SERA TR 04-43-17-03c

Clopyralid - Human Health and Ecological Risk Assessment - Final Report

Prepared for:

USDA, Forest Service

Forest Health Protection

GSA Contract No. GS-10F-0082F
USDA Forest Service BPA: WO-01-3187-0150
USDA Purchase Order No.: 43-1387-3-0716
Task No. 17

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December 5, 2004

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ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
a.e.	acid equivalents
AEL	adverse-effect level
a.i.	active ingredient
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
bw	body weight
CBI	confidential business information
CI	confidence interval
cm	centimeter
CNS	central nervous system
DAA	days after application
DAT	days after treatment
d.f.	degrees of freedom
EC_x	concentration causing X% inhibition of a process
EC_{25}	concentration causing 25% inhibition of a process
EC_{50}	concentration causing 50% inhibition of a process
ExToxNet	Extension Toxicology Network
F	female
FH	Forest Health
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FQPA	Food Quality Protection Act
g	gram
ha	hectare
HQ	hazard quotient
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
k_a	absorption coefficient
k_e	elimination coefficient
kg	kilogram
$K_{o/c}$	organic carbon partition coefficient
$K_{o/w}$	octanol-water partition coefficient
K_p	skin permeability coefficient
L	liter
lb	pound
LC_{50}	lethal concentration, 50% kill
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
m	meter
M	male
MMAD	mass median aerodynamic diameter
MCS	multiple chemical sensitivity

mg	milligram
mg/kg/day	milligrams of agent per kilogram of body weight per day
mL	milliliter
mM	millimole
MOS	margin of safety
MRID	Master Record Identification Number
MSDS	material safety data sheet
MW	molecular weight
NCI	National Cancer Institute
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
ppm	parts per million
RBC	red blood cells
RED	re-registration eligibility decision
RfD	reference dose
SERA	Syracuse Environmental Research Associates
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SRC	Syracuse Research Corporation
TWA	time-weighted average
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
µ	micron
▸	greater than
≥	greater than or equal to
<	less than
≤	less than or equal to
=	equal to
≃	approximately equal to
~	approximately

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

PROGRAM DESCRIPTION

Clopyralid is a selective herbicide used primarily in the control of broadleaf weeds. The Forest Service uses only a single commercial formulation of clopyralid, Transline. The Forest Service uses Transline almost exclusively in noxious weed control. Relatively minor uses include rights-of-way management, wildlife openings, and facilities maintenance. Transline is a liquid formulation of clopyralid that is manufactured by Dow AgroSciences and contains 40.9% clopyralid as the monoethanolamine salt and 59.1% inert ingredients. The identity of the inerts in Transline is proprietary with the exception of isopropyl alcohol (List 4) and a polyglycol (List 3). Technical grade clopyralid contains hexachlorobenzene and pentachlorobenzene as contaminants. Nominal or average concentrations of hexachlorobenzene are less than 2.5 ppm. Nominal or average concentrations of pentachlorobenzene are less than 0.3 ppm. The most common methods of ground application for Transline involve backpack (selective foliar) and boom spray (broadcast foliar) operations. Although Transline is registered for aerial applications, the Forest Service does not and does not intend to use Transline in aerial applications. The typical application rate in Forest Service programs is about 0.35 lb a.e./acre and the range of application rates that are likely to be used in Forest Service programs is about 0.1 to 0.5 lb a.e./acre. The total annual use of clopyralid by the Forest Service is about 2.2 percent of the agricultural use.

HUMAN HEALTH RISK ASSESSMENT

Hazard Identification **–** Although no information is available on the toxicity of clopyralid to humans, the toxicity of clopyralid has been relatively well-characterized in mammals. All of this information is contained in unpublished studies submitted to the U.S. EPA as part of the registration process for clopyralid.

Two different manufacturing processes may be used for clopyralid: the penta process and the electrochemical process. The limited available information indicates that technical grade clopyralid samples from the electrochemical process may be somewhat more toxic (LD_{50} values in the range of about 3000 mg/kg) than the penta process (LD_{50} > 5000 mg/kg). These differences, however, are not substantial and may be due to random variability. In experimental animals, a common symptom of acute, high-dose clopyralid exposure is central nervous system (CNS) depression. Clopyralid also has a low order of chronic toxicity. For chronic or subchronic exposures, no effects have been observed in laboratory mammals at doses of 50 mg/kg/day or less. At doses of 100 mg/kg/day or greater, various effects have been observed in different species and different bioassays. These effects include weight loss, changes in liver and kidney weight, thickening of epithelial tissue lining the stomach, irritation of the lungs, and decreases in red blood cell counts. These effects appear to be non-specific toxicity; they do not implicate clopyralid in any specific target-organ toxicity.

Technical grade clopyralid has been subject to several chronic bioassays for carcinogenicity and none of the bioassays have shown that clopyralid has carcinogenic potential, although technical grade clopyralid does contain low levels of hexachlorobenzene. Hexachlorobenzene has shown carcinogenic activity in three mammalian species and has been classified as a potential human

carcinogen by the U.S. EPA. Thus, this effect is considered both qualitatively and quantitatively in this risk assessment.

No studies specifically mentioning Transline, the formulation used in Forest Service programs, were located in the search of the studies submitted to U.S. EPA for product registration. Dow AgroSciences (2003) provided clarification of this issue and identified the studies submitted to U.S. EPA that were accepted as relevant to Transline. These studies do not indicate any substantial differences between Transline and clopyralid. This is consistent with the publically available information on the three inerts contained in transline, two of which are approved for use as food additives.

Exposure Assessment – Exposure assessments are conducted for both workers and members of the general public for the typical application rate of 0.35 lb/acre. The consequences of using the maximum application rate, 0.5 lb/acre, are discussed in the risk characterization. For both workers and members of the general public, the upper ranges of all acute exposures are below 2 mg/kg and most exposures are much lower. The highest modeled exposure is about 1.8 mg/kg and is associated with the consumption of contaminated water by a child following an accidental spill of clopyralid into a small pond. The upper ranges of non-accidental acute exposure scenarios for members of the general public are associated with doses from about 0.0002 to 0.2 mg/kg. The highest dose estimates for non-accidental exposure scenarios are associated with the consumption of fish. Exposures from dermal contact or drinking contaminated water (other than an accidental spill) are likely to be much lower.

General exposure assessments for workers are in the range of exposures modeled for the general public. For workers, three types of application methods are modeled: directed ground, broadcast ground, and aerial. Central estimates of exposure span a relatively narrow range: 0.005 to 0.008 mg/kg. The upper ranges of exposures are also similar for the different groups of workers: 0.03 to 0.05 mg/kg/day. All of the accidental exposure scenarios for workers involve dermal exposures. Because clopyralid is not readily absorbed across the skin, all of these accidental exposures lead to estimates of dose that are either in the range of or substantially below the general exposure estimates for workers.

Hexachlorobenzene is a contaminant in technical grade clopyralid. The concentration of hexachlorobenzene in technical grade clopyralid is about 2.5 ppm or less. For all exposure assessments detailed in this risk assessment, the concentration of 2.5 ppm is used. Hexachlorobenzene is ubiquitous and persistent in the environment. The major sources of general exposure for the public to hexachlorobenzene involve industrial emissions, proximity to hazardous waste sites, and the consumption of contaminated food. Virtually all individuals are exposed to hexachlorobenzene and virtually all individuals have detectable concentrations of hexachlorobenzene in their bodies. Based on current concentrations of hexachlorobenzene in environmental media and food, daily doses of hexachlorobenzene (i.e., background levels of exposure) are in the range of 0.000001 (1×10^{-6}) mg/kg/day. Based on the amount of hexachlorobenzene in clopyralid and the amount of clopyralid used in Forest Service programs, the use of clopyralid by the Forest Service will not substantially contribute to any wide-spread increase of ambient levels of hexachlorobenzene. Nonetheless, the potential impact of local

contamination is considered for workers as well as for several acute and chronic exposure scenarios for members of the general public. For workers, the upper range of longer term exposure scenarios result in dose estimates of about 7×10^{-8} mg/kg/day to 1×10^{-7} mg/kg/day, below general background levels of exposure by about a factor of 10 to 14. For members of the general public, the upper range of longer term exposure scenarios are about 3×10^{-11} mg/kg/day to 2×10^{-8} mg/kg/day, below general background levels of exposure by about a factor of 50 to 33,000. The upper range of estimated doses associated with acute exposure scenarios for both workers and members of the general public are about 0.0005 mg/kg/day, higher than background levels of exposure by about a factor of 500.

Dose-Response Assessment – The Office of Pesticide Programs of the U.S. EPA has derived an acute RfD of 0.75 mg/kg/day and a chronic RfD of 0.15 mg/kg/day for clopyralid. The acute RfD is based on a short-term NOAEL of 75 mg/kg/day and an uncertainty factor of 100. The chronic RfD is based on a 2-year dietary NOAEL in rats of 15 mg/kg/day and an uncertainty factor of 100. Other studies in rats, mice, and dogs have noted general decreases in body weight, increases in liver and kidney weight, as well as a thickening in some epithelial tissue. Decreases in body weight and changes in organ weight are commonly observed in chronic toxicity studies and can indicate either an adaptive or toxic response. Changes in epithelial tissue are less commonly observed and the toxicologic significance of this effect is unclear. The data on the toxicity of clopyralid are adequate for additional dose-response or dose-severity modeling. Because none of the anticipated exposures substantially exceed the RfD and the great majority of anticipated exposures are far below the RfD, such additional modeling is not necessary for the characterization of risk.

The contamination of technical grade clopyralid with hexachlorobenzene and pentachlorobenzene can be quantitatively considered to a limited extent. The U.S. EPA has derived RfDs for both pentachlorobenzene and hexachlorobenzene and a cancer potency factor for hexachlorobenzene. Based on the levels of contamination of technical grade clopyralid with these compounds and the relative potencies of these compounds to clopyralid, this contamination is not significant in terms of potential systemic-toxic effects. This assessment, however, does not impact the potential carcinogenicity associated with hexachlorobenzene and this risk, based on the U.S. EPA's cancer potency parameter, is quantitatively considered in the risk characterization.

Risk Characterization – The risk characterization for potential human health effects associated with the use of clopyralid in Forest Service programs is relatively unambiguous. Based on the estimated levels of exposure and the criteria for acute and chronic exposure developed by the U.S. EPA, there is no evidence that typical or accidental exposures will lead to dose levels that exceed the level of concern for workers. In other words, all of the anticipated exposures for workers are below the acute RfD for acute exposures and below the chronic RfD for chronic exposures. For members of the general public, none of the longer-term exposure scenarios approach a level of concern and none of the acute/accidental scenarios exceed a level of concern, based on central estimates of exposure, although the upper limit of the hazard quotient for the consumption of water after an accidental spill slightly exceeds the level of concern – i.e., a hazard quotient of 2.

Irritation and damage to the skin and eyes can result from exposure to relatively high levels of clopyralid (i.e., placement of clopyralid directly onto the eye or skin). From a practical perspective, eye or skin irritation is likely to be the only overt effect as a consequence of mishandling clopyralid. These effects can be minimized or avoided by prudent industrial hygiene practices during the handling of clopyralid.

The only reservation attached to this assessment of clopyralid is that associated with any risk assessment: ***Absolute safety cannot be proven and the absence of risk can never be demonstrated.*** No chemical, including clopyralid, has been studied for all possible effects and the use of data from laboratory animals to estimate hazard or the lack of hazard to humans is a process that is fraught with uncertainty. Prudence dictates that normal and reasonable care should be taken in the handling of this or any other chemical. Notwithstanding these reservations, the use of clopyralid does not appear to pose any risk of systemic toxic effects to workers or the general public in Forest Service programs.

The contamination of clopyralid with hexachlorobenzene and pentachlorobenzene does not appear to present any substantial cancer risk. Administratively, the Forest Service has adopted a cancer risk level of one in one-million (1÷1,000,000) as a trigger that would require special steps to mitigate exposure or restrict and possibly eliminate use. Based on relatively conservative exposure assumptions, the risk levels estimated for members of the general public are below this trigger level. The highest risk level is estimated at about 3 in 100 million, a factor of 33 below the level of concern. The exposure scenario associated with this risk level involves the consumption of contaminated fish by subsistence populations (i.e., groups that consume relatively large amounts of contaminated fish). The consumption of fish contaminated with hexachlorobenzene is a primary exposure scenario of concern because of the tendency of hexachlorobenzene to bioconcentrate from water into fish. This is also consistent with the general observation that exposure to hexachlorobenzene occurs primarily through the consumption of contaminated food.

ECOLOGICAL RISK ASSESSMENT

Hazard Identification **–** The toxicity of clopyralid is relatively well characterized in experimental mammals but few wildlife species have been assayed relative to the large number of non-target species that might be potentially affected by the use of clopyralid. Within this admittedly substantial reservation, clopyralid appears to be relatively non-toxic to terrestrial or aquatic animals, is highly selective in its toxicity to terrestrial plants, and relatively non-toxic to aquatic plants. Thus, the potential for substantial effects on non-target species appears to be remote. Consistent with this assessment of toxicity to non-target species, one long-term (8-year) field study has been conducted that indicates no substantial or significant effects on plant species diversity.

The toxicity to non-target terrestrial animals is based almost exclusively on toxicity studies using experimental mammals (i.e., the same studies used in the human health risk assessment). Some additional studies are available on birds, bees, spiders, and earthworms that generally support the characterization of clopyralid as relatively non-toxic. An additional study of the toxicity of clopyralid to non-target invertebrates also suggests that clopyralid has a low potential for risk. A

caveat in the interpretation of this study is the limited detail in which the experimental data are reported. As with terrestrial species, the available data on aquatic species, both plants and animals, suggest that clopyralid is relatively non-toxic.

The toxicity of clopyralid to terrestrial plants has been examined in substantial detail in studies that have been published in the open literature as well as studies that have been submitted to the U.S. EPA to support the registration of clopyralid. Clopyralid is a plant growth regulator and acts as a synthetic auxin or hormone, altering the plant's metabolism and growth characteristics, causing a proliferation of abnormal growth that interferes with the transport of nutrients throughout the plant. This, in turn, can result in gross signs of damage and the death of the affected plant. The phytotoxicity of clopyralid is relatively specific to broadleaf plants because clopyralid is rapidly absorbed across leaf surfaces but much less readily absorbed by the roots of plants. For the same reason, clopyralid is much more toxic/effective in post-emergent treatments (i.e., foliar application) rather than pre-emergent treatment (i.e., application to soil).

Clopyralid does not bind tightly to soil and thus would seem to have a high potential for leaching. While there is little doubt that clopyralid will leach under conditions that favor leaching—sandy soil, a sparse microbial population, and high rainfall—the potential for leaching or runoff is functionally reduced by the relatively rapid degradation of clopyralid in soil. A number of field lysimeter studies and a long-term field study indicate that leaching and subsequent contamination of ground water are likely to be minimal. This conclusion is also consistent with a monitoring study of clopyralid in surface water after aerial application.

Exposure Assessment – Terrestrial animals might be exposed to any applied herbicide from direct spray, the ingestion of contaminated media (vegetation, prey species, or water), grooming activities, or indirect contact with contaminated vegetation. In acute exposure scenarios, exposures from direct spray for small terrestrial vertebrates could reach up to about 8.5 mg/kg under the conservative assumption of 100% absorption. Acute exposures from the consumption of contaminated vegetation could lead to doses of about 6 to 9 mg/kg under typical conditions with an upper range of 17 to 27 mg/kg. In chronic exposures, estimated daily doses for the a small vertebrate from the consumption of contaminated vegetation are in the range of 0.0002 to 0.2 mg/kg/day. The upper ranges of exposure from contaminated vegetation far exceed doses that are anticipated from the consumption of contaminated water – i.e., about 0.0004 mg/kg/day to 0.0007 mg/kg/day. Based on general relationships of body size to body volume, larger vertebrates will be exposed to lower doses and smaller animals, such as insects, to much higher doses than small vertebrates under comparable exposure conditions.

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 rates considered in this risk assessment, 0.35 lb a.e./acre. Estimates for the other routes of exposure are much less. All of these exposure scenarios are dominated by situational variability because the levels of exposure are highly dependent on site-specific conditions. Thus, the exposure estimates are intended to represent conservative but plausible ranges that could occur but these ranges may over-estimate or under-estimate actual exposures in some cases. Spray drift is based on estimates AGDRIFT. The proportion of the

applied amount transported off-site from runoff is based on GLEAMS modeling of clay, loam, and sand. The amount of clopyralid that might be transported off-site from wind erosion is based on estimates of annual soil loss associated with wind erosion and the assumption that the herbicide is incorporated into the top 1 cm of soil. Exposure from the use of contaminated irrigation water is based on the same data used to estimate human exposure from the consumption of contaminated ambient water and involves both monitoring studies as well as GLEAMS modeling.

Exposures to aquatic plants and animals is based on essentially the same information used to assess the exposure to terrestrial species from contaminated water. The peak estimated rate of contamination of ambient water associated with the normal application of clopyralid is 0.02 (0.005 to 0.07) mg a.e./L at an application rate of 1 lb a.e./acre. For longer-term exposures, average estimated rate of contamination of ambient water associated with the normal application of clopyralid is 0.007 (0.001 to 0.013) mg a.e./L at an application rate of 1 lb a.e./acre. For the assessment of potential hazards, these contamination rates are adjusted based on the application rates considered in this risk assessment.

Dose-Response Assessment – For terrestrial mammals, the dose-response assessment is based on the same data as the human health risk assessment (i.e., an acute NOAEL of 75 mg/kg/day and a chronic NOAEL of 15 mg/kg/day). None of the exposure scenarios, acute or longer term, result in exposure estimates that exceed this NOAEL. A comparison of gavage studies between mammals and birds suggest that birds may be more sensitive than mammals by about a factor of 3. Based on a comparison of short-term dietary NOAELs, however, birds appear to be somewhat less sensitive with an acute dietary NOAEL of about 670 mg/kg/day, a factor of about 9 above the acute NOEL of 75 mg/kg/day for mammals. Since most of the exposure assessments developed in this risk assessment involve gradual intake during the day rather than gavage like exposures, the dietary NOEL of 696 mg/kg/day is used for the risk characterization in birds. No chronic toxicity studies in birds have been encountered and the chronic NOAEL for mammals of 15 mg/kg/day is used in this risk assessment to assess the risks associated with longer term exposures.

The toxicity of clopyralid to terrestrial plants can be characterized relatively well and with little ambiguity. Clopyralid is more toxic to broadleaf plants than grains or grasses and is more toxic in post-emergence applications (i.e., foliar spray) than pre-emergence applications (i.e., soil treatment). For assessing the potential consequences of exposures to nontarget plants via runoff, the NOEC values for seed emergence are used for sensitive species (0.025 lb a.e./acre) and tolerant species (0.5 lb a.e./acre). For assessing the impact of drift, bioassays on vegetative vigor will be used with NOEC values of 0.0005 lb/acre for sensitive species and 0.5 lb/acre for tolerant species.

