *Raphanus sativus*	0.0, 1.1, 2.2, 4.4, 8.8, 17.5, 35, 70, 140, or 280 g a.e./ha (in soil)	34 days after treatment: NOEL = 17.5 g a.e./ha EC_{25} = 33.7 g a.e./ha EC_{50} = 67.3 g a.e./ha	Weseloh and Stockdale 1989 MRID 41296501
Potassium salt of picloram (K-salt) containing 0.2885% picloram	Tomato, *Lycopericum esculentum*	0.0, 0.125, 0.25, 0.5, 1.1, 2.2, 4.4, or 8.8 g a.e./ha (in soil)	34 days after treatment: NOEL = 0.25 g a.e./ha EC_{25} = 0.58 g a.e./ha EC_{50} = 1.0 g a.e./ha	Weseloh and Stockdale 1989 MRID 41296501
Potassium salt of picloram (K-salt) containing 0.2885% picloram	Sunflower, *Helianthus annus*	0.0, 0.125, 0.25, 0.5, 1.1, 2.2, 4.4, or 8.8 g a.e./ha (in soil)	34 days after treatment: NOEL = 0.5 g a.e./ha EC_{25} = 1.5 g a.e./ha EC_{50} = 3.1 g a.e./ha	Weseloh and Stockdale 1989 MRID 41296501
Potassium salt of picloram (K-salt) containing 0.2885% picloram	Oilseed rape, *Brassica napus napus*	0.0, 1.1, 2.2, 4.4, 8.8, 17.5, 35, 70, 140, or 280 g a.e./ha (in soil)	34 days after treatment: NOEL = 8.8 g a.e./ha EC_{25} = 20.6 g a.e./ha EC_{50} = 39.2 g a.e./ha	Weseloh and Stockdale 1989 MRID 41296501

A3 Table 3: Seed Germination				
Form	**Species**	**Exposure**	**Response**	**Reference [1]**
Monocots				
Tordon K (24.1% a.i.)	Barley *(Hordeum* sp.*)*	Doses: 1.3 to 80 g a.e./ha	EC_{25} > 80 g a.e./ha	Schwab 1994 MRID 43276601
Potassium salt of picloram (K-salt) containing 0.2885% picloram	Field corn, *Zea mays*	0.0, 17.5, 35, 70, 140, 280, or 560 g a.e./ha in Petri dish	6 days after treatment: NOEL = 560 g a.e./ha EC_{25} >560 g a.e./ha EC_{50} >560 g a.e./ha	Weseloh and Stockdale 1989 MRID 41296501
Potassium salt of picloram (K-salt) containing 0.2885% picloram	Spring wheat, *Triticum aestivum*	0.0, 17.5, 35, 70, 140, 280, or 560 g a.e./ha in Petri dish	6 days after treatment: NOEL = 560 g a.e./ha EC_{25} >560 g a.e./ha EC_{50} >560 g a.e./ha	Weseloh and Stockdale 1989 MRID 41296501
Potassium salt of picloram (K-salt) containing 0.2885% picloram	Onion, *Allium cepa*	0.0, 17.5, 35, 70, 140, 280, or 560 g a.e./ha in Petri dish	6 days after treatment: NOEL = 280 g a.e./ha EC_{25} >560 g a.e./ha EC_{50} >560 g a.e./ha	Weseloh and Stockdale 1989 MRID 41296501
Potassium salt of picloram (K-salt) containing 0.2885% picloram	Spring barley, *Hordeum vulgare*	0.0, 1.1, 2.2, 4.4, 8.8, 17.5, 35, or 70 g a.e./ha in Petri dish	6 days after treatment: NOEL = 4.4 g a.e./ha EC_{25} >70 g a.e./ha EC_{50} >70 g a.e./ha	Weseloh and Stockdale 1989 MRID 41296501
Dicots				
Tordon K (24.1% a.i.)	Rape (*Brassica oleracea)*	Doses: 1.3 to 80 g a.e./ha	EC_{25} = 48 g a.e./ha EC_{50} = 205 g a.e./ha	Schwab 1994 MRID 43276601
Potassium salt of picloram (K-salt) containing 0.2885% picloram	Soybean, *Glycine max*	0.0, 0.25, 0.5, 1.1 2.2, 4.4, 8.8, or 17.5 g a.e./ha in Petri dish	6 days after treatment: NOEL = 0.25 g a.e./ha EC_{25} = 3.5 g a.e./ha EC_{50} = 17.0 g a.e./ha	Weseloh and Stockdale 1989 MRID 41296501
Potassium salt of picloram (K-salt) containing 0.2885% picloram	Dry bean, *Phaseolus vulgaris vulgaris*	0.0, 0.25, 0.5, 1.1 2.2, 4.4, 8.8, or 17.5 g a.e./ha in Petri dish	6 days after treatment: NOEL = 0.25 g a.e./ha EC_{25} = 5.0 g a.e./ha EC_{50} = 19.2 g a.e./ha	Weseloh and Stockdale 1989 MRID 41296501
Potassium salt of picloram (K-salt) containing 0.2885% picloram	Radish, *Raphanus sativus*	0.0, 17.5, 35, 70, 140, 280, or 560 g a.e./ha in Petri dish	6 days after treatment: NOEL = 280 g a.e./ha EC_{25} >560 g a.e./ha EC_{50} >560 g a.e./ha	Weseloh and Stockdale 1989 MRID 41296501
Potassium salt of picloram (K-salt) containing 0.2885% picloram	Tomato, *Lycopericum esculentum*	0.0, 17.5, 35, 70, 140, 280, or 560 g a.e./ha in Petri dish	6 days after treatment: NOEL = 560 g a.e./ha EC_{25} >560 g a.e./ha EC_{50} >560 g a.e./ha	Weseloh and Stockdale 1989 MRID 41296501
Potassium salt of picloram (K-salt) containing 0.2885% picloram	Sunflower, *Helianthus annus*	0.0, 1.1, 2.2, 4.4, 8.8, 17.5, 35, or 70 g a.e./ha in Petri dish	6 days after treatment: NOEL = 35 g a.e./ha EC_{25} = 89.9 g a.e./ha EC_{50} = 360 g a.e./ha	Weseloh and Stockdale 1989 MRID 41296501
Potassium salt of picloram (K-salt) containing 0.2885% picloram	Oilseed rape, *Brassica napus napus*	0.0, 1.1, 2.2, 4.4, 8.8, 17.5, 35, or 70 g a.e./ha in Petri dish	6 days after treatment: NOEL = 70 g a.e./ha EC_{25} >70 g a.e./ha EC_{50} >70 g a.e./ha	Weseloh and Stockdale 1989 MRID 41296501

A3 Table 4: Other Toxicity Studies

Species	Exposure	Response	Reference
Soybean seeds	Pre-emergence application by tractor-mounted spray rig of 1, 5, 10, then 20 g/ha Tordon K to three fields planted with soybeans; controls received no spray treatments. ***The largest environmental difference between sites was soil organic matter:*** ***Geneseo IL: 5.7%*** ***Greenfield, IN: 1.7%*** ***Wayside, MS: 1.3%***	Seedling emergence: Picloram had no effect on the number of seedlings that emerged at any test site. Plant height: soil application of 10 and 20 g/ha picloram caused significant reductions at Greenfield, IN and Wayside, MS; no effect on plant height observed at Geneseo, IL Final grain yield: soil application of 10 and 20 g/ha picloram caused significant reductions at Greenfield, IN and Wayside, MS; no effect on final grain yield observed at Geneseo, IL Visual plant injury: significant visual injury and reductions in final grain yields at 10 and 20 g/ha. Injury varied from site to site, being greatest at Greenfield, IN and significantly less at Geneseo, IL. NOEC (plant injury) < 1 g/ha at Greenfield, IN, where the most injury was measured. EC_{25} = 4.55 g/ha at Greenfield, IN, where the most injury was measured. Visual injury was most sensitive endpoint measured.	Wright 2000 MRID 45289601
Radishes (*Raphanus sativus*)	Picloram (99% a.i.) in sand-soil medium. Nominal concentrations: 0, 0.01, 0.1, 1, 10, or 100 mg/kg soil	NOEC (growth) = 0.1 mg/kg soil EC50 (growth): 1 mg/kg soil	Garten and Frank 1984

A3 Table 4: Other Toxicity Studies

Species	Exposure	Response	Reference
Bush beans (*Phaseolus vulgaris*) **Substituted for the original test species, soybeans (*Glycine max*), in most tests because of consistently poor germination success of soybeans.**	Picloram (99% a.i.) in sand-soil medium. Nominal concentrations: 0, 0.01, 0.1, 1, 10, or 100 mg/kg	NOEC (growth) = not determined; at 0.1 mg/kg, growth was significantly less than that of control plants. 0.1 mg/kg = concentration at which plant growth was inhibited by 50% or more.	Garten and Frank 1984
Barley (*Hordeum vulgare*)	Picloram (99% a.i.) in sand-soil medium. Nominal concentrations: 0, 0.01, 0.1, 1, 10, or 100 mg/kg	NOEC (growth) = 0.1 mg/kg 1 mg/kg = concentration at which plant growth was inhibited by 50% or more.	Garten and Frank 1984
Sunflower (*Helianthus annus*), seedlings, approx. 5 cm shoot height (germinated in sand) and transferred to glass jars	Nutrient solutions: ***Picloram acid***: 0,0.025, 0.05, 0.1, or 0.2 ppm for 6 days ***6-hydroxy picloram II* (potential metabolite)**: 0, 0.5, 1, 2, 4, 5, 10, 15, or 20 ppm ***Decarboxy picloram III* (potential metabolite)**: 0, 1, 5, 10, or 15 ppm ***6-hydroxy-decarboxy-picloram IV* (potential metabolite)**: 0, 10, 20, 40, 60, 80, or 100 ppm 6-day tests were conducted without aeration of the nutrient solutions; on day 6, the shoots were cut and fresh weights of the shoots were recorded.	Toxicity was determined by GR_{50} values (concentration in ppm for a growth reduction of sunflower shoots of 50% as determined by fresh weight) ***Picloram acid*** GR_{50} = 0.03 ppm ***6-hydroxy picloram*** GR_{50} = 10 ppm ***Decarboxy picloram*** GR_{50} = 9 ppm ***6-hydroxy-decarboxy-picloram*** GR_{50} = 86 ppm	Grover et al. 1975
Four seeds each of **sorghum** *(Sorghum vulgare*), **oat** *(Avena sativa*) and **cucumber** *(Cucumis sativus*) pre-germinated for 2 days and planted in petri dishes.	Technical grade picloram at 1 or 10 ppm for 2 days.	50% or greater inhibition of root growth	Kratky and Warren 1971

A3 Table 4: Other Toxicity Studies

Species	Exposure	Response	Reference
Five seeds each of **sorghum** *(Sorghum vulgare*) and **oat** *(Avena sativa*), pre-germinated for 2 days and planted 2-cm deep in a waxed paper cup	Technical grade picloram at 1 or 10 ppm for 4 days	50% or greater inhibition of shoot growth	Kratky and Warren 1971

A3 Table 5: Field Studies

Application	Observations	Reference
Picloram (potassium salt) applied at 0.01, 0.05, 0.10, or 0.25 lb/acre directly to cotton plants using a hand-held sprayer. Cotton plants were designated in 30-ft segments, separated by an untreated row. Treatments took place in late July and mid-August near Chillcothe in north central Texas in 1987 and 1988.	Foliar application of 0.05 lb/acre to cotton in the pre-bloom growth stage, significantly reduced yields; yield reductions were 35 to 45% reduced with post-bloom treatments of 0.10 lb/acre or more. Staple length was not greatly reduced by picloram pre-bloom applications but was reduced by post-bloom treatments. Working Note: Application rates appear to be in a.i./acre. Thus, the NOAEC for cotton appears to be 0.043 lb a.e./acre (≈48 g/ha) with an LOAEC of 0.086 lb a.e./acre (96 g a.e./ha).	Jacoby et al. 1990
Three plots in North Carolina treated with 0.025, 0.25, 2.5 and 25.0 g a.i./ha picloram (Tordon 22K) in 1980 only. Contaminated fertilizer was applied at 025 and 0.25 g a.i./ha.; Tobacco was transplanted annually through 1982 at two locations and through 1984 at one location.	Young tobacco plants destroyed by 25 g/ha picloram applied by broadcast pre-plant incorporated spray. At two sites in 1980, significant yield reductions of flue-cured tobacco were caused by 2.5 g/ha applied by broadcast and 0.25 g/ha applied as a band of contaminated fertilizer 4-5 days after transplanting. Adverse signs of treatment from 24.0 g/ha were evident at two/three locations in 1982 and at one location in 1984; however, significant yield reductions were not observed at any of the three locations in 1981 or thereafter. Tobacco quality was somewhat less affected than yield. Working Note: For broadcast applications, the NOAEC is 0.25 g a.i./ha (≈0.0002 lb a.e./acre) with a LOAEL of 2.5 g a.i./ha (≈0.002 lb a.e./acre). For applications via contaminated fertilizer, the NOAEL/LOAELs are a factor of 10 lower.	Sheets and Harrell 1986

Appendix 4: Toxicity to fish.

Notes on Nomenclature:

The term *TLm* designates the Median Tolerance limit, which is functionally equivalent to the LC_{50}. This appendix uses the terms specified in the reference.

Rainbow trout are designated as *Salmo gairdneri* in the older literature and *Oncorhynchus mykiss* in the more recent literature. The designations used in the this appendix are the designations used in the specified reference.