The data on toxicity to fish are limited. No chronic studies or even long-term studies on fish egg-and-fry have been encountered. The dose-response assessment uses admittedly limited data suggesting that at least some fish species may be more sensitive to clopyralid than daphnids. For acute exposures, an acute LC_{50} value of 103.5 mg/L is used to characterize risk for sensitive fish species and an acute LC_{50} value of 1645 mg a.e./L is used to characterize risk for tolerant fish

species. Based on differences in acute toxicity between sensitive fish and daphnids, the longer term NOEC for sensitive species is based on the 23.1 mg a.e./L from daphnids but adjusted downward by a factor of 2 and then rounded to one significant digit – i.e. 10 mg/L. For sensitive aquatic plants, risk is characterized using the lowest reported EC_{50} of 6.9 mg a.e./L. Conversely, for tolerant aquatic plants, the highest reported EC_{50}, 449 mg/L, is used. The available data on aquatic plants are not sufficient to support separate dose-response assessments for macrophytes and algae.

Risk Characterization – Clopyralid is an herbicide and the most likely damage to nontarget species will involve terrestrial plants. Sensitive plant species could be adversely affected by the off-site drift of clopyralid under a variety of different scenarios depending on local site-specific conditions that cannot be generically modeled. If clopyralid is applied in the proximity of sensitive crops or other desirable sensitive plant species, site-specific conditions and anticipated weather patterns will need to considered if unintended damage is to be avoided. More tolerant plant species are not likely to be affected unless they are directly sprayed or subject to substantial drift. Because of the tendency for clopyralid to move into soil rather than to be transported by runoff and because of the greater toxicity of clopyralid by foliar deposition compared to soil contamination, off-site movement of clopyralid by soil runoff does not appear to be substantial risk to nontarget plant species. Aquatic plants do not appear to be at any substantial risk from any plausible acute or chronic exposures. In the very extreme case of an accidental spill of a large amount of the herbicide into a relatively small body of standing water, sensitive aquatic plants could be damaged.

No adverse effects are anticipated in terrestrial or aquatic animals from the use of clopyralid in Forest Service programs at the typical application rate of 0.35 lb a.e./acre. The same qualitative assessment holds for the maximum application rate of 0.5 lb a.e./acre except for the large bird feeding exclusively on contaminated vegetation over a 90 day period. Other more plausible scenarios – i.e., the longer term consumption of vegetation contaminated by drift or the longer term consumption of contaminated water or fish – yield hazard quotients that are in the range of 0.00005 to 0.02, far below a level of concern.

The risk characterization for both terrestrial and aquatic animals is limited by the relatively few animal and plant species on which data are available compared to the large number of species that could potentially be exposed. This limitation and consequent uncertainty is common to most if not all ecological risk assessments.

1. INTRODUCTION

The USDA Forest Service uses the herbicide, clopyralid, in its vegetation management programs. Only one commercial formulation, Transline, is used by the Forest Service. The present document provides risk assessments for human-health effects and ecological effects to support an assessment of the environmental consequences of using clopyralid in future Forest Service programs. This is an update to a previous risk assessment on clopyralid (SERA 1999).

This document has four chapters, including the introduction, program description, risk assessment for human health effects, and risk assessment for ecological effects or effects on wildlife species. Each of the two risk assessment chapters has four major sections, including an identification of the hazards associated with clopyralid and its commercial formulation, an assessment of potential exposure to the product, an assessment of the dose-response relationships, and a characterization of the risks associated with plausible levels of exposure. These are the basic steps recommended by the National Research Council of the National Academy of Sciences (NRC 1983) for conducting and organizing risk assessments.

Although this is a technical support document and addresses some specialized technical areas, an effort was made to ensure that the document can be understood by individuals who do not have specialized training in the chemical and biological sciences. Certain technical concepts, methods, and terms common to all parts of the risk assessment are described in plain language in a separate document (SERA 2001).

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. No published reviews regarding human health or ecological effects of clopyralid have been encountered. Moreover, almost all of the mammalian toxicology studies and most of the ecotoxicology studies are unpublished reports submitted to the U.S. EPA as part of the registration process for clopyralid.

Because of the lack of a detailed, recent review concerning clopyralid and the preponderance of unpublished relevant data in U.S. EPA files, a complete search of the U.S. EPA FIFRA/CBI files was conducted. Full text copies of relevant studies were kindly provided by the U.S. EPA Office of Pesticide Programs. These studies were reviewed, discussed in Sections 3 and 4 as necessary, and synopses of the most relevant studies are provided in the appendices to this document. While this document discusses the studies required to support the risk assessments, it makes no attempt to summarize all of the information. The Forest Service will update this and other similar risk assessments on a periodic basis and welcomes input from the general public on the selection of studies included in the risk assessment. This input is helpful, however, only if recommendations for including additional studies specify why and/or how the new or not previously included information would be likely to alter the conclusions reached in the risk assessments.

For the most part, the risk assessment methods used in this document are similar to those used in risk assessments previously conducted for the Forest Service as well as risk assessments

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

Variability and *uncertainty* may be dominant factors in any risk assessment, and these factors should be expressed. Within the context of a risk assessment, the terms *variability* and *uncertainty* signify different conditions.

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

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

In considering different forms of variability, almost no risk estimate presented in this document is given as a single number. Usually, risk is expressed as a central estimate and a range, which is

sometimes very large. Because of the need to encompass many different types of exposure as well as the need to express the uncertainties in the assessment, this risk assessment involves numerous calculations.

Most of the calculations are relatively simple, and the very simple calculations are included in the body of the document. Some of the calculations, however, are cumbersome. For those calculations, a set of worksheets is included as an attachment to the risk assessment. The worksheets provide the detail for the estimates cited in the body of the document. The worksheets are divided into the following sections: general data and assumptions, chemical specific data and assumptions, exposure assessments for workers, exposure assessments for the general public, and exposure assessments for effects on nontarget organisms. Further documentation for these worksheets are included in SERA (2003). As detailed in SERA (2003), two versions of the worksheets are available: one in a word processing format and one in a spreadsheet format. The worksheets that are in the spreadsheet format are used only as a check of the worksheets that are in the word processing format. Both sets of worksheets are provided with the hard-text copy of this risk assessment as well as with the electronic version of the risk assessment.

Technical grade clopyralid contains hexachlorobenzene as a contaminant and hexachlorobenzene is classified as a carcinogen. Because of the importance of and level of concern for this endpoint in humans, the human health risk assessment discusses the potential effects of hexachlorobenzene in some detail and a separate subset of worksheets for hexachlorobenzene are provided at the end of this document. Again, these worksheets are provided in both a word processing format and one in a spreadsheet format.

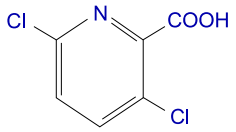
2. PROGRAM DESCRIPTION

2.1. OVERVIEW

Clopyralid is a selective herbicide used primarily in the control of broadleaf weeds. The Forest Service uses only a single commercial formulation of clopyralid, Transline. The Forest Service uses Transline almost exclusively in noxious weed control. Relatively minor uses include rights-of-way management, wildlife openings, and facilities maintenance. Transline is a liquid formulation of clopyralid that is manufactured by Dow AgroSciences and contains 40.9% clopyralid as the monoethanolamine salt and 59.1% inert ingredients. The identity of the inerts in Transline is proprietary with the exception of isopropyl alcohol (List 4) and a polyglycol (List 3). Technical grade clopyralid contains hexachlorobenzene and pentachlorobenzene as contaminants. Nominal or average concentrations of hexachlorobenzene are less than 2.5 ppm. Nominal or average concentrations of pentachlorobenzene are less than 0.3 ppm. The most common methods of ground application for Transline involve backpack (selective foliar) and boom spray (broadcast foliar) operations. Although Transline is registered for aerial applications, the Forest Service does not and does not intend to use Transline in aerial applications. The typical application rate in Forest Service programs is about 0.35 lb a.e./acre and the range of application rates that are likely to be used in Forest Service programs is about 0.1 to 0.5 lb a.e./acre. The total annual use of clopyralid by the Forest Service is about 2.2 percent of the agricultural use.

2.2. CHEMICAL DESCRIPTION AND COMMERCIAL FORMULATIONS

Clopyralid is the common name for 3,6-dichloro-2-pyridinecarboxylic acid:



Selected chemical and physical properties of clopyralid are summarized in Table 2-1. Additional information is presented in worksheet B03.

There are two different manufacturing processes used in the synthesis of clopyralid: the penta process and the electrochemical process. The penta process is the original method used in the manufacturing of clopyralid. The electrochemical process is a new procedure. The two processes yield "slightly different ingredient profiles" (Dow AgroSciences 1998). Details of these methods have been submitted to the U.S. EPA but are considered proprietary and are not detailed in this risk assessment. Nonetheless, some comparative information is available on the acute toxicity of clopyralid produced by both the penta and electrochemical processes and these data are summarized in sections 3 and 4.

Technical grade clopyralid contains hexachlorobenzene and pentachlorobenzene as contaminants. Nominal or average concentrations of hexachlorobenzene are less than 2.5 ppm. Nominal or average concentrations of pentachlorobenzene are less than 0.3 ppm (Lade 1998). The impact of these contaminants to this risk assessment is detailed in Section 3.1.15.

Transline is the only formulation of clopyralid used by the Forest Service. Transline is produced by Dow AgroSciences and is formulated as a liquid containing the monoethanolamine (2-amino-1-ethanol) salt of clopyralid (40.9% w/v). This is equivalent to a concentration of 3 lb a.e./gallon. The remaining 59.1% of the formulation consists of inerts. The identity of the inerts in Transline is proprietary with the exception of isopropyl alcohol and a polyglycol. The polyglycol is identified as Polyglycol 26-2 with a CAS No. 069029-39-6 (C&P Press 2003). On the U.S. EPA list of inerts used in pesticides (U.S. EPA/OPP 2003), the polyglycol with this CAS number is listed as polyoxypropylene mono(di-sec-butylphenyl) ether and classified as a List 3 inert. List 3 inerts designate those inerts for which the available toxicology data are insufficient to classify the the compound as of toxicologic concern (List 1), possible toxicologic concern (List 2), or of minimal concern (List 4) (U.S. EPA/OPP 2003). Isopropyl alcohol is classified by the U.S. EPA as a List 4 inert. These inerts are listed on the Transline MSDS but the amount of inerts in the formulation is not disclosed (C&P Press 2003). The potential significance of these inerts in Transline to this risk assessment is discussed further in section 3.1.14. The Northwest Coalition for Alternatives to Pesticides (NCAP) has obtained information on the identity of the inerts in Transline from U.S. EPA under the Freedom of Information Act and has listed this information on the NCAP web site (http://www.pesticide.org/FOIA/clopyralid.html). No inerts other than isopropyl alcohol, Polyglycol 26-2, and water are listed at this site.

Transline is labeled for use only in non-crop areas. The uses for Transline recommended on the product label include selective postemergence control of broadleaf weeds on rights-of-way and the maintenance of wildlife openings, tree plantations, rangeland, and permanent grass pastures (C&P Press 2003). As specified on the product label, surfactants may be used to improved the efficacy of Transline.

2.3. APPLICATION METHODS

The most common methods of ground application for Transline 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 acres/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 1989b, p 2-9 to 2-10).

Although Transline is registered for aerial applications (C&P Press 2003), the Forest Service does not and does not intend to use Transline in aerial applications.

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), lbs a.i. per acre (designating the amount of the monoethanolamine salt of clopyralid), or lbs a.e. per acre (designating the amount of the clopyralid acid equivalents). Unless otherwise specified, all application rates and other expressions of amounts are based on acid equivalents.

Recommended labeled application rates range from ¼ to 1⅓ pints Transline/acre. In California, the maximum application rate is ⅔ pints per acre per growing season (C&P Press 2003). The application rates of ¼ to 1⅓ pints Transline/acre are equivalent to about 0.03125 to 0.1666 gallons Transline per acre (0.125 pints/gallon). Given that there is 3 lbs clopyralid a.e./gallon in the Transline formulation, these rates correspond to 0.09375 to 0.5 lbs clopyralid a.e./acre. The lower range of the application rate is recommended only for small (3" to 6") actively growing weeds.

The use of clopyralid in Forest Service Programs for fiscal years 2001 through 2003 is summarized in Table 2-2 (USDA 2004). Clopyralid is used currently in Forest Service Programs almost exclusively in noxious weed control (95%). Four applications of triclopyr in Region 2 were reported as agricultural weed control and accounted for about 4.7% of the total reported use (USDA 2004). Based on the total amount used and total number of acres treated, the average application rate for all regions combined is about 0.25 lb/acre (Table 2-2).

For this risk assessment, the typical application rate will be taken as 0.35 lb a.e./acre. This is the approximate average application rate used in Region, the region that accounted for the greatest proportion of triclopyr use by the Forest Service between 2001 and 2003 1 (Table 2-2). The range of application rates will be taken as 0.1 lbs a.e./acre to 0.5 lbs a.e./acre, the approximate range of application rates recommended on the product label. Lower application rates have been reported and these reports may involve spot applications conducted sporadically over a relatively large area. The worksheets that accompany this risk assessment are based on the typical application rate of 0.35 lb/acre rather than the full range of application rates. The consequences of varying application rates within the range of 0.1 to 0.5 lb/acre is considered in the risk characterization for human health (Section 3.4) and ecological effects (Section 4.4).

For ground applications, spray volumes of 10 gallons or more per acre are recommended and the minimum labeled spray volume is 2 gallons per acre (C&P Press 2003). For this risk assessment, 2 gallons per acre is taken as the minimum spray volume. A spray volume of 40 gallons per acre is taken as an upper range. The central estimate of spray volume is taken as 10 gallons/acre – i.e., the most concentrated solution that is likely to be used in ground applications. The extent to which the Transline 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 clopyralid in the applied spray). The higher the concentration (or lower the dilution) of clopyralid , the greater the risk.

It should be noted that the selection of application rates and dilution volumes in this risk assessment is intended to simply reflect typical or central estimates as well as plausible lower and upper ranges. In the assessment of specific program activities, the Forest Service may use program specific application rates in the worksheets that are included with this report to assess any potential risks for a proposed application.

2.5. USE STATISTICS

The USDA Forest Service tracks and reports use by geographical areas referred to as "*Regions*" (USDA 2004). As illustrated in Figure 2-1, 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.] As illustrated in Figure 2-1, the greatest proportion clopyralid use (relative to the total use by the Forest Service) occurs in the northern central regions: Region 1 (Northern), Region 2 (Rocky Mountain), and Region 4 (Inter-mountain).

Clopyralid is used on a number of crops and a summary of the agricultural uses of clopyralid is presented in Figure 2-3 (USGS 1998). These use statistics are for 1992, the most recent year for which data are available. As indicated in this figure, over 125,000 lbs of clopyralid are applied to crops annually, primarily to wheat and other grains (41% of total), sugar beets (30% of total), and mint (22% of total). Other minor uses include oats, barley, field and grass seed, and canola. The geographic distribution of the agricultural uses of clopyralid are somewhat broader than those of the Forest Service, with most of the agricultural applications of clopyralid occurring in Regions 1, 2, 6, and 9.

As noted in Table 2-2, the total use of clopyralid by the Forest Service from 2001 to 3003 is 6923 lbs or about 2307 lbs/year, which is 1.85 percent of the agricultural use [2307 lbs ÷ 125,000 lbs = 0.018456]. Thus, there is no basis for asserting that Forest Service programs will substantially contribute to general concentrations of clopyralid nationally. The potential for local contamination of environmental media by the use of clopyralid in Forest Service programs is discussed in detail in the human health risk assessment (Section 3) and the ecological risk assessment (Section 4).

More recent data are available on the total amounts of pesticides applied in California in 2001 (California Department of Pesticide Regulation 2002). During 2001, about 14,713 lbs of clopyralid was applied in California (California Department of Pesticide Regulation 2002, pp. 90-91). While dicamba was not used by the Forest Service in California during 2001, less than 12 lbs of clopyralid was used by the Forest Service in California (USDA 2004) – i.e., less than 0.1% of the amount used in California in 2001.

Thus, based both on the national data from 1992 (USGS 1998) as well as the more recent data from California (California Department of Pesticide Regulation 2002), it appears that the use of dicamba in Forest Service programs is minor relative to the total amount of dicamba used in agriculture and in other non-Forest Service applications.

3. HUMAN HEALTH RISK ASSESSMENT

3.1. HAZARD IDENTIFICATION

3.1.1. Overview. Although no information is available on the toxicity of clopyralid to humans, the toxicity of clopyralid has been relatively well-characterized in mammals. All of this information is contained in unpublished studies submitted to the U.S. EPA as part of the registration process for clopyralid.

Two different manufacturing processes may be used for clopyralid: the penta process and the electrochemical process. The limited available information indicates that technical grade clopyralid samples from the electrochemical process may be somewhat more toxic (LD_{50} values in the range of about 3000 mg/kg) than the penta process (LD_{50} > 5000 mg/kg). These differences, however, are not substantial and may be due to random variability. In experimental animals, a common symptom of acute, high-dose clopyralid exposure is central nervous system (CNS) depression. Clopyralid also has a low order of chronic toxicity. For chronic or subchronic exposures, no effects have been observed in laboratory mammals at doses of 50 mg/kg/day or less. At doses of 100 mg/kg/day or greater, various effects have been observed in different species and different bioassays. These effects include weight loss, changes in liver and kidney weight, thickening of epithelial tissue lining the stomach, irritation of the lungs, and decreases in red blood cell counts. These effects appear to be non-specific toxicity; they do not implicate clopyralid in any specific target-organ toxicity.

Technical grade clopyralid has been subject to several chronic bioassays for carcinogenicity and none of the bioassays have shown that clopyralid has carcinogenic potential, although technical grade clopyralid does contain low levels of hexachlorobenzene. Hexachlorobenzene has shown carcinogenic activity in three mammalian species and has been classified as a potential human carcinogen by the U.S. EPA. Thus, this effect is considered both qualitatively and quantitatively in this risk assessment.

No studies specifically mentioning Transline, the formulation used in Forest Service programs, were located in the search of the studies submitted to U.S. EPA for product registration. Dow AgroSciences (2003) provided clarification of this issue and identified the studies submitted to U.S. EPA that were accepted as relevant to Transline. These studies do not indicate any substantial differences between Transline and clopyralid. This is consistent with the publically available information on the three inerts contained in transline, two of which are approved for use as food additives.