A4 Table 1: Acute Toxicity

Species	Exposure	Response	Reference
Bluegill sunfish *(Lepomis macrochirus*) NOS	Tordon (NOS). Temperature not specified in publication.	24-hour TLm = 43 ppm (a.e.) 48-hour TLm = 43 ppm (a.e.)	Hughes and Davis 1964
Bluegill sunfish (*Lepomis macrochirus*), 1.93 ± 0.19 cm, 0.16 ± 0.05 g	Technical picloram acid (93.8% a.i.) under static conditions. Nominal concentrations: water control, acetone control, 6, 9, 14, 21, 34, or 50 mg/L	96-hour LC_{50} = 44.5 mg a.e./L (95%f CI = 33.9-88.2 mg a.e./L) *Corrected for compound purity*: 96-hour LC_{50} = 41.7 mg a.e./L	Mayes and Dill 1984
Bluegill sunfish (*Lepomis macrochirus*), 2.06 ± 0.17 cm, 0.17 ± 0.05 g	Picloram potassium salt (43.5% a.i) under static conditions. Nominal concentrations: control, 25, 40, 63, 100, 158, or 250 mg/L	96-hour LC_{50} = 137 mg a.i./L (95%f CI = 114-166 mg a.i./L) *Acid equivalent*: 96-hour LC_{50} = 51.4 mg a.e./L Note: Based on above acid assay, the ratio of LC_{50}s for the K-salt to the acid is ≈1.23.	Mayes and Dill 1984
Bluegill sunfish (*Lepomis macrochirus*), avg. wt: 1.2 g (range 1.0-1.3 g) n=20	Tordon (91% pure); 12.5 mg/L *as formulated was made into the potassium salt for the stock used in the bioassays*, 80°F (26.7°C). Working Note: LC_{50}s appear to be reported as a.i.	As reported: 24-hour TL_m = 69 mg/L 48-hour TL_m = 69 mg/L 72-hour TL_m = 45 mg/L 96-hour TL_m = 24 mg/L Acid equivalent: 96-hour LC_{50} = 20.7 mg a.e./L	Alexander and Batchelder 1965 MRID 00041475 Results published by Mayes and Oliver 1986
Bluegill sunfish (*Lepomis macrochirus*), fingerlings, 0.9 g	Picloram, technical material (90-100%) Temp = 22°C	96-hour LC_{50} = 23.0 mg a.e./L (95% CI = 17.8-29.9 mg a.e./L)	Johnson and Finley 1980

Appendix 4: Toxicity to fish *(continued)*

A4 Table 1: Acute Toxicity			
Species	**Exposure**	**Response**	**Reference**
Bluegill sunfish (*Lepomis macrochirus*), fingerlings, 0.9 g	Picloram potassium salt (24.9%) Temp = 18°C Working Note: LC_{50}s appear to be reported as a.i.	As reported: 96-hour LC_{50} = 26.8 mg/L (95% CI = 22.9-31.3 mg/L) Acid equivalent: 96-hour LC_{50} = 23.2 mg a.e./L Note: Based on above acid assay, the ratio of LC_{50}s for the K-salt to the acid is ≈1.009.	Johnson and Finley 1980
Bluegill sunfish (*Lepomis macrochirus*), mean weight = 0.13 g	Technical grade picloram (93.8% a.e.)	96-hour LC_{50} = 21.9 mg a.e./L (95% CI = 18.0-27.5 mg/L)	Mayes and Oliver 1986
Bluegill sunfish (*Lepomis macrochirus*), mean weight = 0.13 g, 25 fish/concentration	Technical grade picloram (92.9% a.e.), 10 to 37 mg/L.	96-hour LC_{50} = 14.5 mg a.e./L (95% CI = 13.7-15.3 mg/L) 20% mortality at lowest concentration.	Batchelder 1974 Also summarized in Mayes and Oliver 1986
Channel catfish (*Ictalurus punctatus*), avg wt: 1.9 g (range 1.8-2.0 g) n=20	Tordon (91% pure); 12.5 mg/L as formulated was made into the potassium salt for the stock used in the bioassays, 80°F (26.7°C). Working Note: LC_{50}s appear to be reported as a.i.	24-hour TL_m = 41 mg/L 48-hour TL_m = 24 mg/L 72-hour TL_m = 16 mg/L 96-hour TL_m = 14 mg/L *Acid Equivalent adjusted for purity*: 96-h LC50: 11 mg a.e./L	Alexander and Batchelder 1965 MRID 00041475 Results published by Mayes and Oliver 1986
Channel catfish (I*ctalurus punctatus*), fingerlings, 1.0 g	Picloram, technical material (90-100%) Temp = 22°C	96-hour LC_{50} = 15.5 mg/L (95% CI = 11.4-20.9 mg/L)	Johnson and Finley 1980
Channel catfish (*Ictalurus punctatus*), fingerlings, 1.4 g	Picloram, technical material (90-100%) Temp = 18°C	96-hour LC_{50} = 6.3 mg/L (95% CI = 3.6-11.1 mg/L)	Johnson and Finley 1980
Channel catfish (*Ictalurus punctatus*), yolk sac fry, swim-up fry, or advanced fry (weight = 0.2-1.2 g)	Picloram (NOS)	96-hour LC_{50} values: Yolk sac fry = 5.8 mg/L Swim up fry = 6.8 mg/L Advanced fry = 16 mg/L	Mayer and Ellersieck 1986
Fathead minnow (*Pimephales promelas*), 1.95 ± 0.37 cm, 0.12 ± 0.06 g	Picloram potassium salt (43.5% a.i) under static conditions. Nominal concentrations: control, 25, 40, 63, 100, 158, or 251 mg/L	96-hour LC_{50} = 201 mg a.i.//L (95%f CI = 161-288 mg/L) *Acid equivalent*: 96-hour LC_{50} = 75 mg a.e./L	Mayes and Dill 1984

Appendix 4: Toxicity to fish *(continued)*

A4 Table 1: Acute Toxicity			
Species	**Exposure**	**Response**	**Reference**
Fathead minnow (*Pimephales promelas*), 2.13 ± 0.31 cm, 0.15 ± 0.06 g	Technical picloram acid (93.8% a.i.) under static conditions. Nominal concentrations: water control, acetone control, 13, 19, 27, 39, 56, or 80 mg/L	96-hour LC_{50} = 55.3 mg a.e./L (95%f CI = 47.4-64.6 mg/L) *a.e. corrected for purity*: 96-hour LC_{50} = 52 mg a.e./L	Mayes and Dill 1984
Flagfish (*Jordanella floridae*), 4 weeks-old, 0.1 g mean wet weight at start, fasted 24-hours, 10/ concentration	Tordon 22K (containing 240 g/L as potassium salt), 25 °C Working Note: Results appear to be expressed as a.i.	48-hour = 50% mortality not attained in highest concentration used. 96-hour LC_{50} = 26.1 mg/L 10-day threshold LC_{50} = 12.3 mg/ (no threshold attained) (95% CI = 9.84-15.4 mg/L) LC_{50} slope = 9.48 *Acid Equivalent:* 96-hour LC_{50} = 22.5 mg a.e./L	Fogels and Sprague 1977
Harlequin fish *(Rasbora heteromorpha),* 1.3 to 3 cm long, 10/group	Tordon 22K, 24% a.e.	24-hour LC_{50}= 66 mg/L Working Note: Units of LC_{50}s are not clear – i.e., formulation, a.i., or a.e. **This study is excluded from analysis.**	Alabaster 1969 **EXCLUDED STUDY. See Section 4.1.3.1.1.1**
Mosquito fish (*Gambusia affinis*), 20/test concentration	Tordon 50-D (4-amino-3,4,6-trichloropicolinic acid), no aeration. 21 to 22 °C Working Note: Tordon 50-D appears to be an Australian formulation containing picloram and 2,4-D. The test material, however, is not identified as a mixture in this publication. Units not clear.	24-hour TL_{50} = 133 mg/L 48-hour TL_{50} = 125 mg/L 96-hour TL_{50} = 120 mg/L Working Note: Units of LC_{50}s are not clear – i.e., formulation, a.i., or a.e – and the agent used is not clear. **This study is excluded from analysis.**	Johnson 1978 **EXCLUDED STUDY. See Section 4.1.3.1.1.1**

Appendix 4: Toxicity to fish *(continued)*

A4 Table 1: Acute Toxicity

Species	Exposure	Response	Reference
Salmon, Coho (*Oncorhynchus kisutch*), yearling, n=20	Tordon 22K (21.5% picloram a.e. as the potassium salt) Working Note: Not clear if results are expressed as formulation, a.i., or a.e.	24-hour LC_{50} = 17.5 mg/L No apparent effect of picloram on the Na, K)-stimulated ATPase activity of the gills. Histopathological examination of fish exposed to nominal concentration of 5 mg/L (measured concentration of 10.54-11.84) Tordon 22K (n=4) for 144 hours revealed abnormal liver and gill tissue. Controls (n=3) had some abnormal liver and gill tissue, but not as marked as the treated fish. When survivors of the Tordon 22K exposure were placed in seawater, a 25% mortality occurred in the group previously exposed to 0.25 mg/L, which the investigators cannot explain.	Lorz et al. 1979 MRID 00129075
Salmon, Coho, (*Oncorhynchus kisutch*), yearling	Tordon 22K (picloram) under static conditions Working Note: Not clear if results are expressed as formulation, a.i., or a.e. Copy of study has poor legibility.	24-hour LC_{50} = 17.5 mg/L No apparent effect on the (Na, K)-stimulated ATPase activity of the gills.	Lorz et al. 1979
Sheepshead minnow, (*Cyprinodon variegatus*), juvenile, 10/replicate (at conclusion of test, control fish had mean total length of 28 mm and an average wet weight of 0.39g).	Tordon 22K (24.1 % picloram potassium salt; 20.8% a.e.) in filtered natural seawater under static conditions. Mean measured concentrations: 0 or 131 mg/L for 96 hours. Working Note: Results appear to be in units of formulation.	No mortality or sublethal effects observed in controls. 96-hour LC_{50}>131 mg/L (HCT) 96-hour NOEC = 131 mg/L *Acid Equivalent:* 96-hour NOEC = 27.2 mg a.i./L	Boeri et al. 1995b MRID 43959502
Trout, Bull (*Salvelinus confluentus*) , 0.55 ± 0.11 g, 42 ± 3 mm, n=20, fasted 48 hours prior to testing	Picloram salt (21.1% a.i. free acid) at concentrations of 14, 27, 54, 109, or 218 mg/L under static conditions, 8 °C Working Note: The test material appears to have contained 21.1% a.e. – i.e., author refer to the acid as the active ingredient. All results appear to be expressed as a.e.	No mortality among controls. 96-hour LC_{50} = 24 mg a.e./L (95% CI = 10-68 mg/L)* 96-hour LC_{10} = 16 mg a.e./L (95% CI = 13-26 mg a.e./L)* *Author Note in publication: No partial mortalities were observed. The next lower and higher exposure concentrations were used as conservative estimates of the 95% Cl.	Fairchild et al. 2007

A4 Table 1: Acute Toxicity

Species	Exposure	Response	Reference
Trout, Cutthroat *(Salmo clarki)*, 0.3-1.6 g	Technical grade picloram (90% a.i.) under static conditions for 96 hours. See tables to right for temperature and other conditions. Working Note: Authors appear to express results as a.e.	Temperature Effects (pH 7.2, soft water) Temp (°C) / 96-h LC_{50}: 5°C / 6.5; 10°C / 5.0; 15°C / 4.1 pH Effect (10 °C, soft water) pH / 96-h LC_{50}: pH 6.5 / 8.6; pH 7.5 / 4.7; pH 8.5 / 4.15 Water Hardness Effect (10 °C, pH 7.8) Water / 96-h LC_{50}: Soft / 3.7; Hard / 3.45; Very hard / 3.45	Woodward 1976
Trout, Cutthroat (*Salmo clarki*), fingerlings, 0.4 g	Picloram, technical material (90-100%) Temp = 12°C Working Note: Authors appear to express results as a.e.	96-hour LC_{50} = 4.8 mg/L (95% CI = 3.8-6.2 mg/L)	Johnson and Finley 1980
Trout, Cutthroat *(Salmo clarki)*, fingerlings, 0.4-0.8 g	Technical grade picloram (90% a.i.) for 96 hours. Temperature not specified. Working Note: This investigator typically would test trout at 10 °C. Results appear to be expressed as a.e.	Two different assays for picloram are reported (Table 1 of study). 96-hour LC_{50} = 4.5 mg a.e./L (95% CI = 3.8-5.3 mg/L) 96-hour LC_{50} = 3.9 mg a.e./L (95% CI = 3.2-4.8 mg/L)	Woodward 1982
Trout, Cutthroat (*Salmo clarki*), fingerlings, 0.9 g	Picloram potassium salt (24.9%) Temp = 10°C. Working Note: Results appear to be expressed as a.e.	96-hour LC_{50} = 1.5 mg/L (95% CI = 0.8-3.0 mg/L)	Johnson and Finley 1980
Trout, Cutthroat (*Salmo clarki*), NOS	Picloram (NOS) either fresh or aged 7 days under static conditions. Working Note: Results appear to be expressed as a.e.	96-hour LC_{50} = 5.8 mg/L (*fresh solution*) 96-hour LC_{50} = 4.8 mg/L (*solution aged 7 days*)	Mayer and Ellersieck 1986

A4 Table 1: Acute Toxicity

Species	Exposure	Response	Reference
Trout, Lake *(Salvelinus namaycush*), 0.3-1.6 g	Technical grade picloram (90% a.i.) under static conditions for 96 hours. Working Note: Authors appear to express results as a.e.	Temperature Effects (pH 7.2, soft water) Temp (°C) | 96-h LC_{50} 5°C | 3.6 10°C | 4.25 15°C | 2.35 pH Effect (10 °C, soft water) pH | 96-h LC_{50} pH 6.5 | 4.95 pH 7.5 | 2.7 pH 8.5 | 2.05 Water Hardness Effect (10 °C, pH 7.8) pH | 96-h LC_{50} Soft | 2.15 Hard | 1.55 Very hard | 2.1	Woodward 1976
Trout, Lake (*Salvelinus namaycush*), fingerlings, 0.3 g	Picloram, technical material (90-100%) Temp = 10°C	96-hour LC_{50} = 4.3 mg a.e./L (95% CI = 4.0-4.5 mg/L)	Johnson and Finley 1980
Trout, Rainbow (*Salmo gairdneri*), yolk sac fry, swim-up fry, or advanced fry (weight = 0.2-1.2 g)	Picloram (NOS)	96-hour LC_{50} values: Yolk sac fry = 8.0 mg/L Swim up fry = 8.0 mg/L Advanced fry = 11 mg/L	Mayer and Ellersieck 1986
Trout, Rainbow (*Oncorhynchus mykiss*), 0.59 ± 0.15 g, 41 ± 4 mm, n=20, fasted 48 hours prior to testing	Picloram salt (21.1% a.i. free acid) at concentrations of 14, 27, 54, 109, or 218 mg/L under static conditions, 8 °C Working Note: The test material appears to have contained 21.1% a.e. – i.e., author refer to the acid as the active ingredient. All results appear to be expressed as a.e.	No mortality among controls 96-hour ALC_{10} = 30 mg/L (95% CI = 14-54 mg/L)* 96-hour ALC_{50} = 41 mg/L (95% CI = 14-54 mg/L)* *No partial mortalities were observed. The next lower and higher exposure concentrations were used as conservative estimates of the 95% Cl.	Fairchild et al. 2007

A4 Table 1: Acute Toxicity			
Species	**Exposure**	**Response**	**Reference**
Trout, Rainbow (*Oncorhynchus mykiss*), juvenile, NOS, 10/group	Tordon 22 K (picloram salt: 21.1% a.i. free acid) 0, 3, 6, 12, 24, or 48 mg/L under flow-through conditions for 96 hours, 8 °C Working Note: The test material appears to have contained 21.1% a.e. – i.e., author refer to the acid as the active ingredient. All results appear to be expressed as a.e.	No mortality among controls. NOEC (mortality) = 12 mg/L at 96 hours 96-hour ALC_{50} = 36 mg/L (95% CI = 33-39 mg/L: slope, 13) 100% mortality at 48 mg/L (HCT) following 96-hour exposure	Fairchild et al. 2009
Trout, Rainbow (*Salmo gairdneri*), 2.74 ± 0.18 cm, 0.22 ± 0.04 g	Technical picloram acid (93.8% a.i.) under static conditions. Nominal concentrations: water control, acetone control, 6, 9, 14, 21, 33, or 50 mg/L	96-hour LC_{50} = 19.3 mg a.e./L (95%f CI = 16.5-21.8 mg/L) *Corrected for purity*: 96-hour LC_{50} = 18 mg a.e./L	Mayes and Dill 1984
Trout, Rainbow (*Salmo gairdneri*), 2.91 ± 0.23 cm, 0.29 ± 0.08 g	Picloram potassium salt (43.5% a.i) under static conditions. Nominal concentrations: control, 15, 22, 32, 46, 68, or 100 mg/L	96-hour LC_{50} = 48 mg/L (95%f CI = 42-54 mg/L) *Acid equivalent*: 96-hour LC_{50} = 18 mg a.e./L Note: Based on above acid assay, the ratio of LC_{50}s for the K-salt to the acid is ≈1.0.	Mayes and Dill 1984
Trout, Rainbow (*Salmo gairdneri*), ave. wt: 1.8 g (range 1.7-2.1 g) n=10 per concentration	Tordon (91% pure); 12.5 mg/L as formulated was made into the potassium salt for the stock used in the bioassays. 60°F (15.6°C) Working Note: LC_{50}s appear to be reported as a.i.	24-hour TL_m = 27 mg/L 48-hour TL_m = 13 mg/L 72-hour TL_m = 13 mg/L 96-hour TL_m = 13 mg/L Acid equivalent: 96-hour LC_{50} = 11.2 mg a.e./L	Alexander and Batchelder 1965 MRID 00041475 Results also in Mayes and Oliver 1986
Trout, Rainbow (*Salmo gairdneri),* fry, 0.8 g	Picloram, technical material (90-100%) Temp = 12°C	96-hour LC_{50} = 12.5 mg a.e./L (95% CI = 9.5-16.5 mg/L)	Johnson and Finley 1980
Trout, Rainbow (*Salmo gairdneri*), mean weight = 1.75 g	Technical grade picloram (92.9% a.e.). Concentrations from 4.2 to 6.5 mg/L.	96-hour LC_{50} = 5.5 mg a.e./L (95% CI = 5.2-5.8 mg/L) 20% mortality at lowest concentration.	Batchelder 1974 Also summarized in Mayes and Oliver 1986

Appendix 4: Toxicity to fish *(continued)*

A4 Table 1: Acute Toxicity			
Species	**Exposure**	**Response**	**Reference**
Trout, Rainbow (S*almo gairdneri*),4 weeks-old, 1.2 g mean wet weight at start, fasted 24-hours, 10/ concentration	Tordon 22K (containing 240 g/L as potassium salt) `Working Note: Results appear to be expressed as a.i.`	48-hour LC_{50} = 31.0 mg/L 96-hour LC_{50} = 26.0 mg/L 10-day threshold LC_{50} = 22.2 mg/L (no threshold attained) (95% CI = 20.4-24.2 mg/L) LC_{50} slope = 1.12 (LC_{84}/LC_{50} and LC_{50}/LC_{16}) Acid Equivalent: 96-h LC_{50}: 22.3 mg a.e./L	Fogels and Sprague 1977
Zebrafish (*Brachydanio rerio*), 4 weeks-old, 0.2 g mean wet weight at start, fasted 24-hours, 10/concentration	Tordon 22K (containing 240 g/L as potassium salt)	48-hour = 50% mortality not attained in highest concentration used. 96-hour LC_{50} = 35.5 mg/L 10-day threshold LC_{50} = 35.5 mg/ (95% CI = 32.7-38.5 mg/L) LC_{50} slope = 1.10 (LC_{84}/LC_{50} and $LC_{50}/LC_{1\,6}$) Acid Equivalent: 96-h LC_{50}: 30.7 mg a.e./L	Fogels and Sprague 1977
Impurities			
Bluegill (*Lepomis macrochirus*), avg wt: 0.74g; avg length: 35.5 mm	Three samples of technical picloram containing various amounts of N’’-(3,4,5,6-tetrachloro-2-pyridinyl) guanidine, an impurity. <u>Samples</u>: Run 6-64 (91.0% picloram; 0.05% “guanidine.” Flobin 547 (89.44% picloram; 0.221% “guanidine.” Lot 623816 (92.74% picloram; 0.2500% “guanidine.” Tests performed under static conditions.	<u>Run 6-64 (0.05% guanidine)</u>: 24-hour LC_{50} = 74.9 mg/L (95% CI = 70.0-104.7 mg/L) 48-hour LC_{50} = 61.3 mg/L (95% CI = 58.2-64.7 mg/L) 72-hour LC_{50} = 54.4 mg/L (95% CI = 49.2-59.2 mg/L) 96-hour LC_{50} = 32.9 mg/L (95% CI = 23.7-58.2 mg/L) <u>Flobin 547 (0.221% guanidine)</u>: 24-hour LC50 = 30.9 mg/L (95% CI = 28.1-33.6 mg/L) 48-hour LC_{50} = 20.4 mg/L (95% CI = 13.5-32.0 mg/L) 72-hour LC_{50} = 17.6 mg/L (95% CI = 14.6-20.2 mg/L) 96-hour LC_{50} = 17.7 mg/L (95% CI = 13.5-24.0 mg/L) <u>Lot #623816 (0.2500% guanidine)</u>: 24-hour LC_{50} = 22.1 mg/L (95% CI = 20.7-23.5 mg/L) 48-hour LC_{50} = 19.4 mg/L (95% CI = 18.0-21.0 mg/L) 72-hour LC_{50} = 19.4 mg/L (95% CI = 18.0-21.0 mg/L) 96-hour LC_{50} = 19.4 mg/L (95% CI = 18.0-21.0 mg/L)	McCarty et al. 1977 MRID 00129078 Working Note: This study is cited but not discussed in U.S. EPA/OPP (1995a). This information is not reviewed in U.S. EPA/OPP (1994b).

Appendix 4: Toxicity to fish *(continued)*

A4 Table 2: Short-term Sublethal Toxicity			
Species	**Exposure**	**Response**	**Reference**
Cutthroat trout *(Salmo clarki)*, 0.9-6.3 g	0, 380, 570, 1000 or 2400 µg/technical grade picloram (90% a.i.)/L under flow-through conditions for 8 days. Exposure continued beyond 96 hours until the mortality for 4 consecutive days was less than 5%. Toxicity was determined at 96 hours and at termination of exposure.	96-hour LC_{50} = 1475 µg/L (95% CI = 1240-1760 µg/L) Terminal day LC_{50} = 1475 µg/L (95% CI = 1240-1760 µg/L)	Woodward 1976
Lake trout *(Salvelinus namaycush*), 0.9-6.3 g	0, 380, 570, 1000 or 2400 µg/technical grade picloram (90% a.i.)/L under flow-through conditions for 12 days. Exposure continued beyond 96 hours until the mortality for 4 consecutive days was less than 5%. Toxicity determined at 96 hours and at termination of exposure.	96-hour LC_{50} = 1850 µg/L (95% CI = 1630-2100 µg/L) Terminal day LC_{50} = 1300 µg/L (95% CI = 1040-1630 µg/L)	Woodward 1976
Cutthroat trout *(Salmo clarki)*, eyed eggs	Technical grade picloram (90% a.i.); stock solutions prepared in acetone on each day of exposure in flow-through diluter. 8 days Exposures were variable and based on field studies designed to mimic the occurrence of picloram in natural waters following field application. Concentrations of 0.001 to 7.9 mg/L as specified in Table 1 of study.	Picloram exposure increased fry mortality at concentrations >1300 µg/L and decreased fry growth at concentrations >610 µg/L. Exposure had no adverse effects on fry (weight, growth, mortality) at in exposure regimes in which the peak exposure did not exceed 0.29 mg a.e./L – i.e., Testing Regime E in Table 1 of study.	Woodward 1979

Appendix 4: Toxicity to fish *(continued)*

A4 Table 3: Longer-term Exposures			
Species	**Exposure**	**Response**	**Reference**
Bull trout (*Salvelinus confluentus*), juvenile, (mean weight, 0.42 ± 0.13 g; mean total length, 35.9 ± 4.7 mm), 20/concentration	**30 days** Tordon 22 K (picloram salt: 21.1% a.i. free acid) at measured concentrations of 0, 0.30, 0.60, 1.18, 2.37, or 4.75 mg/L under flow-through conditions for 30 days, 8 °C Working Note: The test material appears to have contained 21.1% a.e. – i.e., author refer to the acid as the active ingredient. All results appear to be expressed as a.e.	No mortality at any concentration. NOEC (growth) = 0.60 mg a.e./L LOEC (growth) = 1.18 mg a.e./L (26% decrease in weight, relative to controls)	Fairchild et al. 2009
Rainbow trout (O*ncorhynchus mykiss*), juvenile, (mean weight, 0.68 ± 0.10 g; mean total length, 43.4 ± 2.1 mm), 20/concentration	**30 days** Tordon 22 K (picloram salt: 21.1% a.i. free acid) at measured concentrations of 0, 0.30, 0.60, 1.18, 2.37, or 4.75 mg/L under flow-through conditions for 30 days, 8 °C Working Note: The test material appears to have contained 21.1% a.e. – i.e., author refer to the acid as the active ingredient. All results appear to be expressed as a.e.	No mortality at any concentration. NOEC (growth) = 1.18 mg a.e./L LOEC (growth) = 2.37 mg a.e./L (16% decrease in weight, relative to controls)	Fairchild et al. 2009

Appendix 4: Toxicity to fish *(continued)*

A4 Table 3: Longer-term Exposures			
Species	**Exposure**	**Response**	**Reference**
Fathead minnow, *Pimephales promelas*, embryos (approx 24-hours-old) to initiate the study, 25/replicate (four replicates/dose), on day 2 of study, all replicates were thinned down to 20 embryos/larvae.	**32 days** Picloram TIPA salt (an active ingredient in Tordon 101M. Nominal concentrations: 0, 1.6, 2.6, 4.3, 7.2, 12, or 20 mg/L for 28 days post-hatch of the controls (32 days total). Mean measured concentrations: 0, 1.60, 2.47, 4.21, 7.19, 11.9, or 20.1 mg/L	Effects on percent survival after thinning and overall percent survival were statistically significant throughout the study at the 20.1 mg/L dose level. No statistically significant effects were noted on length or dry weight at any dose level. Sublethal effects, including lethargy and pale coloration were noted sporadically during the study (10/168 total observations indicated sublethal effects); however, the appearance of the sublethal effects were not consistent or concentration-dependent. They, were, therefore, not considered to be a significant effect of the study. NOEC (all endpoints) = 7.19 mg/L LOEC = 11.9 mg/L MATC = 9.2 mg picloram TIPA/L	Weinberg et al. 1996 MRID 43959504
Lake trout *(Salvelinus namaycush*), eyed-eggs, 10-days before hatching, 25/concentration	**60 days (Egg-to-Fry)** 0, 35, 75, 240, 500, or 1000 µg/technical grade picloram (90% a.i.)/L under flow-through conditions for 60 days after hatching.	At 35 µg a.e./L, fry survival was reduced and growth was significantly inhibited ($p<0.05$); most mortality occurred during yolk sac absorption which was 4- to 5-days longer in treated fry. NOAEC: <0.035 mg a.e./L	Woodward 1976

Appendix 4: Toxicity to fish *(continued)*

A4 Table 3: Longer-term Exposures			
Species	**Exposure**	**Response**	**Reference**
Rainbow trout (*Salmo gairdneri*), embryos (10 days pre-hatch), n=30/replicate, 4 replicates/concentration	**60 days (Egg-to-Fry)** Technical grade picloram (93.8 ± 0.8% purity) Average measured concentrations: nd, 0.23 ± 0.01, 0.38 ± 0.02, 0.55 ± 0.02, 0.88 ± 0.02, 1.34 ± 0.04, or 2.02 ± 0.05 mg/L for 60 days post day-to-mean hatch. Stock solutions were prepared by mixing technical grade picloram (acid) in deionized water and adjusting the pH to 8 with potassium hydroxide	No significant concentration-related effects on percent hatch, terata (defined as scoliosis, siamese twins, and microcephalia), or time to swim-up (16 days post day-to-mean hatch). The highest test concentration (2.02 mg/L), significantly reduced larval survival (72.5% of controls) At concentrations ≥0.88 mg/L, the weight and length of larvae were significantly decreased from those of controls. The effect is described as a well defined concentration-response. NOAEC: 0.55 mg a.e./L LOAEC: 0.88 mg a.e./L (decrease growth based on length and weight) Working Note: Based on NOAECs, rainbow trout are more sensitive than fathead minnows (Weinberg et al. 1996) by a factor of 13. Based on species sensitivity distribution of acute LC_{50}s, the different in sensitivity is a factor of about 5 [62.4 ÷ 13.2 mg a.e./L ≈ 4.7].	Mayes et al. 1984 MRID 00151784 Also published in open literature as Mayes et al. 1987

Appendix 5: Toxicity to aquatic invertebrates

Note: Assays on technical grade picloram are given as mg/L. This designates mg a.e./L. The term *mg a.e./L* is used explicitly only when units of formulation or a.i. are converted to mg a.e./L.

A5 Table 1: Acute Toxicity

Species	Exposure	Response	Reference
Daphnia magna, first instar	Technical picloram acid (93.8% a.i.) under static conditions. 20±1 °C Nominal concentrations: control, 25, 35, 55, 85, 130, or 200 mg/L	48-hour LC_{50} = 50.7 mg/L (95%f CI = 44.7-57.6 mg/L) *Acid equivalent corrected for purity*: 48-hour $_{LC50}$ = 48 (41.9-54.0) mg a.e./L	Mayes and Dill 1984
Daphnia magna, first instar	Picloram potassium salt (43.5% a.i) under static conditions. 20±1 °C Nominal concentrations: control,32,46, 68, 100, 147, 213, 316, 464, or 681 mg/L	48-hour LC_{50} = 212 mg/L (95%f CI = 180-253 mg/L) *Acid equivalent*: 48-hour LC_{50} = 79 (68-95) mg a.e./L	Mayes and Dill 1984
Daphnia magna, first instar, 3 replicates, 10 daphnids per replicate per dose	Potassium picloram (88.6% a.i.), 25°C. Concentrations: 10, 18, 32, 56, 75, and 100 mg/L Test material is referenced as a *formulation* not otherwise specified.	48-hour LC_{50} = 226 mg/L (95%f CI = 120 - 1712 mg/L) Maximum response of 17% mortality at 100 mg/L. No mortality at 10, 32, and 56 mg/L. *Acid equivalent corrected for purity*: 48-hour LC_{50} = 173 (92-1310) mg a.e./L	McCarty 1977, MRID 129077 Not cited in U.S. EPA/OPP 1994b, 1995a
Daphnia magna, neonates (<24-hours-old), 30/dose group	Technical picloram (93.8 ± 0.8% pure) at 0, 12.7, 20.5, 34.5, 57, or 94.4 mg a.e./L) under static conditions for 48 hours. 20.0 °C to 20.9 °C	No mortality among controls 48-hour LC_{50} =68.3 mg/L (95% CI = 63.0-75.0 mg/L) No kill level = 34.5 mg/L Partial kill level = 57.0 mg/L 100% kill level = 94.4 mg/L Working Note: The NOAEC for mortality, 34.5 mg a.e./L is only marginally above the NOAEC 11.8 mg a.e./L for longer-term reproductive effects. See Table 2 in this appendix below	Gersich et al. 1984 MRID 00151783 Also published as Gersich et al. 1985; Mayes and Oliver 1986

A5 Table 1: Acute Toxicity

<table>
<tr><th>Species</th><th>Exposure</th><th>Response</th><th>Reference</th></tr>
<tr><td>*Daphnia similis*, <24-hours-old, 20/dose group</td><td>Tordon 24K, 20±1 °C
Nominal Concentrations: 0, 18, 32, 56, 100, and 180 mg/L.