3.1.2. Mechanism of Action. While the mechanism of action of clopyralid in plants is well understood (Section 4.1.2.4), no specific mechanism of action in humans or experimental animals has been established. As discussed in Section 3.1.4, the most sensitive effect of clopyralid in mammals appears to involve effects on the liver, kidney, and body weight. The data from kinetics studies (Section 3.1.3) suggests that clopyralid is not extensively metabolized, thus, it is unlikely that compensatory metabolic activation could account for the apparent sensitivity of the liver to clopyralid. Similarly, the etiologies of the renal effects and body weight changes are unknown.

3.1.3. Kinetics and Metabolism. Dow AgroSciences (1998) provides a summary of the results from metabolism studies in animals:

> *In rats, nearly all of the radiolabeled clopyralid, given as a 5 mg/kg i.v. or a 150 mg/kg oral dose was rapidly absorbed and excreted from the body, with the majority being rapidly excreted in the urine (half-time of 3 hours) in the first 24 hours (79 to 96% of the dose). Only clopyralid was recovered from the urine; no metabolites were apparent. The predominant fecal radioactive residue was also clopyralid. There were no apparent differences between (parenteral and oral) doses with respect to tissue distribution or elimination patterns. There were no apparent differences between sexes with respect to tissue residues, carcass residues, or excretion routes and rates.*

The excretion of largely unmetabolized clopyralid was also found in metabolism studies using hens and goats (Dow AgroSciences 1998). Male and female Sprague-Dawley rats were administered ^{14}C-labeled clopyralid as a single oral dose at 10 mg/kg in a phosphate buffer. Absorption from gut was rapid and virtually complete. Of the administered dose, 92% was excreted in urine unchanged within 120 hours (biphasic urinary excretion of 96% at an initial rate with a halftime of three hours and a terminal rate of 24.7 hours); 2.7% of administered dose was excreted in feces and 4.1% remained in carcass at 120 hours (Torkelson et al. 1975; also published as Ramsey et al. 1975). Four young lambs were fed clopyralid (100 ppm in diet) for 8 weeks (Yackovich et al. 1974). No discussion of health effects was provided. A six-hour fermentation study conducted with freshly drawn rumen fluid revealed no metabolic or chemical changes to clopyralid. One male lamb received one oral dose of ^{14}C-labeled clopyralid. Rapid and nearly complete urinary excretion was noted within 72 hours (~98%) with about 4% in feces. The authors (Yackovich et al. 1974) did not comment on recovery of more than 100% of administered dose of radiolabeled clopyralid. Bauriedel (1983) administered ^{14}C-labeled clopyralid to two lactating goats orally for 7 days. Of the original dose, 93–96% was excreted in urine (mostly as unchanged, but <3% as glycine conjugate), 0.7–9.4 % excreted in feces, 1.4–2.2 % remained in the gastrointestinal (GI) tract, and <1% was present in tissues and excreted in milk (Bauriedel 1983).

3.1.4. Acute Oral Toxicity. Standard acute toxicity studies have been conducted with rats using clopyralid produced from both the penta process, the original method used in the manufacture of clopyralid, and the electrochemical process, a more recently developed method for the commercial synthesis of clopyralid (Appendix 1). In the preparation of this risk assessment, full copies of most of studies submitted to the U.S. EPA were obtained from the U.S. EPA and reviewed. In some cases, as indicated in Appendix 1, summaries of some the studies on toxicity to mammals are based on the review by Dow AgroSciences (1998). Where possible, the original references for the studies summarized by Dow AgroSciences (1998) are designated in Appendix 1.

Oral LD_{50} in male rats is >5000 mg/kg and, in female rats, the LD_{50} is 4300 mg/kg (3390–5440 mg/kg). No clinical signs or symptoms of toxicity were noted (Rampy et al. 1973). This study was also published as (Morgan et al. 1973; Rampy and Keeler 1978). Gilbert and Crissman (1995) observed gross changes in the stomach of rats that died after being given a single dose of

clopyralid (electrochemical) by gavage at a dose of 5000 mg/kg. This effect is not reported in this study at lower dose levels (i.e., 500 or 2000 mg/kg). In laboratory rats, symptoms of clopyralid poisoning include watery eyes, diarrhea, and lethargy. These symptoms appear between 2 and 48 hours after clopyralid ingestion (U.S. EPA 1990a). Other acute oral studies have reported LD_{50} values >5000 mg/kg in male and female rats (Saunders et al. 1983) (See Appendix 1 for more details).

As summarized in Dow AgroSciences (1998), the LD_{50} of clopyralid from the penta process is >5000 mg/kg (no deaths at the highest dose tested) and the LD_{50} of clopyralid from the electrochemical process is 3738 mg/kg for male rats and 2675 mg/kg for female rats. This information appears to be a summary of the studies by Jeffrey et al. (1987b) and Gilbert and Crissman (1995) on the penta and electrochemical process, respectively, detailed in Appendix 1. While these data suggest that clopyralid from the newer electrochemical process may be somewhat more toxic than the clopyralid from the older penta process, this assessment is based on only a few studies for each type of clopyralid. In addition, these studies were conducted at different times, and the results of acute toxicity studies will vary both among and within laboratories when assays of the same compound are conducted at different times (Streibig et al. 1995). Thus, the apparent differences between the two studies should not be overly interpreted.

The available data do not suggest that Transline would be more or less toxic than clopyralid following acute oral exposure. Carreon and New (1981) reported an LD_{50} >5000 mg/kg for a formulation with no deaths at a dose level of 5000 mg/kg; lethargy was the only treatment-related effect.

No data are available on the dermal absorption of clopyralid and this is a serious limitation. As discussed further in Section 3.2.2.2, structure-activity relationships are used to estimated the dermal absorption rates for clopyralid.

3.1.5. Subchronic or Chronic Systemic Toxic Effects. As summarized in Appendix 1, several subchronic and chronic studies have been conducted on clopyralid. These studies were submitted to the U.S. EPA in support of the registration of clopyralid; none of the studies are published in the open literature.

Systemic toxicity encompasses virtually any effects that a chemical has after the chemical has been absorbed. Certain types of effects, however, are of particular concern and are assessed with a specific subset of toxicity tests. Such effects are considered in following subsections and include effects on the nervous system (Section 3.1.6), immune system (Section 3.1.7), endocrine function (Section 3.1.8), development or reproduction (Section 3.1.9), and carcinogenicity or mutagenicity (Section 3.1.10). This section summarizes the available information on other systemic effects and non-specific toxicity.

The most consistent effects associated with dietary exposures to clopyralid are decreased body weight (Barna-Lloyd et al. 1986; Humiston et al. 1977; McColloster et al. 1983; Young et al. 1986) and increases in relative kidney weight (Barna-Lloyd et al. 1986), and relative liver weight (Barna-Lloyd et al. 1986; Breckenridge et al. 1984a,b; Humiston et al 1976b; McColloster et al.

1983). In addition, Barna-Lloyd et al. (1986) reported hyperplasia and thickening of the gastric epithelium of rats after dietary exposures to clopyralid that resulted in daily doses of 150 mg/kg/day.

As discussed further in Section 3.3 and Appendix 1, the U.S. EPA has identified a chronic no-observed-effect level (NOEL) in rats of 15 mg/kg/day as the basis for the chronic RfD (U.S. EPA 2002) with a corresponding lowest-observed-adverse-effect level (LOAEL) of 150 mg/kg/day based on gastric epithelial hyperplasia (Barna-Lloyd et al. 1986).

Based on the study by Breckenridge et al. (1984), a dose of 100 mg/kg/day is also a NOEL in dogs, although the endpoint, changes in hematologic parameters, is different from the endpoint seen in rats. In the Breckenridge et al. (1984) study, six Beagle dogs per sex were used at each nominal dose levels: 0 (control), 100, 320, and 1000 mg/kg/day. Actual doses based on measured food consumption and body weights were 99, 301, and 983 mg/kg/day for males and 99, 319, and 977 mg/kg/day for females. The primary toxic effect noted was a significant and dose-related reduction in red blood cell counts in males and females at the 320 and 1000 mg/kg/day nominal dose levels when given in feed. These effects were not statistically significant in the 100 mg/kg/day dose groups. Significant decreases in total protein, serum albumin, and serum globulin were also noted in high-dose males and females at 14 weeks and mid- and high-dose groups at 27 weeks. At 52 weeks, these differences were not statistically significant. Also in the mid and high-dose groups, Breckenridge et al. (1984) noted a significant increase in absolute liver weight. In the high-dose group, this was accompanied by increases in relative kidney and heart weights. No changes at any dose level, however, were observed in serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), or alkaline phosphatase—all indicators of effects on the liver—and signs of histopathologic damage were not apparent. Assays of cytochrome P-450 levels or liver mixed-function oxidases were not conducted. Adrenal weights were significantly reduced in low-dose males. This effect, however, was not seen in high-dose males or any females and is probably incidental. Humiston et al. (1976b) fed Beagle dogs (4/sex/dose) 0, 15, 50, or 150 mg/kg/day clopyralid in diet for six months. No changes were observed in food consumption, appearance, demeanor, body weight, hematology, clinical chemistry, or urinalysis. No change in absolute or relative organ weights were observed in males. In females, relative liver weight was increased in all 4 high-dose (150 mg/kg/day) dogs relative to controls. Changes in urinary bladder (cystitis, urethritis, and prostatitis) were noted among male dogs receiving clopyralid (0/4 control; 1/4 at 15 mg/kg/day; 2/4 at 50 mg/kg/day; 1/4 at 150 mg/kg/day). The etiology of the bladder effects is unknown. No other gross or histological organ pathology was noted. This is also known as Rampy et al. (1973). Using a similar protocol, Hart and McConnell (1975a,b) could not reproduce the bladder injury in Beagle dogs and reported no toxicity at all dose levels tested.

3.1.6. Effects on Nervous System. As discussed in Durkin and Diamond (2002), a neurotoxicant is a chemical that disrupts the function of nerves, either by interacting with nerves directly or by interacting with supporting cells in the nervous system. This definition of neurotoxicant distinguishes agents that act directly on the nervous system (direct neurotoxicants) from those agents that might produce neurologic effects that are secondary to other forms of

toxicity (indirect neurotoxicants). Virtually any chemical will cause signs of neurotoxicity in severely poisoned animals and, thus, can be classified as an indirect neurotoxicant.

Using these definitions, clopyralid can be classified as an indirect neurotoxicant but not as a direct neurotoxicant. At high doses that produce a broad spectrum of toxicologic effects, clinical signs of clopyralid poisoning include neurotoxicity, manifest as ataxia, tremors, convulsions, and weakness, following acute exposure (Carreon and New 1981; Smith et al. 1960b). Similar effects at high doses have been seen in birds (Fink et al. 1980). These reports, however, do not implicate clopyralid as a direct neurotoxicant.

No studies designed specifically to detect impairments in motor, sensory, or cognitive functions in animals or humans exposed to clopyralid have been reported in the open literature or in the studies submitted to the U.S. EPA to support the registration of clopyralid. In addition, none of the studies in the clopyralid database reported histopathological changes in nervous tissue. Specifically, the U.S. EPA (2003) has standard protocols for neurotoxicity studies including a neurotoxicity screening battery (Guideline 870.6200), and an acute and 28-day delayed neurotoxicity assay of organophosphorus substances (Guideline 870.6100). Neither of these types of studies have been conducted on clopyralid. This is not surprising, since the undertaking of such studies on a substance such as clopyralid, for which the clinical and experimental toxicology experience provides no reason to suspect a direct neurotoxic potential, would be highly unusual.

3.1.7. Effects on Immune System. There is very little direct information on which to assess the immunotoxic potential of clopyralid. The only studies specifically related to the effects of clopyralid on immune function are skin sensitization studies (Section 3.1.11). While these studies provide information about the potential for clopyralid to act as a skin sensitizer, they provide no information useful for directly assessing the immunosuppressive potential of clopyralid.

The toxicity of clopyralid has been examined in numerous acute, subchronic, and chronic bioassays. Although many of these studies did not focus on the immune system, changes in the immune system were not observed in any of the available studies (Appendix 1). The only study directly assaying immune function is that conducted by Dabbert et al. (1997) on bobwhite quail chicks. As discussed in Section 4.1.2.2, Dabbert et al. (1997) found that direct spray of clopyralid to bobwhite quail eggs up to 0.56 kg a.e./ha caused no effect on the immune function of the chicks.

3.1.8. Effects on Endocrine System. In terms of functional effects that have important public health implications, effects on endocrine function would be expressed as diminished or abnormal reproductive performance. This issue is addressed specifically in the following section (Section 3.1.9). Mechanistic assays are generally used to assess the potential for direct action on the endocrine system (Durkin and Diamond 2002). Clopyralid has not been tested for activity as an agonist or antagonist of the major hormone systems (e.g., estrogen, androgen, thyroid hormone), nor have the levels of circulating hormones been measured following clopyralid exposures. Thus, all inferences concerning the potential effect of clopyralid on endocrine function must be

based on inferences from standard toxicity studies. The available toxicity studies have not reported any histopathologic changes in endocrine tissues that have been examined as part of the standard battery of tests. As indicated in the following section (Section 3.1.9), extensive data are available on the reproductive and developmental effects of clopyralid in experimental animals.

3.1.9. Reproductive and Teratogenic Effects. As detailed in Appendix 1, two oral teratogenicity studies have been conducted in rabbits, one gavage teratogenicity study has been conducted in rats, and four dietary reproduction studies have been conducted in rats. Other than a decrease in maternal body weight, which is consistent with results of subchronic and chronic toxicity assays of clopyralid, these studies report few signs of toxicity in dams or offspring. At doses that cause no signs of maternal toxicity (i.e., doses below about 100 mg/kg/day) no reproductive or teratogenic effects are apparent. The available data suggest that clopyralid does not produce developmental effects at doses that do not produce maternal toxicity.

3.1.10. Carcinogenicity and Mutagenicity. Several chronic bioassays have been conducted on clopyralid in mice (West and Willigan 1976; Young et al. 1986), rats (Barna-Lloyd et al. 1986), and Beagle dogs (Breckenridge et al. 1984). In these experimental animals, no evidence of carcinogenic activity has been detected. In addition, clopyralid is inactive in several different standard bioassays of mutagenicity (De Marco et al. 2000; Fabrizio 1973a,b,c; Sibinovic 1973).

Technical grade clopyralid, however, is contaminated with hexachlorobenzene and pentachlorobenzene (Lade 1998b). Hexachlorobenzene has shown carcinogenic activity in three mammalian species and has been classified as a potential human carcinogen by the U.S. EPA (1997a). A recent review of the extensive toxicity data on hexachlorobenzene is available from ATSDR (2002). Pentachlorobenzene is not classifiable as to human carcinogenicity based on lack of available human and animal data (U.S. EPA 1995). The risk of cancer from exposure to these contaminants is considered both qualitatively and quantitatively in this risk assessment (Section 3.3).

3.1.11. Irritation and Sensitization (Effects on the Skin and Eyes). After direct instillation into the eyes, clopyralid manufactured by the penta and electrochemical process can cause persistent damage to the eyes. The damage is characterized as slight to marked redness, swelling of the conjunctiva and discharge, with reddening of the iris, and moderate to marked opacity of the cornea. Acute exposure to clopyralid is also *'severely irritating'* to eyes, with symptoms (opaque cornea, inflamed iris, redness, and discharge) lasting up to 21 days after exposure (U.S. EPA 1990b). Details of these studies are presented in Appendix 1.

Other than signs of transient dermal redness shortly after application (Appendix 1), there is no evidence to suggest that clopyralid is a potent skin irritant. Dow AgroSciences (1998) indicates that neither penta process clopyralid nor electrochemical process clopyralid causes skin sensitization. As detailed in Appendix 1, this statement is consistent with and appears to be based on the studies by Jeffery (1987c), presumably using penta process clopyralid and Gilbert (1995d), presumably using electrochemical process clopyralid.

Studies on formulations comparable or equivalent to Transline (Dow AgroSciences 2003) have been conducted by Jeffrey (1986) and Jeffrey et al. (1987a) for dermal irritation and Carreon and New (1981) for ocular irritation. These studies indicate that the irritant effects of Transline are comparable to those of technical grade clopyralid.

3.1.12. Systemic Toxic Effects from Dermal Exposure. The available toxicity studies summarized in Appendix 1 suggest that dermal exposure to 2000 mg/kg clopyralid was not associated with any signs of systemic toxicity in rabbits based on standard acute/single application bioassays with 14-day observation periods. The available data suggest that the dermal absorption of clopyralid is poor. No systemic effects were reported by a dermal study in which New Zealand white rabbits were exposed to 2000 mg/kg clopyralid for 24 hours (Morgan et al. 1973).

An *in vitro* study of clopyralid transport through lipid membranes demonstrated a concentration-independent transfer rate of $5\text{-}8 \times 10^{-10}$ M/s (Saratovskikh et al. 2000). Although there are no *in vivo* data concerning the dermal absorption kinetics of clopyralid *in vivo*, dermal absorption is typically less rapid than absorption after oral exposure and dermal LD_{50}'s are typically higher than oral LD_{50}'s (Gaines 1969). Since the reported acute oral LD_{50}'s of clopyralid are all more than 2000 mg/kg, the lack of apparent toxicity at dermal doses up to 2000 mg/kg/day is to be expected and these studies add little to the assessment of risk for clopyralid.

The systemic effects from dermal exposure to the formulation may be influenced by the presence of other adjuvants which may alter the rate at which the parent chemical moves through the skin. The available data do not suggest that the Transline formulation has greater potential for persistent systemic toxicity than clopyralid, although lethargy waw observed following acute dermal exposure (Carreon and New 1981).

The dermal exposure route is important to this and other similar risk assessments. 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 with an estimated acceptable level of oral exposure based on subchronic or chronic toxicity studies. Thus, it is necessary to assess the consequences of dermal exposure relative to oral exposure and the extent to which clopyralid is likely to be absorbed from the surface of the skin.

3.1.13. Inhalation Exposure. Compared with oral exposure data, data regarding the inhalation toxicity of clopyralid are extremely limited. As detailed in Appendix 1, two relatively detailed inhalation studies have been submitted to the U.S. EPA in support of registration of clopyralid (Hoffman 1995; Streeter et al. 1987). At nominal concentrations of 1 mg/L or greater over 4-hour exposure periods, the only effects noted during exposure were labored breathing and red stains around the nares. After a two-week recovery period, Hoffman (1995) noted discoloration of the lungs in rats exposed to nominal concentrations of 1.2 mg/L, but not in rats exposed to nominal concentrations of 5.5 mg/L. As noted by Hoffman (1995), both of these nominal concentrations were comparable in terms of respirable particles (i.e., $\leq$1.0 microns).