Working Note: Tordon 24K appears to be a Brazilian formulation. Based on the product label, this contains 24% a.e. Based on the laboratory notes, the study reports concentrations as formulation.</td><td>48-hour LC_{50} =50.29 mg/L
(95% CI = 44.23-57.19 mg/L)

Acid Equivalents:
48-hour LC_{50} =12 mg a.e./L
(95% CI = 10.6-13.7 mg a.e./L)</td><td>Perina and Pedrolli 1996</td></tr>
<tr><td>Eastern oyster (*Crassostrea virginica*), larvae</td><td>Tordon 10K Pellets Brush Killer contains 11.6% picloram potassium salt (10% a.e.) at nominal concentrations of 0, 56, 100, 320, 560 or 1000 mg/L in static seawater for 48 hours. 20±1 °C</td><td>Criterion for effect was failure to develop normally to the straight-hinge stage:

48-hour EC_{50} >1000 ppm

Acid Equivalent:
>100 mg a.e./L

<u>% abnormal development:</u>
3%: 0-100 mg/L
9%: 320 mg/L
7%: 560 mg/L
11%: 1000 mg/L</td><td>Heitmuller 1975a
MRID 00111560

Results also published by Mayes and Oliver 1986</td></tr>
<tr><td>Eastern oyster (*Crassostrea virginica*), larvae</td><td>Tordon 22K Weed Killer contains 24.9% potassium picloram (21.5% a.e.) at nominal concentrations of 0, 1.0, 5.6, 10, 18, or 32 ppm in static seawater for 48 hours. 20±1 °C

Working Note: Units appear to be expressed as formulation.</td><td>Criterion for effect was failure to develop normally to the straight-hinge stage within 48 hours.

<table><tr><th>Formul-ation ppm</th><th>mg a.e./L</th><th>% Abnormal</th></tr><tr><td>0</td><td>0</td><td>3</td></tr><tr><td>1.0</td><td>0.215</td><td>3</td></tr><tr><td>5.6</td><td>1.2</td><td>3</td></tr><tr><td>10</td><td>2.15</td><td>1</td></tr><tr><td>18</td><td>3.87</td><td>4</td></tr><tr><td>32</td><td>6.88</td><td>100</td></tr></table>Note: 200 larvae assayed in each group. No significant different in any group except for the high dose group.

EC_{50}: >3.9 <6.9 mg a.e./L
[Geometric mean of above range is 5.2 mg a.e./L]</td><td>Heitmuller 1975b
MRID 00129073

Results also published by Mayes and Oliver 1986</td></tr>
</table>

Appendix 5: Toxicity to Aquatic Invertebrates *(continued)*

A5 Table 1: Acute Toxicity			
Species	**Exposure**	**Response**	**Reference**
Fiddler crab (*Uca pugilator*)	Tordon 22K Weed Killer contains 24.9% picloram as the potassium salt at nominal concentrations of 0, 320, 560, 750, 870, or 1000 mg/L in static seawater for 96 hours. 15±1 °C	Criterion for effect was complete loss of equilibrium 96-hour EC_{50} >1000 ppm Crabs exhibited no apparent effects to test concentrations ≤1000 ppm. *Acid Equivalents*: EC_{50}: > 215 mg a.e./L NOAEC: 215 mg a.e./L	Heitmuller 1975b MRID 00129073
Fiddler crab (*Uca pugilator*), 2-3 cm	Tordon 10K Pellets Brush Killer contains 11.6% picloram potassium salt (10% picloram) at nominal concentrations of 0, 320, 560, 750, 870, or 1000 mg/L in static seawater for 96 hours. 15±1 °C	Criterion for effect was immobilization or complete loss of equilibrium 96-hour EC_{50} >1000 ppm *Acid Equivalents*: 96-hour EC_{50} >100 mg a.e./L	Heitmuller 1975a MRID 00111560
Pink shrimp (*Penaeus duorarum*)	Tordon 10K Pellets Brush Killer contains 11.6% picloram potassium salt (10% picloram) at nominal concentrations of 0, 870, 1000, 1200, 1400, or 1600 mg/L in static seawater for 96 hours. 15±1 °C	96-hour LC_{50} = 1230 mg/L (95% CI = 702-2140 mg/L) NOAEC (mortality): 24 hours – 1600 mg/L 48 hours – 1200 mg/L *Acid Equivalents*: 96-hour LC_{50} = 123 mg a.e./L	Heitmuller 1975a MRID 00111560 Results published by Mayes and Oliver 1986
Pink shrimp (*Penaeus duorarum*)	Tordon 22K Weed Killer contains 24.9% picloram as the potassium salt at nominal concentrations of 0, 110, 120, 140, 160, or 180 ppm in static seawater for 96 hours. 15±1 °C	Criterion for effect was mortality: 96-hour LC_{50} = 125 ppm (95% CI = 114-138 ppm) Mortality ranged from 0% at nominal concentration of 110 ppm to 100% at nominal concentrations of 160 and 180 ppm. *Acid Equivalents*: 96-hour LC_{50} = 26.9 mg a.e./L	Heitmuller 1975b MRID 00129073 Results published by Mayes and Oliver 1986
Scud (*Gammarus fasciatus*), mature	Picloram, technical material (90-100%), 21 °C	96-hour LC_{50} = 0.027 mg /L (95% CI = 0.020-0.037 mg/L) Working Note: Cannot identify the primary source.	Johnson and Finley 1980 **EXCLUDED STUDY. See Section 4.1.3.3.1**

A5 Table 1: Acute Toxicity			
Species	**Exposure**	**Response**	**Reference**
Scud (*Gammarus lacustris*), NOS	Picloram, technical grade under static conditions, purity of compound not specified, 70 °F (21°C)	24-hour LC_{50} = 50 mg a.e./L (95% CI = 35-71 mg/L) 48-hour LC_{50} = 48 mg a.e./L (95% CI = 34-67 mg/L) 96-hour LC_{50} = 27 mg a.e./L (95% CI = 20-37 mg/L) Working Note: The above 96-h entry from Johnson and Finley (1980) [a secondary source] differs from the 96-h LC_{50} in this primary source precisely by a factor of 1000 for both the mean and 95% CI.	Sanders 1969
Scud (*Gammarus pseudolimnaeus*), 0.036g. 2 replicates of 10 organisms per replicate per dose.	Picloram acid, 18±1°C, 96 hours Nominal Concentrations: 0, 17, 28, 47, 78, and 130 mg/L. Measured Conc.: ND, 17.6, 28.9, 48.6, 81.6, and 135 mg/L.	48-h LC_{50}: 123 mg a.e./L 96-h LC_{50}: 56.6 mg a.e./L NOAEC: not defined LOAEC: 17.6 mg a.e./L (15% mortality)	Boeri et al. 2002b
Stonefly genus NOS, (*Pteronarcys*), 20-40 mm long [specified as YC2. This is clarified on p.3 as 20 to 40 mm organisms.]	Picloram, technical material (90-100%), 15 °C	96-hour LC_{50} = 0.048 mg/L (95% CI = 0.037-0.062 mg/L)	Johnson and Finley 1980 **EXCLUDED STUDY. See Section 4.1.3.3.1**
Stonefly (*Pteronarcys californica*), naiad, 30-35 mm.	Picloram, technical grade under static conditions. 15.5 °C	24-hour LC_{50} = 120 mg a.e./L (95% CI = 100-140 mg/L) 48-hour LC_{50} = 90 mg a.e./L (95% CI = 68-120 mg/L) 96-hour LC_{50} =48 mg a.e./L (95% CI = 37-62 mg/L) Working Note: Discusses standard signs of pre-lethal toxicity but no information on sublethal effects. Working Note: As with the amphipod entries above, the above 96-h entry from Johnson and Finley (1980) [a secondary source] differs from the 96-h LC_{50} in this primary source precisely by a factor of 1000 for both the mean and 95% CI.	Sanders and Cope 1968
Stonefly, (*Pteronarcella*), naiad	Picloram, technical material (90-100%), 10 °C	96-hour LC_{50} >10 mg a.e./L	Johnson and Finley 1980

A5 Table 2: Chronic toxicity

Species	Exposure	Response	Reference
Daphnia magna, neonates (<24-hours-old), 20/dose group	Technical picloram (93.8 ± 0.8% pure), 19.5-20.5 °C, Nominal concentrations: 0, 8, 12, 20, 31, 50 mg/L for 21 days. Mean measured concentrations: ND, 7.6, 11.8, 18.1, 29.6, or 49.6 mg/L Test performed for 21 days under conditions of static renewal.	Control mortality = 5% 11.8 mg a.e./L: No effects on survival, body weight, brood size, and number of offspring/adult 18.1 mg a.e./L: Significant decreases from controls in mean brood size/adult and mean total young/adult. More pronounced effects at higher concentrations. NOAEC: 11.8 mg a.e./L LOAEC: 18.1 mg a.e./L	Gersich et al. 1984 MRID 00151783 Also published as Gersich et al. 1985
Daphnia magna, neonates (<24-hours-old), 10 replicates or 1 daphnid per replicate per dose group.	Picloram acid, 20±2 °C, 21-days Nominal concentrations: 0, 3.3, 6.5, 13, 25, 50 mg/L for 21 days. Mean measured concentrations: ND, 3.56, 6.79, 13.5,25.9, and 50.3 mg/L	Control mortality = 0% NOAEC: 6.79 mg a.e./L LOAEC: 13.5 mg/L based on significant decrease in number of surviving young per female. Two higher concentrations: Delay in time to first brood, size and weight of offspring, and sublethal effects – i.e., immobilization, changes in behavior or appearance.	Boeri et al. 2002

Appendix 6: Toxicity to Aquatic Plants

A6 Table 1: Algae

Species	Exposure	Response	Reference
Anabaena flos aquae Freshwater blue-green alga.	Tordon K (analyzed at 27.9% picloram K salt; 24.1% picloram, a.e.) Nominal concentrations: 0.0, 63,130, 250, 500, or 1000 mg/L Tordon K Mean measured concentrations: ND, 54, 110, 200, 390, or 760, mg/L Tordon K Test performed under static conditions for 120 hours; cell counts made after 72, 96, and 120 hours of exposure. Tier 2 aquatic plant toxicity study.	**72 hours**: EC_{25} = 72 mg/L (95% CI 36-150 mg/L) EC_{50} = 250 mg/L (95% CI 170-380 mg/L) **96 hours**: EC_{25} = 550 mg/L (95% CI 360-850 mg/L) EC_{50} = 740 mg/L (95% CI 610-890 mg/L) **120 hours**: EC_{25} = 430 mg/L (95% CI 290-640 mg/L) EC_{50} = 590 mg/L (95% CI 470-740 mg/L) 120-hour NOEC = 390 mg/L Tordon K. *Acid Equivalents:* 120-h EC_{50}: 142 mg a.e./L NOAEC: 94 mg a.e./L	Boeri et al. 1994b MRID 43230308
Chiarella pyrenaidasa, optical density 0.11 and *Lyngbya birgei*, optical density 0.99	0.1, 1.0, or 10.0 μM picloram NOS. Concentrations correspond to about 0.24 to 24 mg a.e./L (regardless of the salt)	Picloram produced no significant difference on growth rates of algae.	Tubea et al. 1981
Chlamydomonas moewusii (Chlorophyceae, Volvocales), green alga, vegetative cells and zygospores.	Picloram (Tordon 22K, as potassium salt, 24.4%) 1.0, 2.5, 5.0, 7.5, 10.0, 15,0, 20.0, 20.0, 40.0, 50.0, 60.0, or 80.0 µM for 7 days.	80.0 µM (19.3 mg a.e./L) concentrations of picloram significantly inhibited zygospore germination, but did not inhibit growth.	Cain and Cain 1983
Chlorella vulgaris, green alga	Picloram (99% a.i.) Nominal concentrations: 0, 0.01, 0.1, 1.0, 10, or 100 mg a.i./L growth medium.	96-hour NOEC (growth) = 10 mg/L 96-hour EC_{50}: ≈100 mg/L See Table 8 of study, p. 19	Garten and Frank 1984
Chlorella vulgaris and *Chlorella pyrenoidosa*	Picloram free acid (NOS)	14-day EC_{50} for growth inhibition >160 ppm	Baarschers et al. 1988

A6 Table 1: Algae			
Species	**Exposure**	**Response**	**Reference**
Chlorella vulgaris and *Chlorella pyrenoidosa*, green algae	Decarboxy picloram (4A-TCP metabolite)	14-day EC_{50} for growth inhibition = 49 ppm (*C. vulgaris*) 14-day EC_{50} for growth inhibition =8 ppm (*C. pyrenoidosa*)	Baarschers et al. 1988
Navicula pelliculosa Freshwater diatom.	Tordon K (analyzed at 27.9% picloram K salt; 24.1% picloram, a.e.) Nominal concentrations: 0.0, 1.0, 2.0, 4.0, 8.0, or 16 mg/L Tordon K Mean measured concentrations: ND, 0.97, 1.9, 3.9, 7.7, or 17, mg/L Tordon K Test performed under static conditions for 120 hours; cell counts made after 72, 96, and 120 hours of exposure. `Working Note: The measured concentrations are clearly expressed (back calculated) in units of formulation.`	**72 hours**: EC_{25} = 0.44 mg/L (95% CI 0.044-4.5 mg/L) EC_{50} = 3.0 mg/L (95% CI 0.83-11 mg/L) **96 hours**: EC_{25} = 0.28 mg/L (95% CI 0.26-3.1 mg/L) EC_{50} = 2.7 mg/L (95% CI 0.76-9.2 mg/L) **120 hours**: EC_{25} = 1.3 mg/L (95% CI 0.42-3.7 mg/L) EC_{50} = 3.9 mg/L (95% CI 2.0-7.8 mg/L) 120-hour NOEC <0.97 mg/L Tordon K. *Acid Equivalents:* 5 day EC_{50}: 0.93 mg a.e./L NOAEC: <0.23 mg a.e./L	Boeri et al. 1994c MRID 43230302
Selenastrum capricornutum (a.k.a., *Raphidocelis subcapitata*), Green alga	Picloram (99% a.i.) Nominal concentrations: 0, 0.01, 0.1, 1.0, 10, or 100 mg a.i./L growth medium.	96-hour NOEC (growth) = 10 mg/L 96 hours EC50: ≈100 mg/L See Table 8 of study, p. 19	Garten and Frank 1984
Selenastrum capricornutum Freshwater green alga	Picloram, potassium salt, 35.2% a.i. Nominal concentrations: 0, 12.5, 25, 50, 100, or 400 mg/L for 5 days. Mean measured concentrations: ND, 13.10, 25.81, 49.06, 98.28, 202.8, or 416.4 mg/L Algal assay bottle test, Tier 2 Results appear to be expressed as a.i.	Results based on mean measured concentrations: 5-day EC_{25} = 52.6 mg/L (95% CI = 43.3-63.9 mg/L) 5-day EC_{50} = 85.5 mg/L (95% CI = 74.6-97.9 mg/L) 5 day NOEC = 13.10 mg/L Acid Equivalents: 5-day EC_{50}: 73.8 mg a.e./L **5-day NOAEC: 11.3 mg a.e./L**	Hughes 1990 MRID 41407702

A6 Table 1: Algae			
Species	**Exposure**	**Response**	**Reference**
Selenastrum capricornutum, Green alga 4- to 7-day-old cells.	16.0 g/L picloram (NOS) in both microplate and flask assays.	Flask assay: 96-hour EC_{50} = 21.7 mg/L (95% CI = 18.4-25.1 mg/L) r^2 = 0.73 Microplate assay: 96-hour EC_{50} = 22.7 mg/L (95% CI = 18.5-27.0 mg/L) r^2 = 0.56	St Laurent et al. 1992
Selenastrum capricornutum Green alga	Tordon 22K, Concentrations from 36-3,600,000 µg/L. Working Note: Concentrations appear to be expressed as a.e.	Oxygen Evolution Assay: 1-day EC_{50} = 115,000 µg/L (95% CI = 86,100-153,000 µg/L) Bottle Test: 14-day EC_{50} = 44,800 µg/L (95% CI = 36,100-54,200 µg/L)	Turbak et al. 1986
Skeletonema costatum Marine diatom	Tordon K (analyzed at 27.9% picloram K salt; 24.1% picloram, a.e.) Nominal concentrations: 0.0, 1.0, 2.0, 4.0, 8.0, 16 or 32 mg/L Tordon K Mean measured concentrations: ND, 1.7, 3.4, 6.7, 15, or 29 mg/L Tordon K Test performed under static conditions for 120 hours; cell counts made after 72, 96, and 120 hours of exposure. Working Note: The measured concentrations are clearly expressed (back calculated) in units of formulation.	**72 hours**: EC_{25} = 15 mg/L (95% CI 7.6-29 mg/L) EC_{50} = 42 mg/L (95% CI 24-74 mg/L) **96 hours**: EC_{25} = 11 mg/L (95% CI 5.7-21 mg/L) EC_{50} = 20 mg/L (95% CI 14-28 mg/L) **120 hours**: EC_{25} = 9.5 mg/L (95% CI 6.7-13 mg/L) EC_{50} = 14 mg/L (95% CI 11-17 mg/L) 120-hour NOEC = 6.7 mg/L Tordon K. *Acid Equivalents*: 5 day EC_{50}: 3.4 mg a.e./L NOAEC: 1.6 mg a.e./L	Boeri et al. 1994d MRID 43230305

A6 Table 2: Macrophytes			
Species	**Exposure**	**Response**	**Reference**
Duckweed, *Lemna gibba*, 5 plants (15 fronds, 3 fronds/plant) Treatment and control groups set in triplicate.	Tordon K herbicide formulation (27.9% picloram potassium salt, ≈24.1% a.e). Nominal concentrations: 0, 0.969, 1.94, 3.88, 7.38, 15.7, 31.3, 62.6, 125, 250, or 500 mg/L. Measured concentrations: ND, 0.792, 1.50, 3.12, 6.20, 12.5, 25.7, 50.5, 103, 199, or 405 mg/L Test carried out aseptically under static conditions for 14 days. Working Note: The measured concentrations are clearly expressed (back calculated) in units of formulation.	**Endpoint: Plants**: EC_{25} = 99.4 mg/L (95% CI = 0.00-250.03 mg/L) EC_{50} = 196.2 mg/L (95% CI = 43.32-349.06) NOEC = 50.5 mg/L **Endpoint: Fronds**: 14-day EC_{25} = 105.1 mg/L (95% CI = 0.00-257.12 mg/L) 14-day EC_{50} = 198.2 mg/L (95% CI = 43.90-352.52 mg/L) 14-day NOEC = 50.5 mg/L *Acid Equivalents* 14-day EC_{50} = 47.8 mg a.e./L 14-day NOEC = 12.2 mg a.e./L	Kirk et al. 1994 MRID 43230311
Duckweed, *Lemna paucicostata*, NOS	Picloram, technical product (NOS) Nominal concentrations: 0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30, 100, 300, or 1000 ppm	Half-withered at 300 ppm Withered at 1000 ppm Working Notes: The results are difficult to compare quantitatively to above study but clearly indicates that Tordon K is more toxic than the material tested in this study.	Nishiuchi 1974
Potamogeton pectinatus L. and *Myriophyllum sibiricum* Komarov	Nominal concentrations of 0.01 or 0.1 mg/L picloram (liquid formulation containing 12 g/L of the diethanolamine salt plus the adjuvants of Tordon 202C) Working Note: Included only for completeness. Not directly relevant to this risk assessment because this formulation is not under consideration.	No effect on weight gain in plants of either species in 30 or 60 days. At 0.1 mg/L concentration, flowering of *M. sibiricum* inhibited to 34% of control rate, which was no longer significant, relative to controls, at 60 days. Occurrence of potentially lethal injuries was significantly more frequent in *M. sibiricum* at both concentrations, relative to controls, at 30 and 60 days post treatment. No treatment related mortality among *P. pectinatus*; among *M. sibiricum*, mortality was only 7 and 3% in the low and high concentrations at 60 days.	Forsyth et al. 1997

Appendix 7: Picloram, Summary of Gleams-Driver Simulations

Picloram

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

Site	Clay	Loam	Sand
Dry and Warm Location	0.000316 (0 - 0.0053)	0 (0 - 0.000054)	0 (0 - 0)
Dry and Temperate Location	0.00032 (0 - 0.0037)	0 (0 - 0.00012)	0 (0 - 0)
Dry and Cold Location	1.83E-05 (0 - 0.00201)	0 (0 - 9.50E-08)	0 (0 - 0)
Average Rainfall and Warm Location	0.00192 (0.000126 - 0.035)	2.25E-05 (2.84E-08 - 0.0029)	0 (0 - 0)
Average Rainfall and Temperate Location	0.00196 (1.71E-05 - 0.0222)	2.51E-06 (0 - 0.00097)	0 (0 - 0)
Average Rainfall and Cool Location	0.00038 (5.80E-06 - 0.0101)	5.10E-07 (0 - 0.000088)	0 (0 - 0)
Wet and Warm Location	0.00122 (0.00004 - 0.0133)	0.000007 (8.00E-09 - 0.0006)	0 (0 - 0)
Wet and Temperate Location	0.00044 (1.64E-05 - 0.0074)	2.57E-06 (1.77E-09 - 0.000165)	0 (0 - 0)
Wet and Cool Location	0.061 (0.0111 - 0.146)	0.00272 (0.000069 - 0.0181)	0 (0 - 0)
		Average of Central Values:	0.002605
		25th Percentile of Lower Bounds:	0
		Maximum Value:	0.146
		Summary of Values:	0.0026 (0 - 0.146)

Appendix 7: Picloram, Summary of Gleams-Driver Simulations (*continued*)

Picloram

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

Site	Clay	Loam	Sand
Dry and Warm Location	0.204 (0.149 - 0.277)	0.179 (0.119 - 0.227)	0.182 (0.119 - 0.261)
Dry and Temperate Location	0.203 (0.139 - 0.276)	0.176 (0.122 - 0.263)	0.176 (0.12 - 0.251)
Dry and Cold Location	0.211 (0.139 - 0.296)	0.196 (0.129 - 0.261)	0.2 (0.131 - 0.261)
Average Rainfall and Warm Location	0.25 (0.174 - 0.314)	0.223 (0.156 - 0.285)	0.199 (0.164 - 0.27)
Average Rainfall and Temperate Location	0.238 (0.178 - 0.295)	0.207 (0.153 - 0.28)	0.194 (0.144 - 0.248)
Average Rainfall and Cool Location	0.216 (0.179 - 0.293)	0.197 (0.15 - 0.25)	0.182 (0.152 - 0.23)
Wet and Warm Location	0.212 (0.189 - 0.277)	0.186 (0.172 - 0.234)	0.183 (0.168 - 0.189)
Wet and Temperate Location	0.192 (0.149 - 0.209)	0.176 (0.149 - 0.186)	0.174 (0.14 - 0.185)
Wet and Cool Location	0.191 (0.179 - 0.21)	0.182 (0.166 - 0.188)	0.173 (0.132 - 0.185)
		Average of Central Values:	0.1964
		25th Percentile of Lower Bounds:	0.1355
		Maximum Value:	0.314
		Summary of Values:	0.196 (0.1355 - 0.314)

Appendix 7: Picloram, Summary of Gleams-Driver Simulations (*continued*)

Picloram

Table 3: Concentration in Top 36 Inches of Soil (ppm)

Site	Clay	Loam	Sand
Dry and Warm Location	0.068 (0.05 - 0.092)	0.06 (0.04 - 0.076)	0.061 (0.04 - 0.087)
Dry and Temperate Location	0.068 (0.046 - 0.092)	0.059 (0.041 - 0.088)	0.059 (0.04 - 0.085)
Dry and Cold Location	0.07 (0.046 - 0.099)	0.066 (0.043 - 0.088)	0.069 (0.044 - 0.087)
Average Rainfall and Warm Location	0.087 (0.059 - 0.108)	0.077 (0.054 - 0.098)	0.075 (0.058 - 0.098)
Average Rainfall and Temperate Location	0.082 (0.059 - 0.101)	0.07 (0.051 - 0.098)	0.076 (0.053 - 0.096)
Average Rainfall and Cool Location	0.081 (0.06 - 0.103)	0.076 (0.051 - 0.095)	0.071 (0.056 - 0.095)
Wet and Warm Location	0.088 (0.066 - 0.109)	0.077 (0.059 - 0.097)	0.067 (0.057 - 0.086)
Wet and Temperate Location	0.069 (0.053 - 0.095)	0.061 (0.051 - 0.08)	0.058 (0.047 - 0.062)
Wet and Cool Location	0.071 (0.061 - 0.09)	0.064 (0.061 - 0.085)	0.061 (0.06 - 0.064)
		Average of Central Values:	0.07
		25th Percentile of Lower Bounds:	0.046
		Maximum Value:	0.109
		Summary of Values:	0.07 (0.046 - 0.109)

Appendix 7: Picloram, Summary of Gleams-Driver Simulations (*continued*)

Picloram

Table 4: Maximum Penetration into Soil Column (inches)

Site	Clay	Loam	Sand
Dry and Warm Location	12 (4 - 24)	8 (4 - 24)	12 (4 - 24)
Dry and Temperate Location	18 (8 - 36)	18 (8 - 36)	18 (8 - 36)
Dry and Cold Location	18 (12 - 30)	18 (12 - 24)	18 (12 - 30)
Average Rainfall and Warm Location	30 (18 - 36)	30 (18 - 36)	36 (24 - 36)
Average Rainfall and Temperate Location	36 (24 - 36)	30 (18 - 36)	36 (24 - 36)
Average Rainfall and Cool Location	36 (30 - 36)	36 (36 - 36)	36 (36 - 36)
Wet and Warm Location	36 (36 - 36)	36 (36 - 36)	36 (36 - 36)
Wet and Temperate Location	36 (36 - 36)	36 (36 - 36)	36 (36 - 36)
Wet and Cool Location	36 (36 - 36)	36 (36 - 36)	36 (36 - 36)
		Average of Central Values:	28.5
		25th Percentile of Lower Bounds:	12
		Maximum Value:	36
		Summary of Values:	28.5 (12 - 36)

Appendix 7: Picloram, Summary of Gleams-Driver Simulations (*continued*)

Picloram

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

Site	Clay	Loam	Sand
Dry and Warm Location	1.11	0	0
	(0 - 14.2)	(0 - 0.17)	(0 - 0)
Dry and Temperate	0.7	0	0
Location	(0 - 10)	(0 - 0.4)	(0 - 7.4)
Dry and Cold Location	0.07	0	0
	(0 - 6.4)	(0 - 0.0004)	(0 - 0)
Average Rainfall and	4.4	0.07	0
Warm Location	(0.18 - 47)	(0.00004 - 20.9)	(0 - 141)
Average Rainfall and	5.4	0.029	0
Temperate Location	(0.024 - 36)	(0 - 2.51)	(0 - 98)
Average Rainfall and Cool	2.49	1	19
Location	(0.06 - 25.5)	(0.004 - 30.3)	(0.6 - 113)
Wet and Warm Location	7.6	13.3	59
	(0.8 - 41)	(0.19 - 68)	(18.1 - 173)
Wet and Temperate	11.2	15.7	50
Location	(2.1 - 36)	(2.42 - 53)	(12.7 - 125)
Wet and Cool Location	58	30	88
	(24.9 - 93)	(9.2 - 85)	(48 - 178)
		Average of Central Values:	13.6
		25th Percentile of Lower Bounds:	0
		Maximum Value:	178
		Summary of Values:	13.6 (0 - 178)

Picloram

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

Site	Clay	Loam	Sand
Dry and Warm Location	0.004	0	0
	(0 - 0.05)	(0 - 0.0005)	(0 - 0)
Dry and Temperate	0.0024	0	0
Location	(0 - 0.04)	(0 - 0.0012)	(0 - 0.03)
Dry and Cold Location	0.00021	0	0
	(0 - 0.027)	(0 - 0.000001)	(0 - 0)
Average Rainfall and	0.018	0.0004	0
Warm Location	(0.0012 - 0.19)	(2.3E-07 - 0.08)	(0 - 1.15)
Average Rainfall and	0.019	0.00009	0
Temperate Location	(0.00026 - 0.13)	(0 - 0.015)	(0 - 0.9)
Average Rainfall and Cool	0.013	0.01	0.19
Location	(0.0005 - 0.18)	(0.000022 - 0.4)	(0.004 - 1.97)
Wet and Warm Location	0.06	0.2	1.46
	(0.005 - 0.8)	(0.0017 - 2.28)	(0.1 - 4)
Wet and Temperate	1.15	1.62	2.58
Location	(0.08 - 4)	(0.2 - 3.7)	(0.6 - 5.3)
Wet and Cool Location	1.34	2.71	4.7
	(0.4 - 4)	(0.16 - 6)	(2.47 - 7)
		Average of Central Values:	0.595
		25th Percentile of Lower Bounds:	0
		Maximum Value:	7
		Summary of Values:	0.6 (0 - 7)

Picloram

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

Site	Clay	Loam	Sand
Dry and Warm Location	0.28 (0 - 5.5)	0 (0 - 0.05)	0 (0 - 0)
Dry and Temperate Location	0.24 (0 - 3.2)	0 (0 - 0.12)	0 (0 - 3.7)
Dry and Cold Location	0.016 (0 - 1.96)	0 (0 - 0.00009)	0 (0 - 0)
Average Rainfall and Warm Location	1.49 (0.06 - 27.6)	0.03 (0.000012 - 9.8)	0 (0 - 117)
Average Rainfall and Temperate Location	1.94 (0.006 - 17.2)	0.012 (0 - 1.25)	0 (0 - 74)
Average Rainfall and Cool Location	0.9 (0.022 - 10.2)	0.5 (0.0015 - 25.4)	13.5 (0.4 - 102)
Wet and Warm Location	3.5 (0.3 - 20)	8 (0.08 - 54)	46 (11.2 - 134)
Wet and Temperate Location	7 (1.09 - 25.6)	10.2 (1.47 - 32)	34 (9.5 - 99)
Wet and Cool Location	20.4 (11.8 - 37)	24.9 (4.3 - 65)	64 (35 - 107)
		Average of Central Values:	8.77
		25th Percentile of Lower Bounds:	0
		Maximum Value:	134
		Summary of Values:	8.77 (0 - 134)