Although Hoffman (1995) did not attribute the changes in the lungs to clopyralid exposure, these changes are consistent with effects noted in a one-year dietary study in dogs (i.e., Breckenridge et al. 1984, detailed in Section 3.1.5). In this study, three low-dose (100 mg/kg/day) animals, three mid-dose (320 mg/kg/day) animals, and five high-dose (1000 mg/kg/day) animals had atypical foci or nodules in the lungs. These lung changes were not noted in any control animals. The study authors attributed these findings to the inhalation of food particles containing clopyralid with subsequent irritation of the lungs from direct clopyralid contact. No occupational exposure criteria have been found for clopyralid. While any effects on the lungs are of substantial concern, such effects have not been seen at lower dietary dose levels in other species. As noted in Section 3.3.2, the current RfD for clopyralid is based on a NOAEL of 15 mg/kg/day from a two-year rats feeding study. This NOAEL (15 mg/kg/day) is a factor of about 6.6 below the lowest dose associated with lung effects in dogs (100 mg/kg/day).

The inhalation toxicity of a formulation comparable or equivalent to Transline (Dow AgroSciences 2003) has been conducted (Gushow et al. 1986). As detailed in Appendix 1, a single 6-hour period of exposure to this formulation at a time-weighted average (TWA) concentration of 3.0 mg/L caused signs of toxicity (i.e., nasal, ocular, and possibly respiratory irritation) (Gushow et al. 1986). As noted in Appendix 1, corneal opacity was noted in 3/6 males and 1/6 females. Similar effects have not been reported following inhalation exposure to technical grade clopyralid (Hoffman 1995; Streeter et al. 1987). These inhalation studies on technical grade clopyralid, however, were conducted at concentrations below 3 mg/L. Corneal opacity has been associated with ocular exposure to technical grade clopyralid (Gilbert 1995d; Jeffery 1987c; Saunders et al. 1983). Thus, the corneal opacity noted in the formulation study by Gushow et al. (1986) may be attributable to clopyralid rather than an inert.

3.1.14. Adjuvants and Inerts. As indicated in Section 2, the commercial formulation of clopyralid used by the Forest Service is Transline, which contains clopyralid as the monoethanolamine salt – i.e., monoethanolamine is considered part of the active ingredient. Transline also contains isopropyl alcohol and polyglycol as adjuvants.

Both monoethanolamine and isopropyl alcohol are approved food additives (Clydesdale 1997), and there is no evidence to assert that these compounds will materially impact the risks associated with the use of clopyralid.

The other inert in Transline is Polyglycol 26-2 (Section 2.2). This compound is classified by the U.S. EPA (2003) as a List 3 inert. In other words, there is insufficient information to categorize this compound as either hazardous (Lists 1 or 2) or non-toxic (List 4). Notwithstanding this classification, surfactants such as Polyglycol 26-2 are surface active agents that can disrupt cellular membranes and lead to a number of different 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 Polyglycol 26-2 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.

As noted in Section 2.2, publically available information at the web site of the Northwest Coalition for Alternatives to Pesticides (http://www.pesticide.org/FOIA/clopyralid.html) indicates that the only other inerts in Transline is water.

As noted above, the toxicity of a formulated product that is comparable to Transline appears to be comparable to that of technical grade clopyralid (Sections 3.1.4, 3.1.11, and 3.1.13).

3.1.15. Impurities and Metabolites. Virtually no chemical synthesis yields a totally pure product. Technical grade clopyralid, as with other technical grade products, undoubtedly contains some impurities. To some extent, concern for impurities in technical grade clopyralid is reduced by the fact that the existing toxicity studies on clopyralid 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. An impurity from the penta production process was identified (4,5,6-trichloro-2-pyridinecarboxylic acid) that may occur at <0.1%. Davies (1987) concluded that the toxic profile of the penta process is not substantially different from the previous production method.

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 clopyralid. As indicated in Section 2, technical grade clopyralid contains hexachlorobenzene and pentachlorobenzene as contaminants. Nominal or average concentrations of hexachlorobenzene are less than 2.5 ppm, and nominal or average concentrations of pentachlorobenzene are less than 0.3 ppm (Lade 1998b). The U.S. EPA has classified hexachlorobenzene as a probable human carcinogen for which the data are adequate to consider risk quantitatively (U.S. EPA 1997a). While a detailed review of hexachlorobenzene and pentachlorobenzene is beyond the scope of this risk assessment, adequate information is available on both of these chemicals to quantify the carcinogenic risk associated with the use of clopyralid (Section 3.3). The ATSDR Toxicological Profile for Hexachlorobenzene (2002) identifies no data that would be expected to change the risk assessment presented in this report. No new information is available concerning the carcinogenicity of pentachlorobenzene.

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 toxicologic consequences of metabolism in the species on which toxicity studies are available will be similar to those in the species of concern, humans in this section. 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.

This general uncertainty, however, has little impact on the risk assessment for clopyralid. As summarized in Section 3.1.3, there is little indication that clopyralid is extensively metabolized by mammals.

3.2. EXPOSURE ASSESSMENT

3.2.1. Overview. Exposure assessments are conducted for both workers and members of the general public for the typical application rate of 0.35 lb/acre. The consequences of using the maximum application rate, 0.5 lb/acre, are discussed in the risk characterization. For both workers and members of the general public, the upper ranges of all acute exposures are below 2 mg/kg and most exposures are much lower. The highest modeled exposure is about 1.8 mg/kg and is associated with the consumption of contaminated water by a child following an accidental spill of clopyralid into a small pond. The upper ranges of non-accidental acute exposure scenarios for members of the general public are associated with doses from about 0.0002 to 0.2 mg/kg. The highest dose estimates for non-accidental exposure scenarios are associated with the consumption of fish. Exposures from dermal contact or drinking contaminated water (other than an accidental spill) are likely to be much lower.

General exposure assessments for workers are in the range of exposures modeled for the general public. For workers, three types of application methods are modeled: directed ground, broadcast ground, and aerial. Central estimates of exposure span a relatively narrow range: 0.005 to 0.008 mg/kg. The upper ranges of exposures are also similar for the different groups of workers: 0.03 to 0.05 mg/kg/day. All of the accidental exposure scenarios for workers involve dermal exposures. Because clopyralid is not readily absorbed across the skin, all of these accidental exposures lead to estimates of dose that are either in the range of or substantially below the general exposure estimates for workers.

Hexachlorobenzene is a contaminant in technical grade clopyralid. The concentration of hexachlorobenzene in technical grade clopyralid is about 2.5 ppm or less. For all exposure assessments detailed in this risk assessment, the concentration of 2.5 ppm is used. Hexachlorobenzene is ubiquitous and persistent in the environment. The major sources of general exposure for the public to hexachlorobenzene involve industrial emissions, proximity to hazardous waste sites, and the consumption of contaminated food. Virtually all individuals are exposed to hexachlorobenzene and virtually all individuals have detectable concentrations of hexachlorobenzene in their bodies. Based on current concentrations of hexachlorobenzene in environmental media and food, daily doses of hexachlorobenzene (i.e., background levels of exposure) are in the range of 0.000001 (1×10^{-6}) mg/kg/day. Based on the amount of hexachlorobenzene in clopyralid and the amount of clopyralid used in Forest Service programs, the use of clopyralid by the Forest Service will not substantially contribute to any wide-spread increase of ambient levels of hexachlorobenzene. Nonetheless, the potential impact of local contamination is considered for workers as well as for several acute and chronic exposure scenarios for members of the general public. For workers, the upper range of longer term exposure scenarios result in dose estimates of about 7×10^{-8} mg/kg/day to 1×10^{-7} mg/kg/day, below general background levels of exposure by about a factor of 10 to 14. For members of the general public, the upper range of longer term exposure scenarios are about 3×10^{-11} mg/kg/day to 2×10^{-8} mg/kg/day, below general background levels of exposure by about a factor of 50 to 33,000. The upper range of estimated doses associated with acute exposure scenarios for both workers and members of the general public are about 0.0005 mg/kg/day, higher than background levels of exposure by about a factor of 500.

3.2.2. Workers. The Forest Service uses a standard set of exposure assessments in all risk assessment documents. While these exposure assessments vary depending on the characteristics of the specific chemical as well as the relevant data on the specific chemical, the organization and assumptions used in the exposure assessments are standard and consistent. All of the exposure assessments for worker as well as members of the general public are detailed in the worksheets on clopyralid that accompany this risk assessment [SERA WPWS 03-43-17-03]. Detailed documentation for these worksheets is presented in SERA WSD 01-2.04, *Documentation for Worksheets Version 2.04 - Human Health and Ecological Risk Assessments*, dated February 25, 2003. A copy of this documentation is available at www.sera-inc.com. This section on workers and the following section on the general public provide a plain verbal description of the worksheets and discuss clopyralid specific data that are used in the worksheets.

A summary of the exposure assessments for workers is presented in Worksheet E02 of the worksheets for clopyralid that accompany this risk assessment. Two types of exposure assessments are considered: general and accidental/incidental. The term *general* exposure assessment is used to designate those exposures that involve estimates of absorbed dose based on the handling of a specified amount of a chemical during specific types of applications. The accidental/incidental exposure scenarios involve specific types of events that could occur during any type of application. The exposure assessments developed in this section as well as other similar assessments for the general public (Section 3.2.3) are based on the typical application rate of 0.35 lbs a.e./acre (Section 2). The consequences of using different application rates in the range considered by the Forest Service are discussed further in the risk characterization (Section 3.4).

3.2.2.1. General Exposures – No worker exposure studies with clopyralid were found in the literature. As described in SERA (2001), worker exposure rates are expressed in units of mg of absorbed dose per kilogram of body weight per pound of chemical handled. Based on analyses of several different pesticides using a variety of application methods, default exposure rates are estimated for three different types of applications: directed foliar (backpack), boom spray (hydraulic ground spray), and aerial. As described in SERA (2001), the ranges of estimated occupational exposure rates vary substantially among individuals and groups, (i.e., by a factor of 50 for backpack applicators and a factor of 100 for mechanical ground sprayers).

The specific assumptions used for each application method are detailed in worksheets C01a (directed foliar), C01b (broadcast foliar), and C01c (aerial). In these worksheets, the central estimate of the amount handled per day is calculated as the product of the central estimates of the acres treated per day and the application rate. The ranges for the amounts handled per day are calculated as the product of the range of acres treated per day and the application rate. Similarly, the central estimate of the daily absorbed dose is calculated as the product of the central estimate of the exposure rate and the central estimate of the amount handled per day. The ranges of the daily absorbed dose are calculated as the range of exposure rates and the range for the amounts handled per day. The lower and upper limits are similarly calculated using the lower and upper ranges of the amount handled, acres treated per day, and worker exposure rate.

An estimate of the number of acres treated per hour is needed to apply these worker exposure rates. These values are taken from previous USDA risk assessments (USDA 1989a,b,c). The number of hours worked per day is expressed as a range, the lower end of which is based on an 8-hour work day with 1 hour at each end of the work day spent in activities that do not involve herbicide exposure. The upper end of the range, 8 hours per day, is based on an extended (10-hour) work day, allowing for 1 hour at each end of the work day to be spent in activities that do not involve herbicide exposure.

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

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

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

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

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

There are various methods for estimating absorbed doses associated with accidental dermal exposure (U.S. EPA/ORD 1992, SERA 2001). Two general types of exposure are modeled: those involving direct contact with a solution of the herbicide and those associated with accidental spills of the herbicide onto the surface of the skin. Any number of specific exposure

scenarios could be developed for direct contact or accidental spills by varying the amount or concentration of the chemical on or in contact with the surface of the skin and by varying the surface area of the skin that is contaminated.

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

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

For both scenarios (the hand immersion and the contaminated glove), the assumption of zero-order absorption kinetics is appropriate. Following the general recommendations of U.S. EPA/ORD (1992), Fick's first law is used to estimate dermal exposure. As discussed in Section 3.1.12, an experimental dermal permeability coefficient (Kp) for clopyralid is not available. Thus, the Kp for clopyralid is estimated using the algorithm from U.S. EPA/ORD (1992), which is detailed in Worksheet A07b. The application of this algorithm to clopyralid, based on molecular weight and the $K_{o/w}$, is given in Worksheet B04.

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

Because no studies are available on the first-order dermal absorption rate of clopyralid, this rate is estimated using the methods detailed in SERA (2000). The details of the method specified in SERA (2000) for estimating the first-order dermal absorption coefficient based on the molecular weight and octanol-water partition coefficient are given in worksheet A07a. The application of this method to clopyralid is detailed in worksheet B03.

The lack of experimental data regarding the dermal absorption of clopyralid adds uncertainty to this risk assessment. Nonetheless, uncertainties in the rates of dermal absorption, although they are substantial, can be estimated quantitatively and are incorporated into exposure assessments involving estimates of dermal absorption for workers and members of the general public.

3.2.3. General Public.

3.2.3.1. General Considerations – Under normal conditions, members of the general public should not be exposed to substantial levels of clopyralid. Nonetheless, any number of exposure scenarios can be constructed for the general public, depending on various assumptions regarding application rates, dispersion, canopy interception, and human activity. Several highly conservative scenarios are developed for this risk assessment.

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

The exposure scenarios developed for the general public are summarized in Worksheet E02. As with the worker exposure scenarios, details of the assumptions and calculations involved in these exposure assessments are given in the worksheets that accompany this risk assessment (Worksheets D01–D09). The remainder of this section focuses on a qualitative description of the rationale for and quality of the data supporting each of the assessments.

3.2.3.2. Direct Spray – Direct sprays involving ground applications are modeled in a manner similar to accidental spills for workers (see Section 3.2.2.2.). In other words, it is assumed that the individual is sprayed with a solution containing the compound and that an amount of the compound remains on the skin and is absorbed by first-order kinetics. For these exposure scenarios, it is assumed that during a ground application, a naked child is sprayed directly with clopyralid. These scenarios also assume that the child is completely covered (that is, 100% of the surface area of the body is exposed). These are extremely conservative exposure scenarios and are likely to represent upper limits of plausible exposure. An additional set of scenarios are included involving a young woman who is accidentally sprayed over the feet and legs. For each of these scenarios, some assumptions are made regarding the surface area of the skin and body weight, as detailed in Worksheet A04.

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. Dislodgeable residues for clopyralid have been assayed by Peacock and Phillips (1999), who noted a fractional dislodgeable residue of about 0.087 relative to the application. This is very close to the value of 0.1 typically used in Forest Service risk assessments (Worksheet A03) and the somewhat higher value of 0.1 is maintained in this risk assessment. No data are available on dermal transfer rates for clopyralid and the estimation methods of Durkin et al. (1995) are used as

defined in Worksheet D02. The exposure scenario assumes a contact period of one hour and assumes that the chemical is not effectively removed by washing for 24 hours. Other estimates used in this exposure scenario involve estimates of body weight, skin surface area, and first-order dermal absorption rates, as discussed in the previous section.

3.2.3.4. Contaminated Water – Clopyralid is stable in water over a range of pH from 5 to 9 (Woodburn 1987) and the rate of photolysis in water is extremely slow (i.e., $t_{½}$=261 days, Concha and Shepler 1994). In addition, clopyralid is extremely stable in anaerobic sediments, with no significant decay noted over a one-year period (Hawes and Erhardt-Zabik 1995). Concern for water contamination is increased because clopyralid is not tightly bound to most soils and thus may have a tendency to leach from soil into ground water (e.g., Cox et al. 1996, 1997; Pik et al. 1977; Woodburn and French 1987).

For this risk assessment, the three types of estimates made for the concentration of clopyralid in ambient water are acute, accidental, and longer-term exposure. The acute accidental exposure scenario is based on a spill of a fixed amount of clopyralid into a body of water of a fixed size assuming instantaneous mixing. The acute non-accidental exposure scenario is associated with peak concentrations in a stream that might be expected after the application of this compound to a 10 acre block that is adjacent to and drains into stream. The longer-term exposure scenario is based on average concentrations that might be expected after a similar application – i.e., a 10 acre block that is adjacent to and drains into a small pond.

3.2.3.4.1. ACUTE EXPOSURE – Two exposure scenarios are presented for the acute consumption of contaminated water: an accidental spill into a small pond (0.25 acres in surface area and 1 meter deep) and the contamination of a small stream by runoff or percolation.

The accidental spill scenario assumes that a young child consumes contaminated water shortly after an accidental spill into a small pond. The specifics of this scenarios are given in Worksheet D05. Because this scenario is based on the assumption that exposure occurs shortly after the spill, no dissipation or degradation of clopyralid is considered. This scenario is dominated by arbitrary variability and the specific assumptions used will generally overestimate exposure. The actual concentrations in the water would depend heavily on the amount of compound spilled, the size of the water body into which it is spilled, the time at which water consumption occurs relative to the time of the spill, and the amount of contaminated water that is consumed. Based on the spill scenario used in this risk assessment, the concentration of clopyralid in a small pond is estimated to range from about 0.8 mg/L to 16 mg/L with a central estimate of about 3.2 mg/L (Worksheet D05).

The other acute exposure scenario for the consumption of contaminated water involves runoff into a small stream. One stream monitoring study reporting concentrations of clopyralid in a stream shortly after application has been encountered in the literature. Leitch and Fagg (1985) determined the concentration of clopyralid in a stream after clopyralid (Lontrel L) was aerially applied at a rate of about 2.5 lb a.i./acre over 56 hectares (i.e., about 140 acres [56 ha × 2.471 acres/ha = 138.376 acres]) to clay-loam soil. This application rate is equivalent to an application rate of about 1.90 lb a.e./acre [2.5 lb a.i./acre × 192 g/mole for acid ÷ 253 g/mole for salt = 1.897

lbs a.e./acre]. Clopyralid was monitored in stream water during application and subsequently for 72 hours after application at a site 0.5 kilometers downstream from the application site (see Leitch and Fagg 1985, Figure 2, p. 203). The limit of detection in this study was 0.001 mg/L. During and immediately after application, only trace levels of clopyralid were detected in the stream water, suggesting that direct spray of or drift to the stream was negligible. The highest levels of clopyralid occurred during or shortly after storm events. The maximum level in the stream water was 0.017 mg/L. Over the 19 day monitoring period, the total rainfall was 133 mm or about 5.2 inches.

While monitoring data provide practical and documented instances of water contamination, monitoring studies may not encompass a broad range of conditions which may occur during program applications – e.g., extremely heavy rainfall – or they may reflect atypical applications that do not reflect program practices. Consequently, for this component of the exposure assessment, the monitored levels in stream water are compared to modeled estimates based on GLEAMS (Groundwater Loading Effects of Agricultural Management Systems). GLEAMS is a root zone model that can be used to examine the fate of chemicals in various types of soils under different meteorological and hydrogeological conditions (Knisel and Davis 2000). As with many environmental fate and transport models, the input and output files for GLEAMS can be complex. The general application of the GLEAMS model and the use of the output from this model to estimate concentrations in ambient water are detailed in SERA (2004).