Picloram

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

Site	Clay	Loam	Sand
Dry and Warm Location	0.009	0	0
	(0 - 0.2)	(0 - 0.0015)	(0 - 0)
Dry and Temperate	0.007	0	0
Location	(0 - 0.12)	(0 - 0.004)	(0 - 0.13)
Dry and Cold Location	0.0005	0	0
	(0 - 0.06)	(0 - 2.4E-06)	(0 - 0)
Average Rainfall and	0.06	0.0017	0
Warm Location	(0.005 - 0.9)	(9.0E-07 - 0.6)	(0 - 8)
Average Rainfall and	0.08	0.0004	0
Temperate Location	(0.0007 - 0.6)	(0 - 0.06)	(0 - 3.4)
Average Rainfall and Cool	0.05	0.028	0.7
Location	(0.0012 - 0.6)	(0.00007 - 1.4)	(0.017 - 6.5)
Wet and Warm Location	0.19	0.6	5.3
	(0.013 - 1.74)	(0.004 - 5.3)	(0.7 - 12.5)
Wet and Temperate	1.5	2.25	4.1
Location	(0.12 - 5.5)	(0.31 - 5)	(1 - 8.6)
Wet and Cool Location	2.16	4.7	8.2
	(0.5 - 5.7)	(0.25 - 10.5)	(4.3 - 13.1)
		Average of Central Values:	1.11
		25th Percentile of Lower Bounds:	0
		Maximum Value:	13.1
		Summary of Values:	1.11 (0 - 13.1)

Appendix 8: Hexachlorobenzene, Summary of Gleams-Driver Simulations

Hexachlorobenzene (0.1 lb/acre)

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

Site	Clay	Loam	Sand
Dry and Warm Location	0.000208 (0 - 0.00191)	0 (0 - 0.00137)	0 (0 - 0)
Dry and Temperate Location	0.000184 (4.80E-06 - 0.00106)	6.40E-06 (0 - 0.00072)	0 (0 - 0)
Dry and Cold Location	2.32E-05 (2.10E-06 - 0.000219)	0 (0 - 0.000034)	0 (0 - 0)
Average Rainfall and Warm Location	0.0039 (0.002 - 0.0125)	0.00303 (0.00109 - 0.0108)	0 (0 - 0.00049)
Average Rainfall and Temperate Location	0.00285 (0.00091 - 0.0081)	0.00209 (0.0004 - 0.0076)	0 (0 - 0)
Average Rainfall and Cool Location	0.00141 (0.00064 - 0.0061)	0.00075 (0.000131 - 0.0047)	0 (0 - 0)
Wet and Warm Location	0.0077 (0.0039 - 0.0193)	0.0086 (0.0036 - 0.0232)	0.000171 (0 - 0.00255)
Wet and Temperate Location	0.0061 (0.00313 - 0.0166)	0.0052 (0.00264 - 0.0124)	0 (0 - 0.00078)
Wet and Cool Location	0.0076 (0.0039 - 0.0227)	0.0055 (0.00272 - 0.0186)	0 (0 - 0.000135)
		Average of Central Values:	0.002049
		25th Percentile of Lower Bounds:	0
		Maximum Value:	0.0232
		Summary of Values:	0.00205 (0 - 0.0232)

Hexachlorobenzene (0.1 lb/acre)

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

Site	Clay	Loam	Sand
Dry and Warm Location	0.193 (0.192 - 0.195)	0.183 (0.181 - 0.186)	0.187 (0.186 - 0.188)
Dry and Temperate Location	0.192 (0.19 - 0.194)	0.182 (0.179 - 0.185)	0.186 (0.184 - 0.187)
Dry and Cold Location	0.184 (0.18 - 0.193)	0.173 (0.172 - 0.183)	0.18 (0.174 - 0.186)
Average Rainfall and Warm Location	0.19 (0.188 - 0.191)	0.18 (0.178 - 0.181)	0.183 (0.182 - 0.184)
Average Rainfall and Temperate Location	0.186 (0.185 - 0.187)	0.177 (0.175 - 0.177)	0.18 (0.179 - 0.181)
Average Rainfall and Cool Location	0.185 (0.182 - 0.187)	0.174 (0.173 - 0.177)	0.179 (0.176 - 0.181)
Wet and Warm Location	0.182 (0.18 - 0.183)	0.173 (0.173 - 0.174)	0.176 (0.175 - 0.178)
Wet and Temperate Location	0.183 (0.182 - 0.184)	0.174 (0.173 - 0.175)	0.178 (0.177 - 0.179)
Wet and Cool Location	0.184 (0.18 - 0.186)	0.174 (0.172 - 0.178)	0.179 (0.175 - 0.181)
		Average of Central Values:	0.1814
		25th Percentile of Lower Bounds:	0.175
		Maximum Value:	0.195
		Summary of Values:	0.181 (0.175 - 0.195)

Hexachlorobenzene (0.1 lb/acre)

Table 3: Concentration in Top 36 Inches of Soil (ppm)

Site	Clay	Loam	Sand
Dry and Warm Location	0.064 (0.064 - 0.065)	0.061 (0.06 - 0.062)	0.062 (0.062 - 0.063)
Dry and Temperate Location	0.064 (0.063 - 0.065)	0.061 (0.06 - 0.062)	0.062 (0.061 - 0.062)
Dry and Cold Location	0.061 (0.06 - 0.064)	0.058 (0.057 - 0.061)	0.06 (0.058 - 0.062)
Average Rainfall and Warm Location	0.063 (0.063 - 0.064)	0.06 (0.059 - 0.06)	0.061 (0.061 - 0.061)
Average Rainfall and Temperate Location	0.062 (0.062 - 0.062)	0.059 (0.058 - 0.059)	0.06 (0.06 - 0.06)
Average Rainfall and Cool Location	0.062 (0.061 - 0.062)	0.058 (0.058 - 0.059)	0.06 (0.059 - 0.06)
Wet and Warm Location	0.061 (0.06 - 0.061)	0.058 (0.058 - 0.058)	0.059 (0.058 - 0.059)
Wet and Temperate Location	0.061 (0.061 - 0.061)	0.058 (0.058 - 0.058)	0.059 (0.059 - 0.06)
Wet and Cool Location	0.061 (0.06 - 0.062)	0.058 (0.057 - 0.059)	0.06 (0.058 - 0.06)
		Average of Central Values:	0.0605
		25th Percentile of Lower Bounds:	0.058
		Maximum Value:	0.065
		Summary of Values:	0.06 (0.058 - 0.065)

Hexachlorobenzene (0.1 lb/acre)

Table 4: Maximum Penetration into Soil Column (inches)

Site	Clay	Loam	Sand
Dry and Warm Location	1 (1 - 6.83)	1 (1 - 6.83)	1 (1 - 6.83)
Dry and Temperate Location	1 (1 - 6.83)	1 (1 - 6.83)	1 (1 - 6.83)
Dry and Cold Location	1 (1 - 6.83)	1 (1 - 1)	1 (1 - 6.83)
Average Rainfall and Warm Location	1 (1 - 6.83)	1 (1 - 6.83)	6.83 (1 - 6.83)
Average Rainfall and Temperate Location	1 (1 - 6.83)	1 (1 - 6.83)	6.83 (1 - 6.83)
Average Rainfall and Cool Location	1 (1 - 6.83)	1 (1 - 6.83)	6.83 (1 - 6.83)
Wet and Warm Location	1 (1 - 6.83)	6.83 (1 - 6.83)	6.83 (6.83 - 12.7)
Wet and Temperate Location	1 (1 - 6.83)	1 (1 - 6.83)	6.83 (6.83 - 12.7)
Wet and Cool Location	1 (1 - 6.83)	6.83 (1 - 6.83)	6.83 (6.83 - 12.7)
		Average of Central Values:	2.73
		25th Percentile of Lower Bounds:	1
		Maximum Value:	12.7
		Summary of Values:	2.73 (1 - 12.7)

Hexachlorobenzene (0.1 lb/acre)

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

Site	Clay	Loam	Sand
Dry and Warm Location	0.11	0	0
	(0 - 2.31)	(0 - 1.51)	(0 - 0)
Dry and Temperate	0.1	0.004	0
Location	(0.004 - 0.6)	(0 - 0.6)	(0 - 0)
Dry and Cold Location	0.012	0	0
	(0.0009 - 0.2)	(0 - 0.03)	(0 - 0)
Average Rainfall and	2.12	1.57	0
Warm Location	(0.8 - 7.5)	(0.5 - 10.2)	(0 - 0.29)
Average Rainfall and	1.51	1.1	0
Temperate Location	(0.4 - 7.5)	(0.27 - 6.6)	(0 - 0)
Average Rainfall and Cool	0.9	0.4	0
Location	(0.27 - 3.6)	(0.07 - 3.7)	(0 - 0)
Wet and Warm Location	3.8	4	0.09
	(1.57 - 13.5)	(1.28 - 11.8)	(0 - 1.21)
Wet and Temperate	2.55	2.26	0
Location	(1.14 - 8.7)	(1.05 - 8.6)	(0 - 0.3)
Wet and Cool Location	3.2	2.93	0
	(1.67 - 13.1)	(1 - 11.7)	(0 - 0.1)
		Average of Central Values:	0.987
		25th Percentile of Lower Bounds:	0
		Maximum Value:	13.5
		Summary of Values:	0.99 (0 - 13.5)

Hexachlorobenzene (0.1 lb/acre)

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

Site	Clay	Loam	Sand
Dry and Warm Location	0.004 (0 - 0.04)	0 (0 - 0.023)	0 (0 - 0)
Dry and Temperate Location	0.0026 (0.000028 - 0.017)	0.00007 (0 - 0.013)	0 (0 - 0)
Dry and Cold Location	0.0005 (0.00004 - 0.005)	0 (0 - 0.0005)	0 (0 - 0)
Average Rainfall and Warm Location	0.09 (0.05 - 0.27)	0.07 (0.028 - 0.21)	0 (0 - 0.007)
Average Rainfall and Temperate Location	0.07 (0.027 - 0.2)	0.04 (0.009 - 0.15)	0 (0 - 0)
Average Rainfall and Cool Location	0.04 (0.017 - 0.12)	0.016 (0.0025 - 0.08)	0 (0 - 0)
Wet and Warm Location	0.2 (0.12 - 0.5)	0.19 (0.1 - 0.4)	0.002 (0 - 0.03)
Wet and Temperate Location	0.14 (0.08 - 0.3)	0.11 (0.06 - 0.23)	0 (0 - 0.006)
Wet and Cool Location	0.15 (0.08 - 0.5)	0.11 (0.05 - 0.31)	0 (0 - 0.0016)
		Average of Central Values:	0.0457
		25th Percentile of Lower Bounds:	0
		Maximum Value:	0.5
		Summary of Values:	0.046 (0 - 0.5)

Hexachlorobenzene (0.1 lb/acre)

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

Site	Clay	Loam	Sand
Dry and Warm Location	0.07 (0 - 0.6)	0 (0 - 0.5)	0 (0 - 0)
Dry and Temperate Location	0.04 (0.0004 - 0.27)	0.0015 (0 - 0.23)	0 (0 - 0)
Dry and Cold Location	0.008 (0.0005 - 0.09)	0 (0 - 0.009)	0 (0 - 0)
Average Rainfall and Warm Location	1.83 (0.7 - 5.1)	1.23 (0.4 - 4.2)	0 (0 - 0.08)
Average Rainfall and Temperate Location	1.34 (0.5 - 5)	0.8 (0.17 - 2.83)	0 (0 - 0)
Average Rainfall and Cool Location	0.7 (0.3 - 2.54)	0.29 (0.04 - 1.5)	0 (0 - 0)
Wet and Warm Location	1.02 (0.4 - 3.5)	0.9 (0.4 - 2.32)	0.008 (0 - 0.11)
Wet and Temperate Location	0.5 (0.25 - 1.42)	0.3 (0.15 - 1.01)	0 (0 - 0.024)
Wet and Cool Location	0.9 (0.4 - 2.61)	0.7 (0.26 - 1.84)	0 (0 - 0.011)
		Average of Central Values:	0.394
		25th Percentile of Lower Bounds:	0
		Maximum Value:	5.1
		Summary of Values:	0.39 (0 - 5.1)

Hexachlorobenzene (0.1 lb/acre)

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

Site	Clay	Loam	Sand
Dry and Warm Location	0.005 (0 - 0.05)	0 (0 - 0.04)	0 (0 - 0)
Dry and Temperate Location	0.004 (0.000008 - 0.026)	0.000022 (0 - 0.021)	0 (0 - 0)
Dry and Cold Location	0.0005 (0.00004 - 0.008)	0 (0 - 0.0006)	0 (0 - 0)
Average Rainfall and Warm Location	0.15 (0.07 - 0.4)	0.1 (0.03 - 0.3)	0 (0 - 0.009)
Average Rainfall and Temperate Location	0.11 (0.05 - 0.3)	0.07 (0.015 - 0.23)	0 (0 - 0)
Average Rainfall and Cool Location	0.06 (0.028 - 0.21)	0.026 (0.004 - 0.11)	0 (0 - 0)
Wet and Warm Location	0.09 (0.05 - 0.17)	0.07 (0.04 - 0.12)	0.0005 (0 - 0.007)
Wet and Temperate Location	0.04 (0.024 - 0.11)	0.026 (0.018 - 0.05)	0 (0 - 0.0009)
Wet and Cool Location	0.07 (0.04 - 0.16)	0.05 (0.025 - 0.12)	0 (0 - 0.0007)
		Average of Central Values:	0.0323
		25th Percentile of Lower Bounds:	0
		Maximum Value:	0.4
		Summary of Values:	0.032 (0 - 0.4)

Appendix 9: Reanalysis of Nolan et al. (1983, 1984)

As discussed in Section 3.1.3.2.1(First-Order Dermal Absorption), Nolan et al. (1984) conducted a pharmacokinetic study in human volunteers following oral doses of 0.5 and 5.0 mg/kg and a dermal dose of 2 mg/kg bw. In the dermal study, a dose of 2 mg/kg was applied to the back of each volunteer (over about a 1000 cm^2 area), and the volunteers were instructed to shower 12-14 hours after application. The mean body weight of the subjects during the dermal phase of the study was 79.2 kg. Thus, the average dermal loading was about 0.16 mg/cm^2 [2 mg/kg x 79.2 kg ÷ 1000 cm^2 = 0.1584 mg/ cm^2]. As discussed further in Section 3.2.2.2, this dermal loading is very similar to the upper bound dermal loadings in the accidental exposure assessments for workers developed in the current risk assessment.