For the current risk assessment, the application site was assumed to consist of a 10 acre square area that drained directly into a small pond or stream. The chemical specific values as well as the details of the pond and stream scenarios used in the GLEAMS modeling are summarized in Table 3-1. The GLEAMS modeling yielded estimates clopyralid runoff, sediment and percolation that were used to estimate concentrations in the stream adjacent to a treated plot, as detailed in Section 6.4 of SERA (2004). The results of the GLEAMS modeling for the small stream are summarized in Table 3-2 and the corresponding values for the small pond are summarized in Table 3-3. These estimates are expressed as both average and maximum water contamination rates (WCR) - i.e., the concentration of the compound in water in units of mg/L normalized for an application rate of 1 lb a.e./acre.

As indicated in Table 3-2, no stream contamination is estimated in very arid regions – i.e., annual rainfall of 10 inches of less. The modeled maximum concentrations in the stream range from about 5 µg/L to nearly 70 µg/L at annual rainfall rates from 15 to 250 inches per year, with the highest concentrations associated with sandy soil. While not detailed in Table 3-3, the losses from sand and loam are associated almost exclusively with percolation (nearly 100%). For clay, losses are associated almost exclusively with runoff.

As noted above, Leitch and Fagg (1985) monitored a maximum concentration 0.017 mg/L (17 µg/L) in stream water following a 5.2 inches of rain after the application of clopyralid at a rate of 1.90 lb a.e./acre to predominately clay-loam soil. This concentration corresponds to a water contamination rate – WCR normalized to 1 lb a.e./acre – of about 9 µg/L per lb a.e./acre applied [17 µg/L ÷ 1.9 lb a.e./acre = 8.95 µg/L per lb a.e./acre]. The rainfall of 5.2 inches of over a 19 day period corresponds to about 0.27 inches per day or about 100 inches per year. As indicated

in Table 3-2, the modeled water contamination rates for streams at an annual rainfall of 100 inches are 10.4 µg/L for clay and 21 µg/L for loam. Thus, the GLEAMS modeling estimates concentrations in water that are only modestly higher than those from the monitoring study by Leitch and Fagg (1985).

The GLEAMS scenarios do not specifically consider the effects of accidental direct spray. For example, the stream modeled using GLEAMS is about 6 feet wide and it is assumed that the herbicide is applied along a 660 foot length of the stream with a flow rate of 4,420,000 L/day. At an application rate of 1 lb/acre, accidental direct spray onto the surface of the stream would deposit about 41,252,800 µg [1 lb/acre = 112,100 µg/m^2 , 6'x660' = 3960 ft^2 = 368 m^2, 112,100 µg/m^2 × 368 m^2 = 41,252,800 µg]. This would result in a downstream concentration of about 10 µg/L [41,252,800 µg/day ÷ 4,420,000 L/day]. As indicated in Table 3-3, the expected peak concentrations from runoff or percolation are generally in the range of about 5 µg/L to nearly 69µg/L and thus encompass the potential effects of accidental direct spray or spray drift.

For the the current risk assessment, the upper range for the short-term water contamination rate will be taken as 70 µg/L per lb/acre, this somewhat higher than the maximum concentration at an annual rainfall rate 250 inches for sand. This value, converted to 0.07 mg/L per lb/acre, is entered into Worksheet B06. The central estimated will be taken as 20 µg/L (0.02 mg/L), about the maximum concentration for loam at an annual rainfall rates of 100 inches or for sand at annual rainfall rates of 50 inches. The lower range will be taken as 5 µg/L (0.005 mg/L), concentrations that might be expected from clay soils in relatively arid regions – i.e., annual rainfall of 15 inches. In very arid regions or in relatively arid regions with loam or sandy soils, lower concentrations are plausible.

3.2.3.4.2. LONGER-TERM EXPOSURE – The scenario for chronic exposure to clopyralid from contaminated water is detailed in worksheet D07. This scenario assumes that an adult (70 kg male) consumes contaminated ambient water from a contaminated pond for a lifetime. The estimated concentrations in pond water are based both the modeled estimates from GLEAMS, discussed in the previous section, as well as NAWQA monitoring data.

The National Water Quality Assessment (NAWQA) of the U.S. Geological Survey (USGS) has involved a large scale monitoring effort to characterize pesticides in surface and ground water. A detailed description of the USGS program may be obtained at http://water.usgs.gov/nawqa/. In brief, the USGS has monitored concentrations of a large number of pesticides, including clopyralid, in over 50 major river basins and aquifers. The monitoring data are given separately for streams and ground water for three types of sites: agricultural land use areas, urban areas, and major aquifers or large rivers of streams. Detailed data for streams and ground water covering a period from 1992 to 2001 are available at http://ca.water.usgs.gov/pnsp/. A subset of the data covering a period from 1992 to 1996 is available at http://ca.water.usgs.gov/pnsp/allsum/#t1. Clopyralid was not detected in any streams or ground water samples at a reporting limit of 0.42 µg/L.

The the essentially negative data from NAWQA and the GLEAMS modeling are not directly comparable. The NAWQA data may be viewed as general exposure levels that are not directly

associated with a fixed application while the GLEAMS modeling is an effort to characterize, at least generically, concentrations that might be expected after applications associated with Forest Service programs. Nonetheless, the failure to detect clopyralid in streams at a concentration of 0.42 µg/L in the NAWQA program is consistent with the GLEAMS modeling in streams (Table 3-2) in which the highest modeled average concentration of clopyralid is about 0.8 µg/L, only modestly higher than the 0.42 µg/L reporting limit used in the NAWQA program. Substantially higher concentrations of clopyralid are modeled in ponds (Table 3-3) with average longer term concentrations reaching up to about 12.5 µg/L – i.e., sandy soil at an annual rainfall rate of 100 inches per year. The NAWQA monitoring data cannot be used to assess the plausibility of the concentrations modeled using GLEAMS.

For this risk assessment, the typical WCR is taken as 7 µg/L or 0.007 mg/L per lb/acre. This is at or somewhat higher than the average concentration that is modeled in ponds using GLEAMS at rainfall rates of about 50 to 250 inches per year in loam. The upper range of the WCR is taken as 13 µg/L or 0.013 mg/L per lb/acre. This is somewhat above the highest average concentration modeled from sandy soil. The lower range is taken as 1 µg/L or 0.001 mg/L per lb/acre. This selection is somewhat arbitrary but would tend to encompass average concentrations in regions with predominantly clay soil.

The WCR values discussed in this section summarized in Worksheet B06 and used for all longer term exposure assessments involving contaminated water. As with the corresponding values for a small stream, these estimates are expressed as the water contamination rates (WCR) in units of mg/L per lb/acre.

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

One study regarding the bioconcentration of clopyralid has been encountered. Bidlack (1982) exposed bluegill sunfish to ^{14}C-labeled clopyralid for 28 days and found no indication of bioconcentration. For exposure assessments based on the consumption of contaminated fish, a BCF of 1 is used (i.e., the concentration in the fish will be equal to the concentration in the water).

For both the acute and longer-term exposure scenarios involving the consumption of contaminated fish, the water concentrations of clopyralid used are identical to the concentrations used in the contaminated water scenarios (see Section 3.2.3.4). The acute exposure scenario is based on the assumption that an adult angler consumes fish taken from contaminated water shortly after an accidental spill of 200 gallons of a field solution into a pond that has an average

depth of 1 meter and a surface area of 1000 m^2 or about one-quarter acre. No dissipation or degradation is considered. Because of the available and well-documented information and substantial differences in the amount of caught fish consumed by the general public and native American subsistence populations (U.S. EPA 1996), separate exposure estimates are made for these two groups, as illustrated in worksheet D08. The chronic exposure scenario is constructed in a similar way, as detailed in worksheet D09, except that estimates of clopyralid concentrations in ambient water are based on GLEAMS modeling as discussed in Section 3.2.3.4.

3.2.3.6. Oral Exposure from Contaminated Vegetation – None of the Forest Service applications of clopyralid will involve the treatment of crops. Thus, under normal circumstances and in most types of applications conducted as part of Forest Service programs, the consumption by humans of vegetation contaminated with clopyralid is unlikely. Nonetheless, any number of scenarios could be developed involving either accidental spraying of crops or the spraying of edible wild vegetation, like berries. In most instances, and particularly for longer-term scenarios, treated vegetation would probably show signs of damage from exposure to clopyralid (Section 4.3.2.4), thereby reducing the likelihood of consumption that would lead to significant levels of human exposure. Notwithstanding that assertion, it is conceivable that individuals could consume contaminated vegetation. One of the more plausible scenarios involves the consumption of contaminated berries after treatment of a right-of-way or some other area in which wild berries grow.

The two accidental exposure scenarios developed for this exposure assessment include one scenario for acute exposure, as defined in Worksheet D03 and one scenario for longer-term exposure, as defined in Worksheet D04. In both scenarios, the concentration of clopyralid on contaminated vegetation is estimated using the empirical relationships between application rate and concentration on vegetation developed by Fletcher et al. (1994) which is in turn based on a re-analysis of data from Hoerger and Kenaga (1972). These relationships are defined in worksheet A04. For the acute exposure scenario, the estimated residue level is taken as the product of the application rate and the residue rate (Worksheet D03).

For the longer-term exposure scenario (D04), a duration of 90 days is used. A large number of studies have been submitted to the U.S. EPA on clopyralid residues in plants (e.g., Biehn 1990, 1991a,b, 1995a,b; Markle 1991; McKellar 1995; Nugent and Schotts 1991; Teasdale and Coombe 1991; Yackovich and Lardie 1990). The most relevant study, however, appears to be that of McMurray et al. (1996), which has been published in the open literature and is summarized in Table 3-4. In this study, pre-bloom strawberries (6- to 8-leaf stage) were treated at application rates ranging from 0.07 to 0.28 kg a.i./ha using a backpack sprayer. While McMurray et al. (1996) report the application rate as a.i. rather than a.e., they did not specify which formulation or salt of clopyralid was applied. This has no impact on this exposure assessment because the McMurray et al. (1996) study is used in this risk assessment only to estimate the foliar half-time. After application, these investigators measured clopyralid residues in the strawberry fruit on days 30, 59, and 87 after treatment. These data are consistent with an exponential model using application rate and duration after treatment as the explanatory variables for the natural log of the residues on the strawberries as the dependent variable. The central estimate of the half-time of clopyralid concentrations on strawberries is 28.3 days with 95%

confidence intervals of 21.2 days to 42.8 days. Details of the statistical analysis are provided in Table 3-4.

The time zero estimate for residues on strawberries at an application rate of 1 lb/acre is 0.12 mg/kg based on the study by McMurray et al. (1996). This is a factor of about 58 less than the 7 mg/kg typical value given by Fletcher et al. (1994, see Worksheet A04). However, these studies are not comparable because the McMurray et al. (1996) study involved the application of clopyralid prior to the formation of the fruit. The Fletcher et al. (1994) estimates, based on a re-analysis of the data in Hoerger and Kenaga (1972), are derived from studies in which a number of different herbicides were applied directly to vegetation and residues were monitored over time. For the longer-term exposure assessment detailed in Worksheet D05, the estimates from Fletcher et al. (1994) are used because the exposure scenario assumes that the fruit is sprayed directly. As with the drinking water exposure scenarios, this very conservative approach has little impact on the characterization of risk because the levels of projected exposure are far below the levels of concern (Section 3.4).

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

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

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

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

A separate scenario involving the consumption of contaminated vegetation by drift rather than direct spray is not developed in this risk assessment. As detailed further in Section 3.4, this elaboration is not necessary because the direct spray scenario leads to estimates of risk that are below a level of concern. Thus, considering spray drift and a buffer zone quantitatively would have no impact on the characterization of risk.

3.2.4. Hexachlorobenzene. As mentioned in Section 2.2, technical grade clopyralid is contaminated with both hexachlorobenzene (≤2.5 ppm) and pentachlorobenzene (≤0.3 ppm). In terms of the potential for systemic toxic effects, the consequences of this contamination have a minimal impact on this risk assessment, as detailed in Section 3.3.3.1, because of the very low levels of the chlorinated benzenes in technical grade clopyralid. However, hexachlorobenzene is classified as a potential human carcinogen (Section 3.1.10) and the U.S. EPA has recommended and derived a cancer potency factor for this compound (Section 3.3.3.2).

As discussed in Section 3.1.15, the potential effect of a contaminant on a risk assessment is often encompassed by the available *in vivo* toxicity studies under the assumption that the toxicologic consequences of the contaminant is encompassed by the use of technical grade material – in this case clopyralid containing chlorinated benzenes. This rationale cannot be applied to hexachlorobenzene, however, because hexachlorobenzene is both more persistent than clopyralid and because hexachlorobenzene is classified as a carcinogen (Section 3.1.10). Thus, in order to quantitatively consider the potential cancer risk from hexachlorobenzene posed by the use of technical grade clopyralid in Forest Service programs, separate exposure assessments are required for hexachlorobenzene. Summaries of the exposure assessments for workers and members of the general public are given in the hexachlorobenzene worksheets that accompany this risk assessment (Supplement 3). All worksheets mentioned in this section refer those in Supplement 3.

The following discussion of the exposure assessments for hexachlorobenzene focuses on aspects of the exposure assessments that differ substantially from those used for clopyralid.

3.2.4.1. Dermal Absorption – No studies have been encountered on the dermal absorption rate of hexachlorobenzene in humans. In a study using rats, Koizumi (1991) estimated a first-order dermal absorption rate coefficient of 0.0014 $hour^{-1}$. Based on empirical relationships of molecular weight and the octanol-water partition coefficient to human dermal absorption rates, central estimate of the first-order dermal absorption rate coefficient for hexachlorobenzene is 0.022 $hour^{-1}$ with a range of about 0.0047 to 0.1 $hour^{-1}$ (Supplement 3, Worksheet B03). While a case could be made for using the lower dermal absorption rate from Koizumi (1991) because it is based on an experimental measurement, the higher first-order dermal absorption rates from Supplement 3, Worksheet B03, are used in the exposure scenarios involving first-order dermal absorption for both workers (Worksheets C03a, C03b) and members of the general public (D01a, D01b, and D02). This approach is taken because of uncertainties in the application of absorption rate data from rats for exposure assessments in humans.

As with first-order dermal absorption, no measurements of dermal permeability (K_p in cm/hr) in humans have been encountered for hexachlorobenzene. As with clopyralid, the K_p for hexachlorobenzene is estimated using the algorithm from U.S. EPA/ORD (1992), which is detailed in Worksheet A07b and applied to hexachlorobenzene in Worksheet B04 of Supplement 3.

3.2.4.2. Acute Exposures – For all of the worker exposure assessments as well as the acute exposure assessments for members of the general public, the exposure estimates follow the same general methods used for the clopyralid exposure assessments, as detailed in Sections 3.2.2 and 3.2.3. The major differences in the exposure assessments for clopyralid and hexachlorobenzene involve lipophilicity and water solubility. Clopyralid is highly water soluble (1000 mg/L, Table 2-1). Consequently, clopyralid does not partition substantially into fatty tissue ($K_{o/w}$ of about 0.0023) and thus dermal absorption, binding to soil, and bioconcentration of clopyralid are low compared to hexachlorobenzene.

Hexachlorobenzene, on the other hand, is highly lipophilic. The $K_{o/w}$ of hexachlorobenzene is about 1,500,000 and the water solubility of hexachlorobenzene is only about 0.006 mg/L. Thus, hexachlorobenzene may be readily absorbed across the skin, will bind tightly to most soils, and will bioconcentrate in fish (ATSDR 2002). Although the amount of hexachlorobenzene in technical grade clopyralid is relatively low, the potential for human exposure, in terms of the proportion of the exposure dose that might be absorbed, is higher than that for clopyralid itself.

Because of the extremely high lipophilicity and low water solubility of hexachlorobenzene, one adjustment considered in the acute exposure assessments concerns the impact of water solubility on the dermal spill scenarios. As detailed in hexachlorobenzene Worksheets B01 and B02, the calculation of the concentration of a compound, either a herbicide or contaminant, in a solution that is applied in the field is dependent on the concentration of the compound in the formulation as well as the dilution rates for the formulation recommended by the manufacturer. For hexachlorobenzene, the range of concentrations in a field solution based on these rates can be calculated as 0.000001 mg/mL to 0.000021 mg/mL (Worksheet B01). The upper range exceeds the water solubility of hexachlorobenzene, which is 0.006 mg/L or 0.000006 mg/mL. Thus, following the dermal exposure guidelines proposed by U.S. EPA (1992a), the functional exposure to hexachlorobenzene would be based on the water solubility of hexachlorobenzene rather than the maximum nominal concentration. For this risk assessment, however, the nominal concentrations are used. This approach is taken both to remain protective and because the presence of adjuvants in a clopyralid formulations may increase the solubility of hexachlorobenzene in the formulations and this may result in a higher water solubility of hexachlorobenzene in dilute aqueous solutions of the formulation – i.e., as in an accidental spill.

For acute exposure scenario involving an accidental spill into a small pond (Worksheets D05), both the central estimated and upper range of the concentration of hexachlorobenzene in the field solution also exceed the nominal concentration of hexachlorobenzene in water. As with the dermal exposure scenarios, and for the same reasons, these concentrations are used in the exposure assessment.

As with clopyralid, both the acute and chronic scenarios for the consumption of fish contaminated with hexachlorobenzene (Worksheets D07 and D10) require estimates of a bioconcentration factor (i.e., the concentration in fish divided by the concentration in water). As reviewed in ATSDR (2002), reported bioconcentration factors in fish range from about 2,000 to 20,000. For this risk assessment, the upper range of these bioconcentration factors is used in the chronic exposure scenarios. The application of a bioconcentration factor of 20,000 to the acute exposure scenario for contaminated fish (hexachlorobenzene D07) is a protective assumption. All of the bioconcentration factors reported in ATSDR (2002) involved exposure periods of at least one month. As detailed by Calabrese and Baldwin (1993, pp. 12–22), the kinetics of bioconcentration in fish are essentially identical to standard pharmacokinetic zero-order absorption and first-order elimination models (e.g., Goldstein et al. 1974). Consequently, for compounds that are extensively bioconcentrated, such as hexachlorobenzene, the levels in fish after one day will reflect bioconcentration factors that are typically much less than those seen after long-term exposures. Thus, for the acute exposure scenarios, the lower range of the bioconcentration factors reported in ATSDR (2002) is used – i.e., a BCF of 2000 L/kg.

3.2.4.3. General Considerations for Chronic Exposures – Hexachlorobenzene is ubiquitous and persistent in the environment. The major sources of general exposure for the public to hexachlorobenzene involve industrial emissions, proximity to hazardous waste sites, and the consumption of contaminated food. Virtually all individuals are exposed to hexachlorobenzene and virtually all individuals have detectable concentrations of hexachlorobenzene in their bodies (ATSDR 2002). Based on current concentrations of hexachlorobenzene in environmental media and food, daily doses of hexachlorobenzene (i.e., background levels of exposure) are in the range of 0.000001 mg/kg/day (ATSDR 2002). The major source of hexachlorobenzene release to the environment is from the manufacture of chlorinated solvents which accounts for an annual release of 70,343 to 241,311 kg (154,000 to 532,000 pounds). The presence of hexachlorobenzene as a contaminant in all pesticides containing hexachlorobenzene results in the release of about 17,366 kg/year (38,285 lbs/year) (ATSDR 2002). As detailed below, only a small fraction of this amount is associated with the use of clopyralid in Forest Service programs.

The average use of clopyralid by the Forest Service is currently about 2307 lbs/year – i.e., 6923.19 / 3 years from Table 2-3 – or about 1050 kg/year [2307 lbs × 0.4536 kg/lb = 1046.46 kg]. Given a concentration of 2.5 ppm hexachlorobenzene in technical grade clopyralid, the amount of hexachlorobenzene released to the environment as a result of Forest Service programs using clopyralid is about 0.003 kg:

$$1050 \text{ kg} \times 0.0000025 = 0.002625 \text{ kg}.$$

This amount represents a factor of about one in 5,600,000 (17,366÷0.003 = 5,588,667) relative to the amount of hexachlorobenzene released as a contaminant in all pesticides and a fraction of about 1 in 25 million (70,343 ÷ 0.003) to 1 in 80 million (241,311 ÷ 0.003) compared to the amount released from the manufacture of contaminated solvents. Thus, the use of clopyralid by the Forest Service will not substantially contribute to any wide-spread increase of ambient levels of hexachlorobenzene.

While the use of clopyralid by the Forest Service will not result in any general increase in environmental levels of hexachlorobenzene, this does not demonstrate that localized contamination would be insignificant. In order to better assess the potential impact of local contamination, three chronic exposure scenarios are considered quantitatively: contaminated vegetation, contaminated water, and contaminated fish.

3.2.4.4. Chronic Exposures Involving Contaminated Vegetation – Immediately after direct foliar application to vegetation, hexachlorobenzene will volatilize relatively rapidly from the surface of the vegetation and relatively little will be absorbed and available for longer-term exposures. Once hexachlorobenzene is absorbed into the soil column, however, it is relatively persistent, with reported half times in soil ranging from 3 to 6 years (ATSDR 2002). Thus, the primary concern for chronic exposures to contaminated vegetation is soil contamination with subsequent uptake by plants. This type of scenario requires estimates of long-term levels in soil as well as bioconcentration factors for terrestrial plants. The highest bioconcentration factor for the uptake of hexachlorobenzene from soil into plants is 19 (ATSDR 2002). This BCF was measured in the edible portion of carrots and is used directly for this exposure assessment

(Worksheets D03 and D04). As illustrated in these worksheets, this bioconcentration factor is multiplied by the concentration of hexachlorobenzene in soil to estimate the concentration of hexachlorobenzene in the plant. The remaining methods for estimating daily dose are identical to those used for clopyralid.

GLEAMS is used to estimate the concentration of hexachlorobenzene in soil. As with clopyralid, GLEAMS simulations were conducted over a wide range of annual rainfall rates in three types of soil: clay, loam, and sand. The chemical and site specific parameters used in the GLEAMS simulations are summarized in Table 3-5. The basic pond and stream scenarios are very similar to the scenarios used for clopyralid except that a root zone of 12 inches is used for hexachlorobenzene rather than the 60 inch root zone used for clopyralid. Most loss of hexachlorobenzene is due to runoff rather than percolation and use of a shallower root zone favors runoff (Knisel and Davis 2000, p. 28). Because of the shallow root zone, only two soil horizons are used, the top 1 inch and the remaining 11 inches. While hexachlorobenzene is extremely persistent in soil once it has become incorporated into the soil, hexachlorobenzene will rapidly volatilize from the soil surface and the relatively short halftime for the upper soil horizon is based on the study by Beall (1976) in which a very rapid decrease in hexachlorobenzene in the upper soil layer (0-2 cm or about 1 inch) was attributed to volatilization. The much longer halftimes for deeper soil layers is taken from a range of soil halftimes reported by ATSDR (2002).

The concentrations of hexachlorobenzene in soil from the GLEAMS simulations are summarized in Table 3-6. As with the corresponding tables for clopyralid, the concentrations are expressed as contamination rates – concentrations associated with an application rate of 1 lb/acre. Adjustments to these concentrations are made in the worksheets in which they are used.

The maximum concentrations in soil are independent of rainfall and reflect initial concentrations in soil immediately after application. Differences among soils are not remarkable. For the acute exposure assessment involving the consumption of contaminated vegetation (Worksheet D03), the highest concentration, 0.67 ppm, is used uniformly. This has no impact on the characterization of risk.

For the longer-term exposure scenario (Worksheet D04), the central estimate of the soil contamination rate is taken as 0.026 mg/kg soil per lb/acre. This is near the simulated values for all soil types over a wide range of rainfall rates. The upper range is only modestly higher, 0.031 mg/kg soil per lb/acre simulated for sandy soil at annual rainfalls of 200 or 250 inches. The lower range is taken as 0.007 mg/kg soil per lb/acre, the simulated value for clay at an annual rainfall of 250 inches.

For comparison, Beall (1976) monitored hexachlorobenzene in the top sandy loam at a concentration of about 0.1 mg/kg after the application of hexachlorobenzene. Although Beall (1976) does not specify an application rate in units of quantity per unit area, such as lb/acre, Beall specifies that the hexachlorobenzene was applied to yield an initial concentration of 10 mg/kg soil in the top 5 cm of soil. With this information, an approximate application rate can be

calculated. A 1 cm^2 soil surface that is 5 cm deep has a volume of 5 cm^3. The soil type used in the Beall (1976) study is specified as sandy loam but detailed soil characteristics are not provided in the publication. Taking a bulk density of 1.6 g/cm^3 for sandy loam soil (Knisel and Davis 2000, p. 46), a 5 cm^3 volume of soil would weigh 0.008 kg:

$$5\ cm^3 \times 1.6 g/cm^3 = 8\ g = 0.008\ kg.$$

To achieve a nominal concentration of 10 mg hexachlorobenzene/kg soil, the amount applied to a 1 cm^2 surface of soil would be :

$$0.008\ kg \times 10\ mg\ HCB/kg\ soil = 0.08\ mg = 80\ \mu g.$$

The application rate can be calculated as 80 $\mu g/cm^2$ or about 7.1 lbs/acre (1.0 lb/acre = 11.21 µg/cm2):

$$80\ \mu g/cm^2 \div (11.21\ \mu g/cm^2 \div 1\ lb/acre) = 7.136\ lbs/acre.$$

Thus, the soil contamination rate from the study by Beall (1976) is about 0.014 mg/kg per lb/acre [0.1 mg/kg ÷ 7.136 lbs/acre], only about a factor of 2 less than the average concentration modeled in GLEAMS and within the range of variability in the GLEAMS simulations.

3.2.4.5. Exposures Involving Contaminated Water – Immediately after application of a pesticide that is contaminated with hexachlorobenzene to soil or plants, there is not likely to be any immediate contamination of water attributable to the hexachlorobenzene in the contaminated pesticide. Nonetheless, because of the persistence of hexachlorobenzene, it will remain in the soil and could be transferred to surface waters where most of the hexachlorobenzene will be bound to sediments or bioconcentrated in aquatic organisms (ATSDR 2002).

No monitoring studies have been encountered that permit a direct estimate of the amount of hexachlorobenzene that would be found in ambient water as a result of applying a herbicide contaminated with hexachlorobenzene. Nonetheless, there are ample monitoring data to indicate that hexachlorobenzene can, over time, be transported to water either by runoff or by volatilization with subsequent redeposition in rainwater. Because hexachlorobenzene binds tightly to and is relatively immobile in soils, hexachlorobenzene is not likely to percolate through soils and directly contaminate ground water (ATSDR 2002). While volatilization may be an important route of environmental transport, volatilized hexachlorobenzene will be rapidly dispersed and transported over a relatively wide area. Although this will contribute to general background levels of hexachlorobenzene, the amounts of hexachlorobenzene released in Forest Service programs will not substantially contribute to background levels of hexachlorobenzene (Section 3.2.4.2). Consequently, for this risk assessment, the contamination of ambient water is based on estimates of hexachlorobenzene runoff from contaminated soil.

Based on the GLEAMS simulations described in the previous section, concentrations in streams and ponds at various annual rainfall rates and soils are summarized in Tables 3-7 and 3-8. The greatest concentrations of hexachlorobenzene will be from runoff sediment from clay, with lesser

concentrations from loam or sand. For acute exposures, a peak concentration rate of 90 µg/L per lb/acre is used as the central estimate for water in a contaminated stream. This is about the maximum concentration from clay at an annual rainfall of 100 inches (Table 3-7). The upper range is taken as 300 µg/L per lb/acre, somewhat above the highest concentration from clay at an annual rainfall of 250 inches. The lower range is set somewhat arbitrarily at 1 µg/L per lb/acre, in the range of concentrations that could be expect from runoff from clay in arid regions. These values are entered into Worksheet B06 and used in all exposure scenarios involving acute exposures to hexachlorobenzene associated with drinking water from a stream.

Longer-term concentrations in streams (Table 3-7) are estimated to be somewhat higher than those in lakes or ponds (Table 3-8). This is because the stream scenario assumes a rocky stream bed and ignores binding to sediment. For this risk assessment, the longer term concentrations are based on the simulations for a stream. The central estimate is taken as 0.5 µg/L per lb/acre, about the simulated concentration from clay at an annual rainfall of 100 inches as well as the the simulated concentration from loam at an annual rainfall of 250 inches. The longer-term concentration is taken as 1 µg/L per lb/acre, somewhat above the simulated concentration from clay at an annual rainfall of 250 inches. The lower limit is again somewhat arbitrarily set at 0.03 µg/L per lb/acre. These values are entered into Worksheet B06 and used in all exposure scenarios involving longer term exposures to hexachlorobenzene associated with drinking water from a stream.

3.2.4.6. Chronic Exposures Involving the Consumption of Contaminated Fish – Calculation of the doses of hexachlorobenzene that might be associated with the consumption of contaminated fish are detailed in hexachlorobenzene Worksheet D09. These calculations are based on the same exposure scenario and estimates of hexachlorobenzene concentrations in ambient water that are detailed in the previous section as well as standard estimates of fish consumption data for the general public as well as subsistence populations (Worksheet A04).

The most important variable unique to this scenario is the bioconcentration factor. This exposure assessment uses a BCF in fish of 10,000. ATSDR (1998) reports BCFs that range from about 2000 to 20,000, depending on the species and experimental design. As with the acute exposure scenario for contaminated fish, a BCF of 10,000 is selected as a reasonably conservative estimate. The subsequent dose estimates vary linearly with the bioconcentration factor. As discussed further in Section 3.4.7.2, this relatively modest variability in this factor has no substantial impact on the characterization of risk.

3.3. DOSE-RESPONSE ASSESSMENT

3.3.1. Overview. The Office of Pesticide Programs of the U.S. EPA has derived an acute RfD of 0.75 mg/kg/day and a chronic RfD of 0.15 mg/kg/day for clopyralid. The acute RfD is based on a short-term NOAEL of 75 mg/kg/day and an uncertainty factor of 100. The chronic RfD is based on a 2-year dietary NOAEL in rats of 15 mg/kg/day and an uncertainty factor of 100. Other studies in rats, mice, and dogs have noted general decreases in body weight, increases in liver and kidney weight, as well as a thickening in some epithelial tissue. Decreases in body weight and changes in organ weight are commonly observed in chronic toxicity studies and can indicate either an adaptive or toxic response. Changes in epithelial tissue are less commonly observed and the toxicologic significance of this effect is unclear. The data on the toxicity of clopyralid are adequate for additional dose-response or dose-severity modeling. Because none of the anticipated exposures substantially exceed the RfD and the great majority of anticipated exposures are far below the RfD, such additional modeling is not necessary for the characterization of risk.

The contamination of technical grade clopyralid with hexachlorobenzene and pentachlorobenzene can be quantitatively considered to a limited extent. The U.S. EPA has derived RfDs for both pentachlorobenzene and hexachlorobenzene and a cancer potency factor for hexachlorobenzene. Based on the levels of contamination of technical grade clopyralid with these compounds and the relative potencies of these compounds to clopyralid, this contamination is not significant in terms of potential systemic-toxic effects. This assessment, however, does not impact the potential carcinogenicity associated with hexachlorobenzene and this risk, based on the U.S. EPA's cancer potency parameter, is quantitatively considered in the risk characterization.

3.3.2. Existing Guidelines for Clopyralid. The U.S. EPA has not derived an agency-wide RfD for clopyralid – i.e., no RfD for clopyralid is listed at the U.S. EPA web site for RfDs, http://www.epa.gov/ngispgm3/iris/ . The U.S. EPA Office of Pesticide Programs has derived two RfDs for clopyralid: an acute RfD of 0.75 mg/kg/day and a chronic RfD of 0.15 mg/kg/day (U.S. EPA 2002). The acute RfD of 0.75 mg/kg/day is attributed to a developmental toxicity study in rats with a maternal NOAEL of 75 mg/kg/day and a corresponding LOAEL associated with decreased weight gain of 250 mg/kg/day. While the U.S. EPA (2002) does not identify the study on which the RfD is based, the study appears to be that of John et al. (1981). As detailed in Appendix 1, this study involved rats given average doses of 0, 15, 75, or 250 mg clopyralid/kg/day on Days 6 to15 of gestation. The U.S. EPA (2002) used an uncertainty factor of 100 (10 for species-to-species extrapolation and 10 for sensitive subgroups in the human population) to derive the acute RfD of 0.75 mg/kg/day (75 mg/kg/day ÷ 100 = 0.75 mg/kg/day). The Food Quality Protection Act requires the U.S. EPA to use an additional uncertainty factor of 10 to encompasses concerns for exposures involving children unless the available toxicologic demonstrate that such an uncertainty factor is unnecessary. The U.S. EPA (2002) elected to waive this uncertainty factor because the available toxicity data do not indicate that young animals are likely to be substantially more sensitive to clopyralid than mature animals. This is consistent with the data summarized in Appendix 1 and discussed in Section 3.1.9.

The chronic RfD of 0.15 mg/kg/day is based on a chronic rat NOAEL of 15 mg/kg/day with a corresponding LOAEL of 150 mg/kg/day (U.S. EPA 2002). As with the acute RfD, U.S. EPA (2002) does not specifically identify the study. The description provided by U.S. EPA (2002) appears to refer to the study by Barna-Lloyd et al. (1986). As summarized in Appendix 1, this study involved dietary exposures of Fisher rats equivalent to doses of clopyralid of 0, 15, 150, and 1500 mg/kg/day bw for 2 years. No effects were noted at 15 mg/kg/day. At 150 mg/kg/day, effects included hyperplasia and thickening of the epithelium of the anterior surface of the gastric limiting ridge (increased cells in the stratum spinosum). As with the acute RfD, the U.S. EPA (2002) used an uncertainty factor of 100 to derive the chronic RfD of 0.15 mg/kg/day – i.e., 15 mg/kg/day ÷ 100 = 0.15 mg/kg/day.

No other criteria for clopyralid have been found on Internet sites of any of the organizations responsible for setting environmental or occupational exposure recommendations, criteria, or standards (i.e., WHO, OSHA, NIOSH, or ACGIH). No published recommendations from these agencies or organizations were encountered in the literature search, which included databases and the Federal Register.

The data in Appendix 1 could be used to develop a more elaborate dose/response or dose/severity assessments. However, as discussed in Section 3.4, none of the exposure scenarios for clopyralid result in doses that substantially exceed the RfD. Consequently, an elaboration of dose-response or dose-severity relationships is unnecessary.

3.3.3. Existing Guidelines for Hexachlorobenzene.

3.3.3.1. Systemic Toxicity – Two contaminants are found in technical grade clopyralid: hexachlorobenzene (<2.5 ppm) and pentachlorobenzene (<0.3ppm) (Section 3.1.15). No guidelines, criteria, or standards have been encountered for pentachlorobenzene. The U.S. EPA has derived an RfD and a cancer potency factor for hexachlorobenzene (U.S. EPA 1997a) as well as an RfD for pentachlorobenzene (U.S. EPA 1988a). More recently, ATSDR (2002) has derived acute, intermediate, and chronic minimal risk levels (MRLs) for hexachlorobenzene.

The U.S. EPA chronic RfD for hexachlorobenzene is 0.0008 mg/kg/day. This RfD is based on a 130-week feeding study in male and female rats that also included a 90-day exposure to offspring. The U.S. EPA judged the NOAEL for liver effects at a dose of 0.08 mg/kg/day with a LOAEL at 0.29 mg/kg/day. The LOAEL was characterized by U.S. EPA (1997a) as "an increase ($p<0.05$) in hepatic centrilobular basophilic chromogenesis" in the offspring of the chronically exposed rats. As with clopyralid and for the same reasons as with clopyralid, the U.S. EPA used an uncertainty factor of 100 to derive the RfD of 0.0008 mg/kg/day.

The U.S. EPA RfD for pentachlorobenzene is also 0.0008 mg/kg/day (U.S. EPA 1988a). This RfD is based on a subchronic feeding study in male and female rats in which hyaline droplets were seen in proximal kidney tubules at 8.3 mg/kg/day, the lowest dose tested. Thus, this study did not identify a NOAEL. The RfD is based on the LOAEL of 8.3 mg/kg/day divided by an uncertainty factor of 10,000. The uncertainty factor of 10,000 is based on four factors of 10 for interspecies variability, variability in the human population, the use of a subchronic rather than chronic study, and the use of a LOAEL rather than a NOAEL.

ATSDR (2002) has derived a chronic oral MRL for hexachlorobenzene of 0.00002 mg/kg/day, a factor of 40 below the corresponding U.S. EPA chronic RfD of 0.0008 mg/kg/day. This chronic oral MRL is based on a LOAEL of 0.016 mg/kg/day from a study in which Sprague-Dawley rats were administered hexachlorobenzene in the diet for 130 weeks. The LOAEL is characterized as changes in liver histology (i.e., peribiliary lymphocytosis and fibrosis). These changes were also seen in a large number of control animals, but the effects were significantly increased ($p<0.05$) in animals exposed to hexachlorobenzene, and the magnitude of the increase was dose-related. In deriving the MRL, ATSDR applied an uncertainty factor of 1000, three factors of 10 for interspecies variability, variability in the human population, and the use of a LOAEL rather than a NOAEL.