Based on a standard two-compartment model (e.g., O'Flaherty 1981), the analysis of the data from the oral phase of the study, including both concentrations of picloram in blood as well as the amounts of picloram excreted in the urine yielded an estimated urinary excretion rate for picloram by humans of 0.775 day^{-1}. As illustrated in Figures 1 and 2 from Nolan et al. (1984), the model offered a satisfactory fit to both the concentrations of picloram in blood and the amounts of picloram excreted in the urine.

For the dermal phase of the study, no picloram was detected in blood. Consequently, Nolan et al. (1984, footnote to Table 1) used the kinetic parameters from the oral study with the urinary excretion data from the dermal phase of the study to estimate the first-order dermal absorption rate constant for picloram. All model parameters were estimated with DACSL (Dow Advanced Continuous Simulation Language), which appears to have been a precursor to the current commercial programs, Advanced Continuous Simulation Language (http://www.acslx.com/).

An average proportion (*P*) of 0.0018 of the applied dose was excreted by six volunteers over a 72-hour period after dosing (Nolan et al. 1984, Table 1, column 3). Among the six volunteers, the proportion of the dose excreted in the urine ranged from 0.0005 to 0.0048 with a mean of 0.0015 (Nolan et al. 1984, Table 1, last column). Based on the model optimization, the average first-order dermal absorption rate constant is given as 0.056 $hour^{-1}$ with a range of 0.031 to 0.075 $hour^{-1}$ (Nolan et al. 1984, Table 1, column 6).

The dermal absorption rates reported by Nolan et al. (1984) do not appear to be consistent with the urinary excretion data following dermal exposure. Under the assumption of first-order absorption, the proportion absorbed (*P*) at time *t* is:

Equation A9-1

$$P = 1 - e^{-kt}$$

Assuming rapid urinary excretion – i.e., a urinary excretion rate of 0.775 day^{-1} as noted in the oral phase of the Nolan et al. (1984) study – a dermal absorption rate of 0.056 $hour^{-1}$ over a 13-hour exposure period (i.e., the central point in the showering interval) the proportion absorbed would be 0.49 or about 50% [$1-e^{-0.056 \times 12} = 0.489$]. As noted above,

however, the average proportion recovered in the urine was only 0.0015 of the applied dose or 0.15%.

The reason for the discrepancy between the dermal absorption rates reported by Nolan et al. (1984) and the urinary recovery reported by Nolan et al. (1984) is not clear. One possible explanation may involve the use of a classical kinetic model for route extrapolation. In general, classical kinetic models are viewed as descriptive but are less well-suited to extrapolations, including route-to-route extrapolations, than physiologically-based pharmacokinetic models (e.g., Thompson et al. 2008). No physiologically-based pharmacokinetic model for picloram, however, has been developed and the development of such a model is beyond the scope of the current effort.

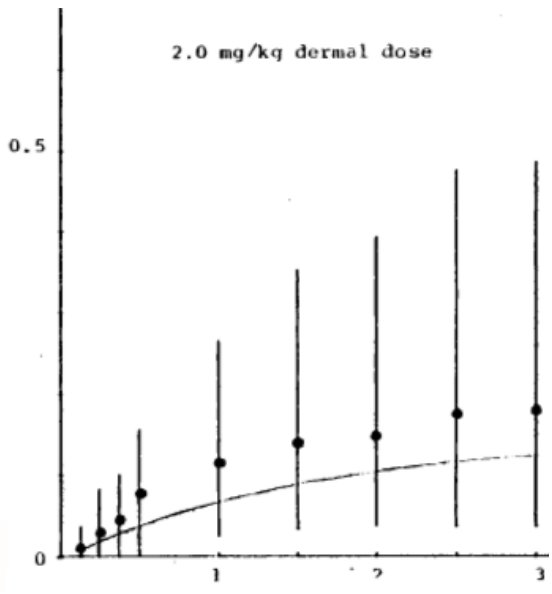


Figure A9-1: Cumulative Urinary Excretion of Picloram Following Dermal Administration from Nolan et al. (1983).

In an attempt to further explore the discrepancy between the dermal absorption rate and urinary excretion data reported by Nolan et al. (1984), additional details of the Nolan et al. (1984) data were requested from Dow AgroSciences. Dow AgroSciences provided a copy of the internal Dow report by Nolan et al. (1983) but this reported does not contain the raw data – i.e., the urinary excretion for each individual for each time period.

Table A9-1: Average Cumulative Proportion of Urinary Excretion Following Dermal Administration from Nolan et al. (1983).

Hours	Prop Excreted %	Ln Prop Remaining
3	0.0113	-0.000113
6	0.0288	-0.000288
9	0.0450	-0.000450
12	0.0775	-0.000775
24	0.1163	-0.001163
36	0.1413	-0.001413
48	0.1488	-0.001489
60	0.1763	-0.001764
72	0.1813	-0.001814

As illustrated in Figure A9-1, however, this report does contain a copy of the average urinary excretion rates with standard errors bars, similar to Figure 2 in Nolan et al. (1984). Figure A9-1 was imported into a graphics program and the data points – i.e., the average cumulative urinary excretion – were estimated. These data are summarized in Table A9-1.

A plot of the data from Table A9-1 is given in Figure A9-1.

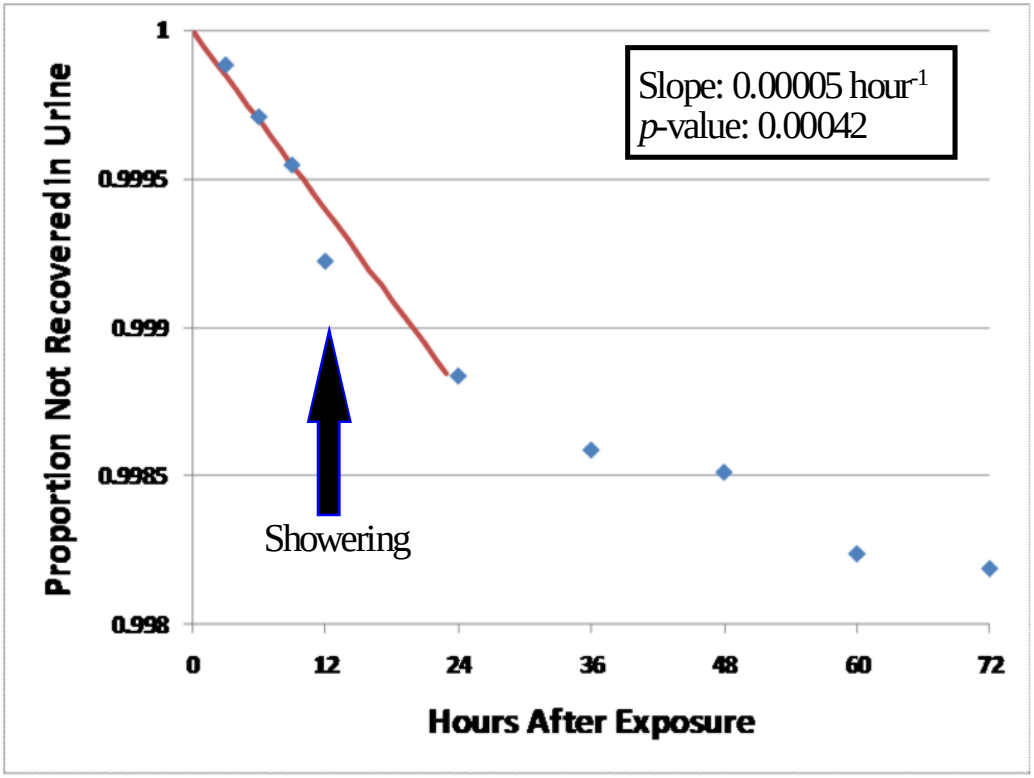


Figure A9-2: Proportion of Picloram Not Recovered in the Urine.
See Table A9-1 for data.

As illustrated in Figure A9-2, a biphasic excretion pattern, similar to that noted by Nolan et al. (1984) in the oral study, is apparent. The slower phase of excretion, however, appears to be associated with the showering interval of 12 to 14 hours. After the individuals showered and removed at least a significant portion of picloram from the surface of the skin, it is reasonable to expect that the rate of excretion of picloram will diminish. This pattern, however, is not associated with a physiologically meaningful deep compartment.

Based on the data in Table A9-1, an alternative estimate of the dermal absorption rate for picloram may be based on the flip-flop principal – i.e., under the assumption that the dermal absorption rate is much less than the excretion rate, the first-order dermal absorption rate constant may be estimated from the excretion rate (e.g., O'Flaherty 1981).

Linear regression was used to estimate the slope of natural logarithm of the proportion of picloram that was not excreted in the urine with time in hours as the independent variable. In order to avoid an underestimate of the absorption rate associated with collection intervals after showering, the analysis was restricted to the 3-hour to 24-hour

collection intervals. The regression analysis yield estimates of the slope, equivalent to the first-order dermal absorption rate constant, of 5.0 (3.0 to 7.1) x 10^{-5} $hour^{-1}$, with a correlation coefficient of 0.954 and a *p*-value for the model of 0.00043.

Appendix 10: Reanalyses of Mach (2002)

As discussed in Section 4.1.2.2.3 (Reproductive Effects in Birds), the only study appropriate for the dose-response assessment for longer-term effects in birds is the study by Mach (2002). This study has not been reviewed by the U.S. EPA/OPP but has been reviewed by the European Union (2007). This appendix focuses on the statistical aspects of Mach (2002). The impact of these analyses on the dose-response assessment is discussed in Section 4.3.2.2.2 (Dose-Response Assessment for Longer-term Exposures in Birds).

Two groups of effects are discussed in this appendix: effects on body weight and effects on survival.

Body Weights

The data on body weights in birds is summarized in Table A10-1 and illustrated in Figure A10-1. The data in Table A10-1 are taken from Appendix C13 (pp. 108-109) in Mach (2002). Note that each entry in Table A10-1 is the mean 14-Day hatchling body weight. The replicates are pens with one pair of quail per pen. The means are the average body weights of 14-Day chicks taken that hatched from Week 12 to Week 23. The weights for each week as given to the nearest gram and the mean value for each pen from Week 12 to Week 23 is expressed in Appendix C13 to the nearest gram. In the statistical reanalysis, only the pen averages over the 12 week period were used – i.e., the pen averages were not independently recalculated. The ANOVA were recalculated in EXCEL.

The analysis of variance is summarized in Table A10-2 all four exposure groups (i.e., 0 ppm, 375 ppm, 750 ppm, and 1500 ppm) and in Table A10-3 for only the three groups exposed to picloram (375 ppm, 750 ppm, and 1500 ppm). For all four groups, Mach (2002, p. 24) indicates a statistically significant effect ($F = 2.76$, calculated $F = 4.562$). These results are independently reproduced in Table A10-2. While not providing detailed statistics, Mach (2002, p. 24) indicates that there were no statistically significant differences among the three exposed groups. This is confirmed in Table A10-3.

Based on these statistical analyses, the exposures of 375 ppm, 750 ppm, and 1500 ppm would be regarded as effect levels and the 375 ppm group would be regarded as the LOEL (lowest-observed-effect-level). As summarized in Table A10-1, however, the magnitude of the average decreases in body weight are 8.55% to 8.92% and are not dose-related, at least in terms of statistical significance. Whether or not these effects should be regarded as adverse is debatable. No generally accepted guidelines for assessing the adversity of weight loss are available. As quoted in Section 4.1.2.2.3, Mach (2002) suggests that the effects are … *biologically negligible*. The assessment by the European Union (2007) is that the …*biological relevance …is not known*. No data on historical controls for 14-day old quail from the performing laboratory are available. In addition, no data are available on the food consumption of the hatchlings. The hatchlings, however, were fed control diets – i.e., no picloram. Thus, organoleptic considerations are not relevant.

Table A10-1 Effect of Picloram on 14-Day Body Weights of Quail Chicks from Mach (2002)

	Average Body Weight (g) for Day 14 Old Chicks at Different Dietary Concentrations of Picloram [1]			
	Control	**Low Dose**	**Mid Dose**	**High Dose**
	0	**375 ppm**	**750 ppm**	**1500 ppm**
	26	24	19	25
	25	24	23	25
	25		25	21
	27	25	26	23
	25	26	21	23
	26	26	28	26
	28		23	28
	35	30	25	24
	25	22	26	26
	26	26	24	25
	24	21	27	20
	29	23	24	25
	27	26	23	21
	29	24	27	26
		26	24	24
	29	23	26	25
	28	25	27	26
	23	23	24	26
	28	27	27	25
	24	20	19	24
Mean	26.79	24.50	24.40	24.40
% Decrease		8.55%	8.92%	8.92%

[1] Replicates based on average body weights from different pens from Week 12 to Week 23.

Source: Mach 2002
See Figure 14 for illustration.

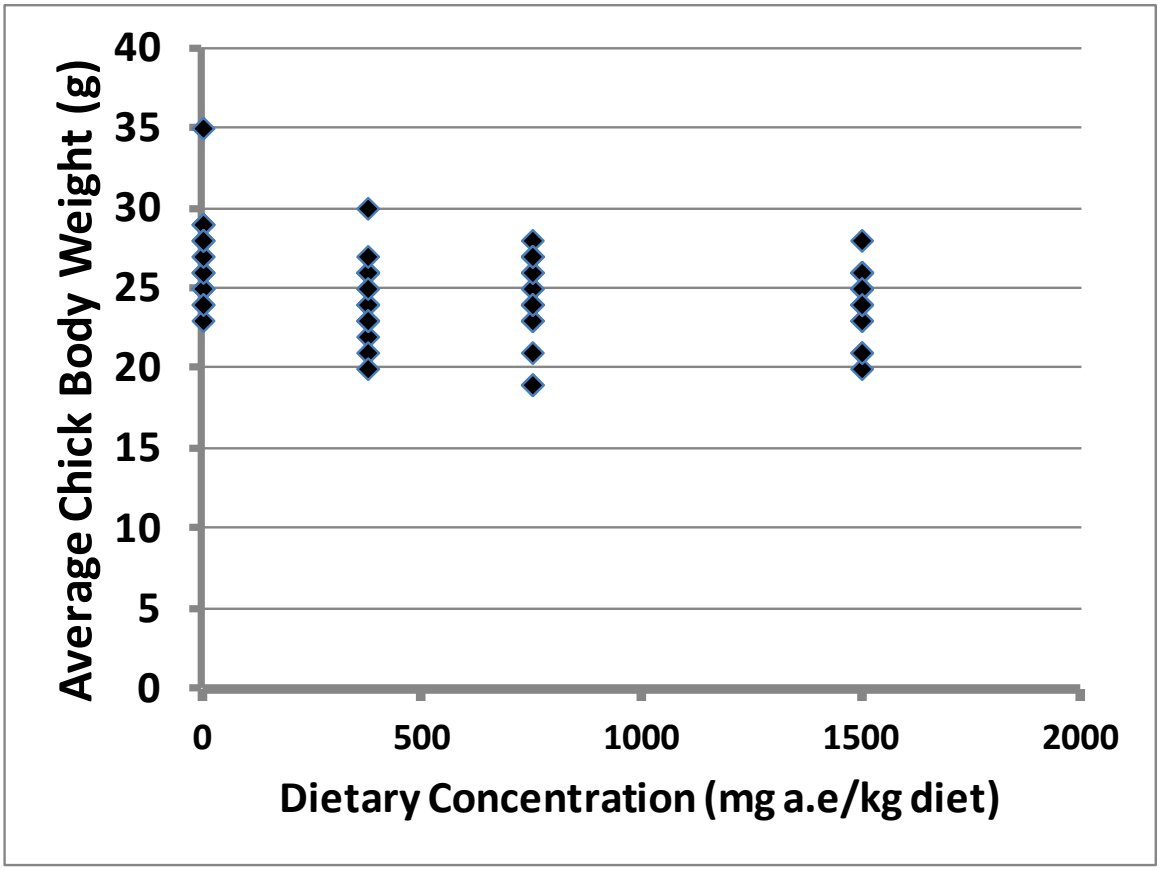


Figure A10-2: Effect of Picloram on 14-Day Body Weights of Quail Chicks from Mach (2002)

Source: Mach 2002
See Table A10-1 for data.