Based on the U.S. EPA RfDs for clopyralid, pentachlorobenzene, and hexachlorobenzene as well as the available information on the levels of these chlorinated benzenes in technical grade clopyralid, the toxicologic significance of the contamination of clopyralid with pentachloro-benzene and hexachlorobenzene can be assessed. RfDs can be treated as estimates of toxicologically equivalent or equitoxic doses (i.e., all RfDs are doses that should cause no adverse effects). The ratio of equitoxic doses is one of the standard definitions of relative potency (e.g., Finney 1971). Using this definition, pentachlorobenzene and hexachlorobenzene may be regarded as about 190-times more potent than clopyralid:

$$0.15 \text{ mg/kg/day} \div 0.0008 \text{ mg/kg/day} = 187.5.$$

One common approach to assessing the hazards of chemical mixtures and the relative contribution that each component makes to the mixture is the concept of *potency weighted dose* under the assumption of dose addition (e.g., Mumtaz et al. 1994). This can be defined as the sum of the products of the relative potencies (B) and amounts or proportions (π) of each of the components in the mixture:

$$D_{mix} = \sum_{i=1}^{n} \mathrm{B}_i \pi_i$$

where the subscript, $\boldsymbol{i}$, designates the i^{th} component in the mixture. For technical grade clopyralid, estimates are available of the proportions of both hexachlorobenzene (a proportion of 0.0000025 or 2.5 ppm) as well as pentachlorobenzene (a proportion of 0.0000003 or 0.3 ppm). The proportion of clopyralid may be calculated by subtracting the proportions of each of these two contaminants:

$$1 - (0.0000025 + 0.0000003) = 0.9999972.$$

Since the toxicity of clopyralid relative to itself is unity (1) by definition, the potency weighted relative toxicity of technical grade clopyralid can be calculated as:

Clopyralid:	0.9999972 × 1 =	0.9999972
Hexachlorobenzene:	0.0000025 × 190 =	0.000475
Pentachlorobenzene:	0.0000003 × 190 =	0.000057
Total:		1.0005292

Thus, in terms of the toxicologic contribution of each component, clopyralid contributed approximately 99.95 % (0.9999972 ÷1.0005292 = 0.99989551) of the toxicity and the two chlorinated benzenes contribute approximately 0.05% of the toxicity.

The same type of calculation can be conducted using the MRL for hexachlorobenzene derived by ATSDR (1998). Using this MRL, the potency of hexachlorobenzene relative to clopyralid is 25,000:

0.15 mg/kg/day ÷ 0.00002 mg/kg/day = 7500.

Thus, the potency weighted relative toxicity of technical grade clopyralid can be calculated as:

Clopyralid:	0.9999972 × 1 =	0.9999972
Hexachlorobenzene:	0.0000025 ×7500 =	0.01875
Pentachlorobenzene:	0.0000003 × 190 =	0.0001875
Total:		1.0189347

Based on this estimate of the chronic toxic potency of hexachlorobenzene, clopyralid accounts for approximately 98% (0.9999972 ÷1.0189347 = 0.98141) of the chronic toxic potency of the technical grade product. Thus, although the two chlorinated benzenes should be regarded as much more potent toxicologically than clopyralid, the chlorinated benzenes do not appear to be present in a significant quantity with respect to systemic toxicity. In addition, all of the toxicity studies on clopyralid used the technical grade clopyralid and thus encompass the likely toxic contribution of the chlorinated benzene contaminants.

As noted above, ATSDR (1998) has also derived acute and intermediate MRLs for hexachloro-benzene. The acute MRL is 0.008 mg/kg/day, identical to the chronic RfD derived by U.S. EPA. The Office of Drinking Water of the U.S. EPA has derived a maximum contaminant level of 0.001 mg/L of drinking water and a maximum short-term health advisory of 0.05 mg/L of drinking water (U.S. EPA 1998).

3.3.3.2. Carcinogenic Potency – In addition to systemic toxicity, hexachlorobenzene has been shown to cause tumors of the liver, thyroid, and kidney in three species of rodents (mice, rats, and hamsters) (ExToxNet 1996; U.S. EPA 1997a). Based on a two-year feeding study in rats, the U.S. EPA (1997a) derived a cancer slope factor for lifetime exposures of 1.6 $(mg/kg/day)^{-1}$. In other words, cancer risk over a lifetime is calculated as the product of the daily dose over a lifetime and the potency parameter:

$$P = d\beta$$

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

$$d = P \div \beta$$

Thus, the lifetime daily dose of hexachlorobenzene associated with a risk of one in one-million (1÷1,000,000 or P=0.000001) is 0.000000625 mg/kg/day:

$$d_{(mg/kg/day)} = 0.000001 \div (1.6\ (mg/kg/day)^{-1}).$$

As noted in Section 3.1.5, clopyralid is not classified as a carcinogen. While it can be argued that the technical grade clopyralid used in the standard bioassays encompasses any toxicologic effects that could be caused by hexachlorobenzene, this argument is less compelling for carcinogenic effects because, for most cancer causing agents, the cancer risk is conservatively viewed as a non-threshold phenomenon (i.e., zero risk is achieved only at zero dose).

The potency factor of 1.6 $(mg/kg/day)^{-1}$ is intended to be applied to lifetime daily doses. As summarized in Section 3.2, many of the exposure assessments used in this risk assessment involve much shorter periods of time. Following the approach recommended by U.S. EPA (2003, p. 3-21), this risk assessment assumes that the average daily dose over a lifetime is the appropriate measure for the estimation of cancer risk. Thus, the lifetime potency of 1.6 $(mg/kg/day)^{-1}$ is scaled linearly when applied to shorter periods of exposure. For example, taking 70 years [70 years × 365 days/year = 25,550 days] as a reference life span, the potency parameter for a one-day exposure is calculated as 0.000063 $(mg/kg/day)^{-1}$:

$$1.6\ (mg/kg/day)^{-1} \times (1\ day \div 25{,}550\ days) = 0.000062622\ (mg/kg/day)^{-1}.$$

For example, taking a dose of 0.001 mg/kg/day, the lifetime risk associated with a one-day exposure at this dose would be calculated as 0.000000063:

$$0.000063\ (mg/kg/day)^{-1} \times 0.001\ mg/kg/day = 0.000000063.$$

This method of estimating risk is used in the worksheets for hexachlorobenzene that are appended to this document.

No explicit dose response assessment is made for the potential carcinogenic effects of pentachlorobenzene. This is consistent with the approach taken by U.S. EPA (1988a) and

reflects the fact the available data on pentachlorobenzene are inadequate to classify this compound as a carcinogen or to estimate carcinogenic potency. Because pentachlorobenzene and hexachlorobenzene are structurally and toxicologically similar and because the chronic RfD for both compounds are identical, a more conservative approach would be to assume that pentachlorobenzene is a carcinogen and that the carcinogenic potency of pentachlorobenzene is equal to that of hexachlorobenzene. If such an approach were taken, the cancer risks taken in this risk assessment would increase by a factor of about 0.1. In other words, pentachlorobenzene has the same potency but occurs at a ten-fold lower concentration relative to hexachlorobenzene. As detailed in the following section, this relatively modest difference has little impact on the characterization of cancer risk.

3.4. RISK CHARACTERIZATION

3.4.1. Overview. The risk characterization for potential human health effects associated with the use of clopyralid in Forest Service programs is relatively unambiguous. Based on the estimated levels of exposure and the criteria for acute and chronic exposure developed by the U.S. EPA, there is no evidence that typical or accidental exposures will lead to dose levels that exceed the level of concern for workers. In other words, all of the anticipated exposures for workers are below the acute RfD for acute exposures and below the chronic RfD for chronic exposures. For members of the general public, none of the longer-term exposure scenarios approach a level of concern and none of the acute/accidental scenarios exceed a level of concern, based on central estimates of exposure, although the upper limit of the hazard quotient for the consumption of water after an accidental spill slightly exceeds the level of concern – i.e., a hazard quotient of 2.

Irritation and damage to the skin and eyes can result from exposure to relatively high levels of clopyralid (i.e., placement of clopyralid directly onto the eye or skin). From a practical perspective, eye or skin irritation is likely to be the only overt effect as a consequence of mishandling clopyralid. These effects can be minimized or avoided by prudent industrial hygiene practices during the handling of clopyralid.

The only reservation attached to this assessment of clopyralid is that associated with any risk assessment: ***Absolute safety cannot be proven and the absence of risk can never be demonstrated.*** No chemical, including clopyralid, has been studied for all possible effects and the use of data from laboratory animals to estimate hazard or the lack of hazard to humans is a process that is fraught with uncertainty. Prudence dictates that normal and reasonable care should be taken in the handling of this or any other chemical. Notwithstanding these reservations, the use of clopyralid does not appear to pose any risk of systemic toxic effects to workers or the general public in Forest Service programs.

The contamination of clopyralid with hexachlorobenzene and pentachlorobenzene does not appear to present any substantial cancer risk. Administratively, the Forest Service has adopted a cancer risk level of one in one-million (1÷1,000,000) as a trigger that would require special steps to mitigate exposure or restrict and possibly eliminate use. Based on relatively conservative exposure assumptions, the risk levels estimated for members of the general public are below this trigger level. The highest risk level is estimated at about 3 in 100 million, a factor of 33 below the level of concern. The exposure scenario associated with this risk level involves the consumption of contaminated fish by subsistence populations (i.e., groups that consume relatively large amounts of contaminated fish). The consumption of fish contaminated with hexachlorobenzene is a primary exposure scenario of concern because of the tendency of hexachlorobenzene to bioconcentrate from water into fish. This is also consistent with the general observation that exposure to hexachlorobenzene occurs primarily through the consumption of contaminated food.

3.4.2. Workers. A quantitative summary of the risk characterization for workers associated with exposure to clopyralid is presented in Worksheet E02 of the clopyralid worksheets. The quantitative risk characterization is expressed as the hazard quotient, which is the ratio of the estimated exposure doses from Worksheet E01 to the acute or chronic RfD (Section 3.3.2).

Given the very low hazard quotients for both general occupational exposures as well as accidental exposures, the risk characterization for workers is unambiguous. None of the exposure scenarios approach a level of concern.

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) they are representative of reasonable accidental exposures. Given that the highest hazard quotient for any of the accidental exposures is a factor of 50 below the level of concern (i.e., a hazard quotient of 0.02 as the upper limit for a spill on to the lower legs for 1 hour), far more severe and less plausible scenarios would be required to suggest a potential for systemic toxic effects. As discussed in Section 3.2, however, confidence in this assessment is diminished by the lack of information regarding the dermal absorption kinetics of clopyralid in humans. Nonetheless, the statistical uncertainties in the estimated dermal absorption rates, both zero-order and first-order, are incorporated into the exposure assessment and risk characterization. Again, these estimates would have to be in error by a factor of over 50 in order for the basic characterization of risk to change.

The hazard quotients for general occupational exposure scenarios are similar to those for the accidental exposure scenarios. As with the highest hazard quotient for accidental exposures, the upper limit of the hazard quotients for both backpack and aerial applications are below the level of concern by a factor of 5 (i.e., hazard quotients of 0.2 relative to a level of concern of one). For broadcast ground applications, the hazard quotient is 0.4, below the level of concern by a factor of 2.5.

All of these hazard quotients are based on a typical application rate of 0.35 lb a.e./acre. As noted in Section 2, the Forest Service may consider applications of up to 0.5 lb a.e./acre, a factor of about 1.5 higher than the typical application rate [0.5 lb a.e./acre ÷ 0.35 lb a.e./acre = 1.429]. Because the hazard quotients are linearly related to exposure and the exposures are linearly related to the application rate, the highest hazard quotient of 0.4 at an application rate of 0.35 lb a.e./acre would correspond to a hazard quotient of about 0.6 at an application rate of 0.5 lb a.e./acre – i.e., $0.4 \times 1.429 = 0.5716$, which rounds to 0.6 using one significant decimal place.

The simple verbal interpretation of this quantitative characterization of risk is that even under the most conservative set of exposure assumptions, workers would not be exposed to levels of clopyralid that are regarded as unacceptable even at the highest application rate that would be considered in Forest Service programs. Under typical application conditions and applications rates, levels of exposure for workers will be far below levels of concern.

As discussed in Section 3.1.11, clopyralid can cause irritation and damage to the skin and eyes. Quantitative risk assessments for irritation are not derived; however, from a practical perspective, eye or skin irritation is likely to be the only overt effect as a consequence of mishandling clopyralid. These effects can be minimized or avoided by prudent industrial hygiene practices during the handling of clopyralid.

3.4.3. General Public. The quantitative hazard characterization for the general public associated with exposure to clopyralid is summarized in clopyralid worksheet E04. Like the quantitative risk characterization for workers, the quantitative risk characterization for the general public is expressed as the hazard quotient using the acute RfD of 0.75 mg/kg/day for acute exposures and the chronic RfD of 0.15 mg/kg/day for longer term exposures.

None of the longer-term exposure scenarios approach a level of concern and none of the acute/ accidental scenarios exceed a level of concern, based on central estimates of exposure, although the upper limit of the hazard quotient for the consumption of water after an accidental spill slightly exceeds the level of concern – i.e., a hazard quotient of 2.

Although there are several uncertainties in the longer-term exposure assessments for the general public, as discussed in Section 3.2, the upper limits for hazard quotients are sufficiently far below a level of concern that the risk characterization is relatively unambiguous: based on the available information and under the foreseeable conditions of application, there is no route of exposure or scenario suggesting that the general public will be at any substantial risk from longer-term exposure to clopyralid. At the upper range of exposures, the highest hazard quotient is 0.2, associated with the consumption of contaminated vegetation. Other hazard quotients are much lower, in the range of 0.000004 to 0.001. As in the risk characterization for workers, these hazard quotients apply to an application rate of 0.35 lb a.e./acre and may be adjusted to the maximum application of 0.5 lb a.e./acre by multiplying by about 1.5. Thus, at the highest application rate, the upper range of the highest hazard quotient for chronic exposure would be 0.3 – i.e., 0.2 ×1.5.

For the acute/accidental scenarios, the exposure resulting from the consumption of contaminated water by a child after an accidental spill is the only scenario that exceeds a level of concern. As discussed in some detail in Section 3.2.3.4.1, the exposure scenario for the consumption of contaminated water is an arbitrary scenario: scenarios that are more or less severe, all of which may be equally probable or improbable, easily could be constructed. All of the specific assumptions used to develop this scenario have a simple linear relationship to the resulting hazard quotient. Thus, if the accidental spill were to involve 20 rather than 200 gallons of a field solution of clopyralid, all of the hazard quotients would be a factor of 10 less. Nonetheless, this and other acute scenarios help to identify the types of scenarios that are of greatest concern and may warrant the greatest steps to mitigate. For clopyralid, as with most other chemicals, spills of relatively large amounts into a small body of standing water would require remedial action to limit exposure.

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 clopyralid. As discussed in Sections 3.1.3 and 3.3.2, the likely critical effect of clopyralid in humans cannot be identified clearly. Clopyralid can cause decreased body weight, increased kidney and liver weight, deceased red blood cell counts, as well as hyperplasia in gastric epithelial tissue in toxicity studies. These effects, however, are not consistent among species or even between different studies in the same species. Thus, it is unclear if individuals with pre-existing diseases of the kidney, liver, or blood would be particularly sensitive to clopyralid exposures, although

individuals with any severe disease condition could be considered more sensitive to many toxic agents.

In addition, some individuals may suffer from multiple chemical sensitivity (e.g., ATSDR 1995). Such individuals may respond adversely to extremely low levels of chemicals and in a manner that is atypical of the general population. There are no data or case reports, however, on idiosyncratic responses to clopyralid.

3.4.5. Connected Actions. Clopyralid may be applied in combination with other herbicides, particularly in combination with 2,4-D or 2,4-D and picloram. There are no data in the literature suggesting that clopyralid will interact, either synergistically or antagonistically with these or other compounds.

3.4.6. Cumulative Effects. As noted above, this risk assessment specifically considers the effect of repeated exposure in the chronic exposure scenarios developed for this risk assessment. Consequently, repeated exposure to levels below the toxic threshold should not be associated with cumulative toxic effects. As indicated in clopyralid Worksheet E04, all longer-term exposures are substantially below the level of concern.

3.4.7. Hexachlorobenzene.

3.4.7.1. Workers – Summaries of the exposure assessments and risk characterization for workers are given in the hexachlorobenzene worksheets that accompany this risk assessment (Supplement 3). Worksheet E01 summarizes the exposure assessment for workers and is analogous to the corresponding worksheet for clopyralid. Worksheet E02 summarizes the risk characterization for workers.

For acute exposures, the hazard quotients are based on ATSDR's short-term MRL of 0.008 mg/kg/day (ATSDR 2002). For chronic exposures, the hazard quotients are based on the chronic RfD from U.S. EPA of 0.0008 mg/kg/day.

For general worker exposures, the hazard quotients associated with hexachlorobenzene toxicity (Worksheet E02) are approximately three orders of magnitude below the corresponding hazard quotients for clopyralid. Thus, for the exposure scenarios covered in this risk assessment, the amount of hexachlorobenzene in technical grade clopyralid is not toxicologically significant.

The cancer risks presented in Worksheet E02 are presented as the estimated exposure divided by the lifetime dose associated with a cancer risk of 1 in one million. Thus, the interpretation of these quotients is identical to that of hazard quotients for toxicity – i.e., if the hazard quotient is below unity, the cancer risk is below 1 in one million. As indicated in Worksheet E02, none of the cancer risks in workers exceed 1 in one million.

As indicated in Section 3, all of these risk characterizations are based on a 2.5 ppm concentration of hexachlorobenzene in technical grade clopyralid. This is the upper range of hexachlorobenzene that may be expected in technical grade clopyralid and thus the actual risks are probably much lower than those given in Worksheet E02.

While there are substantial uncertainties involved in any cancer risk assessment, the verbal interpretation of the numeric risk characterization derived in this risk assessment is relatively simple. Using the assumptions and methods typically applied in Forest Service risk assessments, there is no plausible basis for asserting that the contamination of clopyralid with hexachlorobenzene will result in any substantial risk of cancer in workers applying clopyralid under normal circumstances.