Table A10-2:ANOVA with All Four Groups

SUMMARY

Groups	*Count*	*Sum*	*Average*	*Variance*
Control	19	509	26.79	7.28655
Low Dose	18	441	24.50	5.558824
Mid Dose	20	488	24.40	6.568421
High Dose	20	488	24.40	3.936842

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	79.72912	3	26.57637	4.562115	0.005513	2.730019
Within Groups	425.2579	73	5.825451			
Total	504.987	76				

Table A10-3: ANOVA with only Low, Mid, and High Dose Groups

SUMMARY

Groups	*Count*	*Sum*	*Average*	*Variance*
Low Dose	18	441	24.5	5.558824
Mid Dose	20	488	24.4	6.568421
High Dose	20	488	24.4	3.936842

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	0.124138	2	0.062069	0.011608	0.988462	3.164993
Within Groups	294.1	55	5.347273			
Total	294.2241	57				

Effects on Survival

The study by Mach (2002) report a number of endpoints relating to hatchling survival in hatchlings up to the 14 day post-hatching observation period. The endpoints that might be at least remotely associated with potential decreases in survival are summarized in Table A10-4 and these data are illustrated in Figure A10-2.

As summarized in the first column of Table A10-3, five endpoints are consider: failure to hatch, abnormal hatchling, 14-day mortality in normal hatchlings, 14-day mortality per eggs laid, and mortality in all hatching. The data are taken from the data tables in Mach (2002) as specified in the first column of Table A10-4.

In his statistical analysis, Mach (2002) used analysis of variance (ANOVA) to look for statistically significant difference among the groups and, if significant differences were noted, *Bonferroni's t-test* was used to assessing significant differences with respect to the control group. *Bonferroni's t-test* appears to refer to the Chi-Square test as an approximation to the Fisher Exact test (e.g., Samuels and Witmer 2003). The reference to Bonferroni appears to refer to the standard Bonferroni correction for multiple comparisons – e.g., if a significance level of 0.05 is desired for a comparison of a control group to three other groups, the p-value is set at about 0.0166 [0.05 ÷ 3].

Based on ANOVA, Mach (2002) notes a significant effect in mortality at Day-14 in *normal* hatchings – i.e., chicks without frank abnormalities as summarized in Data Set 3 in Table A10-4). This effect, however, was discounted because no significant differences were noted between any of the dose groups with respect to the control group using the t-test.

In terms of the incidence of mortality (i.e., failure to survive) to Day-14 per number of eggs laid, Mach (2002) did not note any significant difference based on ANOVA but did note a significant ($p<0.05$) difference between the control group and the high dose group.

Mach (2002) does not discuss the discordance between ANOVA and the *Bonferroni's t-test* for either of the above two data sets. As discussed in Section 4.1.2.2.3, the European Union (2007) has reviewed the Mach (2002) study and concurred with the analysis presented by Mach (2002). There is no clear indication, however, that the review by the European Union (2007) involved a statistical reanalysis. In the review of a registrant submitted study, the U.S. EPA/OPP will typically conduct a complete statistical reanalysis, using the same or different statistical methods used by the study author(s).

All of the responses summarized in Table A10-4 are quantal – i.e., all or none effects. For quantal responses, alternative statistical methods included the Fisher Exact test for pair wise comparisons and the Cochran-Armitage test for dose-related trends (e.g., Haseman 1986). To explore the discordance between ANOVA and the *Bonferroni's t-test* noted in the Mach (2002) analyses, the Fisher Exact and Cochran-Armitage tests were applied to the five data sets summarized in Table A10-4. As summary of these results are given in the last column of this table, along with a summary of the statistical analyses by Mach (2002). The Fisher Exact test were conducted in Mathematica using

the algorithm from Abell et al. (1999). The Cochran-Armitage tests were conducted using the U.S. EPA's Benchmark Dose Software (U.S. EPA/NCEA 2011). In conducting the Cochran-Armitage test, the data must be expressed as the number of responders and the total number exposed. As summarized in Table A10-4, Mach (2002) reports data in terms of non-responders for the first four endpoints. These were converted to the number of responders as detailed in Footnote 1 to Table A10-4.

For the number of abnormal hatchlings (Data Set 2), the quantal methods yield results identical to those reported by Mach (2002) – i.e., there is no statistically significant effect. For Data Set 1 (failure of viable embryos to hatch) and Data Set 5 (mortality in all hatchlings), Mach (2002) noted no significant effects. The quantal methods, however, noted statically significant dose-response trends and, in all but one case, statistically significant differences using the Fisher Exact Test. For failure to hatch, the dose-related trend and Fisher Exact tests were all highly significant – i.e., *p*-values of ≈0.0016 to ≈6.8×10^{-15}.

As discussed in Section 4.1.2.2.3, the 14-Day mortality per total number of eggs laid (Data Set 4 in Table A10-4) was selected by the European Union (2007) as the basis for designating the NOEL and LOEL. Consistent on the results of the Bonferroni t-test in the analysis by Mach (2002), the European Union designated 750 ppm as a NOEL and 1500 ppm as a LOEL. If judged solely on statistical significance, this classification does not appear to be tenable statistically based on the quantal methods given both the significant dose-response trend ($p<0.0001$) as well as the highly significant difference based on the Fisher Exact test ($p=1.20 \times 10^{-7}$) for the 375 ppm dose group. The Bonferroni correction for multiple comparisons would have no impact on the assessment of significance. Nonetheless and as illustrated in Figure A10-2, the dose-response relationship for this endpoint is scattered. Applying the Bonferroni correction (i.e., p=0.01666…), the response in the mid-dose group (p=0.036685) would not be viewed as statistically significant.

As also illustrated in Figure A10-2, however, the dose-response assessment for failure to hatch (Data Set 1 in Table A10-2) is somewhat more compelling and is uniformly monotonic. In addition, all dose groups yield statistically significant results with the application of the Bonferroni correction.

In addition to the assessment of dose-related trends and statistical significance with respect to controls, the magnitude of the response needs to considered. The most reasonable approach to considering the magnitude of the response is Abbott's correction:

$$P = \frac{P^* - C}{1 - C} \qquad \text{(Eq. A1-1)}$$

where ***P**** is the proportion of responders in the dosed group, ***C*** is the proportion of responders in the control group, and ***P*** is the proportion of responders attributable to the treatment. As discussed by Finney (1971, p. 125), Abbott's correction is simply the standard approach for combining independent probabilities.

As discussed above, the most compelling data set in terms of dose-related trends and the Fisher Exact test is failure to hatch (Data Set 1 in Table A10-2). Applying Abbott's correction, the responses associated with treatment are about 6% for the low-dose group, 6.3% for the mid-dose group, and 16.7% for the high dose group.

As discussed in the section of this appendix dealing with weight loss, there are no generally accepted guidelines for assessing the biological significance of a given loss in body weight. In terms of estimating a functional NOAEL from dose-response data, however, the U.S. EPA will generally consider a response rate of 10% as a functional NOAEL (U.S. EPA/NCEA 2011). The use of a 10% response rate is not entirely arbitrary as this rate is typically near the limit of sensitivity of most bioassays (http://www.epa.gov/ncea/bmds/bmds_training/methodology/intro.htm). Using this criterion, the high dose group would be classified as a LOAEL and the mid-dose group would be classified as a NOAEL. This approach would be functionally identical to the approach taken by the European Union (2007) but based on a fuller analyses of the data from Mach (2002). This approach is discussed further in the dose-response assessment for chronic effects in birds (Section 4.3.2.2.2).

Table A10-4: Endpoints Related to Hatchling Survival

Data Sets [1]	Dietary Conc. (ppm)	Response[2]				Notes on Analyses [3]
		Non-Resp.	Resp.	N	% Resp.[4]	
1. Failure to Hatch, Table XV.	0	782	118	900	13.1	ANOVA: N.S.
	375	715	160	875	**18.3**	Cochran-Armitage Trend Test: p<**0.0001**
	750	746	170	916	**18.6**	Fisher Exact: Low dose group: p=0.001658 Mid dose group: p=0.0000904 High dose group: p=6.8x10^{-15}.
	1500	704	267	973	**27.6**	
2. Abnormal Hatchlings, Table XVI	0	776	6	782	0.8	ANOVA: N.S.
	375	709	6	715	0.8	Cochran-Armitage Trend Test: p=0.1597
	750	743	3	746	0.4	Other: No significant differences from control group based on Fisher Exact test.
	1500	695	9	704	1.3	
3. 14-Day Mortality in Normal Hatchlings, Table XVII	0	749	27	776	3.5	ANOVA: ***p*<0.05** No significant differences with Bonferroni's t-test.
	375	661	48	709	**6.8**	Cochran-Armitage Trend Test: ***p*=0.0228**
	750	722	20	742	2.7	Fisher Exact: Low dose group: p=0.002702 Mid dose group: p=848448 High dose group: p=0.002927
	1500	649	47	696	**6.8**	
4. 14-Day Mortality per Eggs Laid, Table XVIII	0	751	266	1017	26.2	ANOVA: N.S. t-Test**: Significant for high dose group with Bonferroni's correction.**
	375	665	388	1053	**36.8**	Cochran-Armitage Trend Test: ***p*<0.0001**
	750	723	307	1030	**29.8**	Fisher Exact: Low dose group: p=1.02x10^{-7} Mid dose group: p=0.036685 High dose group: p=3.75x10^{-13}
	1500	654	453	1107	**40.9**	
5. Mortality in All Hatchlings, Table XIX	0		31	782	4.0	ANOVA: N.S.
	375		50	715	**7.0**	Cochran-Armitage Trend Test: p=**0.0306**
	750		22	746	2.9	Fisher Exact: Low dose group: p=0.006625 Mid dose group: p=0.889751 High dose group: p=0.005397
	1500		50	704	**7.1**	

[1] Details of Endpoints
1. (Viable Embryos - Hatchlings)/Viable Embryos (Mach 2002, Table XV, p. 40).
2. Number of Abnormal Hatchlings/Total Number of Hatchlings (Mach 2002, Table XVI, p. 41).
3. (Number of Normal Hatchlings – 14-Day Survivors)/Number of Normal Hatchlings (Mach 2002, Table XVII, p. 42).
4. (Number of Normal 14-Day Survivors- Number of Number of Eggs Laid)/Number of Number of Eggs Laid (Mach 2002, Table XVIII, p. 43).
5. Dead Hatchlings/Number of Hatchlings including Hatchling Found Dead (Mach 2002, Table XIX, p. 44).
6. Number dead of 11 Week Hatching Period/Number of Normal Hatchings (Number dead from p. 23, number of normal hatchlings from Table VII, p. 42).

[2] For the first four endpoints, Mach (2002) reported data in terms of non-responders. For analyses with the trend test, the data were transformed to the number of responders. See text for discussion.

[3] ANOVA and t-tests from Mach (2002). Trend test from BMDS Version 2.2. (U.S. EPA/NCEA 2011). Fisher Exact Test implemented in Mathematica from Abell et al. (1999).

[4] Values in bold are significantly different from controls based on Fisher Exact test.

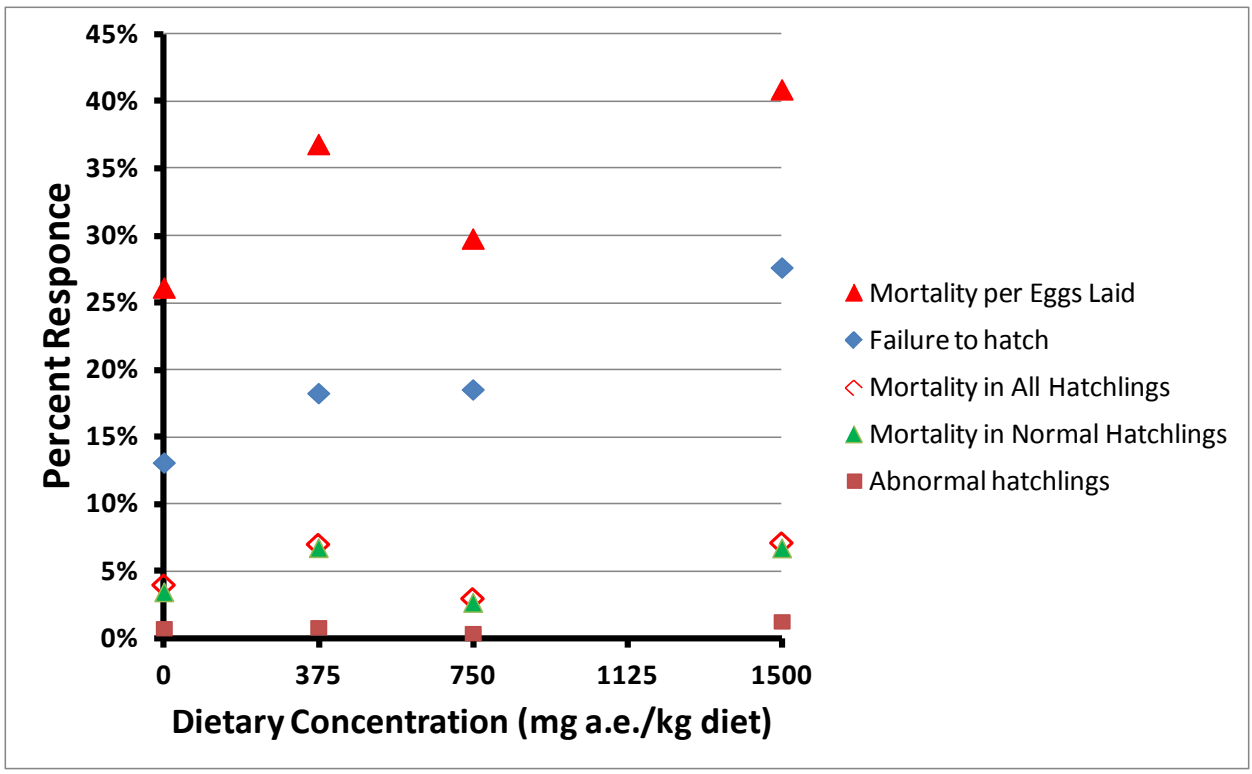


Figure A10-2: Endpoints Relating to Survival