While the chronic cancer potency could be scaled linearly and the cancer risk associated with short term exposures could be calculated, this sort of extrapolation is highly uncertain and, more importantly, ignores the normal background exposures to hexachlorobenzene from other sources. For example, background levels of exposure to hexachlorobenzene are in the range of 0.000001 mg/kg/day or 1×10^{-6} mg/kg/day (Section 3.2.4.3). As summarized in Worksheet E01, even the upper range general worker exposure values are below this background dose – i.e., in the range of 7×10^{-8} to 1×10^{-7} mg/kg/day. As discussed in the next section, the upper range of the longer term exposure scenarios for the general public are substantially below the background dose – i.e., about 3×10^{-11} to 2×10^{-8}. Thus, there is no basis for asserting that the presence of pentachlorobenzene or hexachlorobenzene in clopyralid will impact substantially cancer risk under conditions characteristic of applications made in Forest Service programs.

The above discussion is not to suggest that general exposures to hexachlorobenzene – i.e., those associated with normal background exposures that are not related to Forest Service applications of clopyralid – are acceptable. As discussed in Section 3.3.3.2, the cancer potency factor for hexachlorobenzene is 1.6 $(mg/kg/day)^{-1}$. At background exposure levels of about 1×10^{-6} mg/kg/day, the background risk associated with exposure to hexachlorobenzene would be 0.0000016 or about 1 in 625,000.

3.4.7.2. General Public – Summaries of the acute exposure assessments and risk characterization for the general public are given in the hexachlorobenzene worksheets that accompany this risk assessment and parallel those for the risk characterization for workers discussed in the previous section: Worksheet E03 summarizes the exposure assessments and Worksheet E04 summarizes the risk characterizations.

Worksheet E04 presents the hazard quotients for the general public associated with the acute exposure scenarios. As with the corresponding worksheet for workers, the hazard quotients for acute exposure are based on the short-term MRL of 0.008 mg/kg/day and the hazard quotients for chronic exposures are based on the U.S. EPA RfD of 0.0008 mg/kg/day.

All exposure scenarios result in hazard quotients that are below unity (i.e., the level of exposure is below the RfD for chronic exposures and below the MRL for acute exposures). The highest acute hazard quotient for hexachlorobenzene is 0.04, the upper range of the hazard quotient associated with the consumption of contaminated fish by subsistence populations.

As with worker exposures, none of the hazard quotients for cancer risk levels of 1 in 1-million exceed unity. As noted in Section 3.2.4.3, the typical background exposure to hexachlorobenzene is about 0.000001 or 1×10^{-6} mg/kg/day (ATSDR 2002). As indicated in hexachlorobenzene Worksheet E03, the highest longer-term exposure rate associated with Forest Service programs is 2.03×10^{-8} mg/kg/day – i.e., the upper range of exposure for the consumption of contaminated fish by subsistence populations. This is below the typical background exposure by a factor of about 50.

As discussed in Section 3.3.3.2., no explicit dose response assessment is made for the potential carcinogenic effects of pentachlorobenzene, another impurity in clopyralid Based on the comparison of apparent toxic potencies and the relative amounts of both hexachlorobenzene and pentachlorobenzene in clopyralid, a case could be made for suggesting that pentachlorobenzene may double the cancer risk over that associated with hexachlorobenzene. Given the extremely low levels of estimated cancer risk, this has essentially no impact on the risk characterization.

The simple verbal interpretation of this risk characterization is that, in general, the contamination of clopyralid with hexachlorobenzene does not appear to pose a risk to the general public. The prolonged use of clopyralid at the highest plausible application rate, 1 lb a.e./acre, could approach a level of concern in areas with small ponds or lakes used for fishing and in areas with local conditions that favor runoff. In such cases, site-specific exposure assessments and/or monitoring of hexachlorobenzene concentrations in water could be considered.

4. ECOLOGICAL RISK ASSESSMENT

4.1. HAZARD IDENTIFICATION

4.1.1. Overview. The toxicity of clopyralid is relatively well characterized in experimental mammals but few wildlife species have been assayed relative to the large number of non-target species that might be potentially affected by the use of clopyralid. Within this admittedly substantial reservation, clopyralid appears to be relatively non-toxic to terrestrial or aquatic animals, is highly selective in its toxicity to terrestrial plants, and relatively non-toxic to aquatic plants. Thus, the potential for substantial effects on non-target species appears to be remote. Consistent with this assessment of toxicity to non-target species, one long-term (8-year) field study has been conducted that indicates no substantial or significant effects on plant species diversity (Rice et al. 1997).

The toxicity to non-target terrestrial animals is based almost exclusively on toxicity studies using experimental mammals (i.e., the same studies used in the human health risk assessment). Some additional studies are available on birds, bees, spiders, and earthworms that generally support the characterization of clopyralid as relatively non-toxic. An additional study of the toxicity of clopyralid to non-target invertebrates also suggests that clopyralid has a low potential for risk (Hassan et al. 1994). A caveat in the interpretation of this study is the limited detail in which the experimental data are reported. As with terrestrial species, the available data on aquatic species, both plants and animals, suggest that clopyralid is relatively non-toxic.

The toxicity of clopyralid to terrestrial plants has been examined in substantial detail in studies that have been published in the open literature as well as studies that have been submitted to the U.S. EPA to support the registration of clopyralid. Clopyralid is a plant growth regulator and acts as a synthetic auxin or hormone, altering the plant's metabolism and growth characteristics, causing a proliferation of abnormal growth that interferes with the transport of nutrients throughout the plant. This, in turn, can result in gross signs of damage and the death of the affected plant. The phytotoxicity of clopyralid is relatively specific to broadleaf plants because clopyralid is rapidly absorbed across leaf surfaces but much less readily absorbed by the roots of plants. For the same reason, clopyralid is much more toxic/effective in post-emergent treatments (i.e., foliar application) rather than pre-emergent treatment (i.e., application to soil).

Clopyralid does not bind tightly to soil and thus would seem to have a high potential for leaching. While there is little doubt that clopyralid will leach under conditions that favor leaching—sandy soil, a sparse microbial population, and high rainfall—the potential for leaching or runoff is functionally reduced by the relatively rapid degradation of clopyralid in soil. A number of field lysimeter studies and the long-term field study by Rice et al. (1997) indicate that leaching and subsequent contamination of ground water are likely to be minimal. This conclusion is also consistent with a short-term monitoring study of clopyralid in surface water after aerial application (Leitch and Fagg 1985).

4.1.2. Toxicity to Terrestrial Organisms.

4.1.2.1. Mammals – As summarized in the human health risk assessment (see Section 3), a substantial number of toxicity studies is available in experimental mammals, specifically rats, mice, rabbits, and dogs exposed to clopyralid. The acute toxicity of clopyralid is relatively low: LD_{50} values of about 3000 mg/kg for clopyralid produced by electrochemical process and >5000 mg/kg for clopyralid produced by the penta process.

The mode of action of clopyralid in plants is well understood; however, its mode of action for causing toxicity in mammals has not been determined. There is no consistent toxic effect or set of toxic effects to an organ or an organ system which can be attributed to clopyralid. The U.S. EPA (1997b) RfD uses decreased body weight in rats as a critical effect—the adverse effect occurring at the lowest dose level. Effects on liver and kidney weight as well as changes in gastric epithelial tissue have also been noted at dose levels similar to those associated with changes in body weight.

4.1.2.2. Birds – As summarized in Appendix 2, the acute toxicity of clopyralid has been assayed using Mallard ducks and Bobwhite quail, both standard test species required by the U.S. EPA in the registration of pesticides. Most of the acute studies in birds involve dietary administration over short periods of time (i.e., 5 days). The LD_{50} data on experimental mammals, however, involve gavage administration of a single dose (placing the compound directly into the stomach by intubation). One gavage study in birds (Fink et al. 1980) is available on the acute toxicity of clopyralid to Mallard ducks. As indicated in Appendix 2, the LD_{50} by gavage in Mallard ducks was 1465 mg/kg bw (1220–1760 mg/kg bw). Since this study was conducted in the early 1980's, clopyralid from the older penta process was probably used. Thus, this LD_{50} in birds is most directly comparable to the reported LD_{50} in rats of >5000 mg/kg (Jeffrey et al. 1987b). As summarized in Appendix 1, the study in rats by Jeffrey et al. (1987b) noted no mortality and no signs of toxicity after single gavage doses of 5000 mg/kg bw to 9-week old male and female Fischer rats. The lower LD_{50} of 1465 mg/kg in ducks (Fink et al. 1980) with dose-related CNS effects at sub-lethal doses suggests that ducks could be somewhat more susceptible than mammals to the acute toxic effects of clopyralid.

This apparent difference in susceptibility between ducks and rats, however, is based on the comparison of only two studies. As discussed in Section 3.1.4 with respect to the comparison of the acute toxicity of penta process and electrochemical process clopyralid to rats, substantial random variation is found in the results from acute toxicity studies on the same material in the same species. Thus, it is possible that this apparent difference between birds and rats is attributable to chance rather than any underlying consistent difference in sensitivity among species or groups of species.

Although no experimental data are available on the Transline formulation, the dietary bioassay studies on birds can be used to assess the potential contribution of the monoethanolamine moiety to the toxicity of Transline, which contains the monoethanolamine salt of clopyralid as the active ingredient. Acute dietary studies can be used, albeit with substantial limitations, to compare the toxicity of clopyralid to the toxicity of the monoethanolamine salt of clopyralid in Mallard ducks (Fink 1973b; Fink et al. 1980) and Bobwhite quail (Fink 1973a). The primary problem with all

of these studies (with the exception of Fink et al. 1980) is that none of the exposures resulted in adequate mortality for the estimation of an LC_{50} or LD_{50} (Appendix 2). Nonetheless, these studies suggest that the dietary LC_{50} values for both clopyralid and the monoethanolamine salt of clopyralid are above 6000 ppm. In other words, mortality rates of less than 50% are seen at dietary concentrations of about 6000 ppm.

In addition to the standard acute toxicity studies, Dabbert et al. (1997) have found that direct spray of bobwhite quail eggs at up to 0.56 kg a.e./ha caused no gross effects (i.e., viability, hatchability, body weight) and no effects on immune function (humoral or cell-mediated) in chicks.

4.1.2.3. Terrestrial Invertebrates – Several studies (Cole 1974a,b; Dow Chemical 1980e; Hinken et al. 1986c) have been conducted on the toxicity of clopyralid to bees—a test required by the U.S. EPA in the registration of pesticides—using both oral and direct contact exposures (Appendix 3). No significant increase in mortality was noted in bees at doses of up to 0.1 mg/bee. Based on the results of a static bioassay on earthworms summarized in Dow AgroSciences (1998), the soil LC_{50} of clopyralid to earthworms is greater than 1000 ppm soil.

In addition to these standard bioassays, Hassan et al. (1994) have provided a summary of an apparently large series of bioassays and field trials on clopyralid as well as a number of other pesticides using a variety of terrestrial invertebrates. The form of clopyralid used in this study was Lontrel 100, a formulation of clopyralid that is no longer marketed commercially (480 g/ha of 0.012% a.i. was used in the experiments). While this publication does not provide detailed dose, exposure, or response data, it does indicate that clopyralid was classified by the study authors as *harmless*—a category that is defined by these investigators as exposures which result in less than 30% mortality—to 14/17 insect parasites and predatory mites in contact bioassays. Higher mortality rates (25–50%) were observed with clopyralid in *Semiadalia 11-notata* (Coccinellidae), *Anthocoris nemoralis* (Anthocoridae), and *Chryosperla carnea* (Chrysopidae). The authors classified this level of mortality as *"slightly harmful"*. A recent laboratory study on spiders (*Theridion impressum*) reported an acute (96-hour) lethality of less than 10% following a direct application clopyralid (Lontrel) at the recommended application rate (Pekar et al. 2002). Additional details of these studies are provided in Appendix 3.

4.1.2.4. Terrestrial Plants (Macrophytes) – Clopyralid is a plant growth regulator and acts as a synthetic auxin or hormone, altering the plant's metabolism and growth characteristics and often causing a proliferation of abnormal growth that interferes with the transport of nutrients throughout the plant. This, in turn, can result in gross signs of damage and the death of the affected plant (Crosswhite et al. 1995). At the biochemical level, clopyralid has been shown to inhibit glutamine synthetase and NADPH reductase in pea and oat chloroplasts (Levchenko et al. 1990). In the honey mesquite, clopyralid interferes with normal carbohydrate balance and the decline and recovery of total nonstructural carbohydrates in stems and roots is similar to that seen after hand cutting (Cralle and Bovey 1996). Clopyralid is not extensively metabolized (Guo 1996), although it may be conjugated to form a methyl ester (Biehn 1990).

Although clopyralid can be absorbed from both the leaves and the roots, foliar absorption predominates. In the sunflower and rapeseed, 97% foliar absorption occurs within 24 hours after foliar application (Hall and Vanden Born 1988). Thus, clopyralid is preferentially toxic to broad-leaf weeds and relatively non-toxic to grasses (Bachman et al. 1995; Crosswhite et al. 1995). Nonetheless, at sufficiently high-soil concentrations, clopyralid can cause significant damage by root absorption, particularly in seedlings (Clay et al. 1996). Root absorption appears to occur by non-facilitated diffusion. The rate of uptake through roots is greater at low pH, suggesting that the undissociated form is more readily absorbed than the anionic form (Devine et al. 1987).

A great deal of information is available on the toxicity of clopyralid to terrestrial plants. A large number of studies have been conducted on efficacy to target species, particularly honey mesquite (Bovey and Whisenant 1991; Bovey et al. 1988a,b, 1990a,b, 1991, 1994; Cralle and Bovey 1996; Whisenant and Bovey 1993; Whisenant et al. 1993). Additional efficacy studies have been conducted on Canada thistle (Devine and Vanden Born 1985), the field pansy *Viola arvensis* (Grundy et al. 1995), wild buckwheat (Kloppenburg and Hall 1990a,b,c), hemp dogbane (Orfanedes and Wax 1991; Orfanedes et al. 1993), wild carrot (Stachler and Kells 1997), and spotted knapweed (Rice et al. 1997). With the exception of the study by Rice et al. (1997), these studies are not directly useful for assessing potential effects on non-target species. Other than to acknowledge the efficacy of this compound and suggest the types of vegetation on which clopyralid might be most often applied, these efficacy studies are not detailed further.

A large number of studies are also available on the toxicity of clopyralid to non-target vegetation. The studies that can be used to identify sensitive as well as resistant species are summarized in Appendix 4. These studies support the generalization that clopyralid can be highly toxic to broadleaf plants but is relatively non-toxic to grasses or grains. For example, at application rates that approach or exceed the upper range of 0.5 lb a.e./acre that might be used by the Forest Service, little damage is likely to be apparent in barley or wheat (O'Sullivan and Kossatz 1984a,b). A more quantitative consideration of the dose-response relationships and species differences in sensitivity to clopyralid is given in Section 4.3.

While many of the toxicity studies on terrestrial plants are relatively short term, some longer-term field studies have been conducted. Rice et al. (1997) conducted an 8-year follow-up study of plots treated with clopyralid at a rate of 0.28 kg a.e./ha by backpack sprayer for the control of spotted knapweed (*Centaurea maculosa*). The formulation of clopyralid used was Stinger which, like Transline, contains the monoethanolamine salt of clopyralid. Four sites were examined, two characterized as fescue grassland and two as seral stage forest habitat. All sites were in west-central Montana and were initially treated in 1989, with two of the sites (one of each type) being re-treated in 1993. Over the 8-year period, clopyralid had no substantial or statistically significant effect on species diversity or species richness in plants. Some plant families, such as *Asteraceae* and *Fabaceae*, were impacted. Clopyralid was not detected in soil below 25 cm. This is consistent with a number of field lysimeter studies that suggest that clopyralid is not likely to leach deeply into soil layers and thus is not likely to contaminate ground water. Although clopyralid has an apparently high potential mobility because it does not bind tightly to soil, the functionally low leaching potential is apparently due to rapid microbial metabolism

(Baloch-Haq et al. 1993; Bergstrom et al. 1991; Bovey and Richardson 1991), as discussed further in Section 4.2.2.4.

4.1.2.5. Terrestrial Microorganisms – Relatively little information is available on the toxicity of clopyralid to terrestrial microorganisms. At concentrations of 1 or 10 ppm soil, clopyralid had no effect on nitrification, nitrogen fixation, or degradation of carbonaceaus material (McCall et al. 1979) (See Appendix 3). Applications of Lontrel EC, an emulsifiable concentrate of clopyralid, at 0.3 kg a.i./ha had no substantial effect on spore germination in *Colletotrichum gloeosporioides*, a fungal bioherbicide for round-leaved mallow (Grant et al. 1990). Dodd and Jeffries (1989) report that Harrier, a formulation of clopyralid with mecoprop (2-(4-chloro-2-methylphenoxy)-propanoic acid) and ioxynil (4-hydroxy-3,5-duodobezonitrile) inhibited the growth of a fungus (*Glomus geosporum*) that is associated with winter wheat. This effect, however, was probably attributable to mecoprop, not clopyralid, because the same effect was seen with other herbicide mixtures containing mecoprop. Clopyralid alone, however, was not tested.

4.1.3. Aquatic Organisms.

4.1.3.1. Fish – Standard toxicity bioassays to assess the effects of clopyralid on fish and other aquatic species are summarized in Appendix 5. For fish, only standard 96-hour acute toxicity bioassays are available. The lowest reported LC_{50} for clopyralid is 103 mg a.e./L in trout (Dow Chemical 1980e). At least for aquatic species, the monoethanolamine salt of clopyralid appears to be substantially less toxic than technical clopyralid. As indicated in Appendix 5, 96-hour LC_{50} values for the monoethanolamine salt of clopyralid are in the range of 2000 mg a.i./L to 4700 mg a.i./L, which is equivalent to 700–1645 mg a.e./L. Since clopyralid has a pK_a of about 2 (Table 2-1), it is reasonable to speculate that the apparently lower toxicity of the monoethanol-amine salt of clopyralid is attributable to buffering of the water pH by the monoethanolamine moiety. No longer-term toxicity studies are available on the toxicity of clopyralid to fish eggs or fry.

4.1.3.2. Amphibians – Neither the published literature nor the U.S. EPA files include data regarding the toxicity of clopyralid to amphibian species.

4.1.3.3. Aquatic Invertebrates – The only species of aquatic invertebrate on which toxicity data are available is *Daphnia magna*, a test species required by the U.S. EPA for the registration of pesticides (Appendix 5). The lowest reported LC_{50} for technical clopyralid to *Daphnia magna* is 225 mg/L (208–245 mg/L) (Batchelder 1980), about a factor of 2 higher than the lowest reported LC_{50} in fish of 103.5 mg/L (Dow Chemical 1980e). Unlike the case with fish, the monoethanol-amine salt appears to only marginally reduce the toxicity of clopyralid—an LC_{50} of 350 mg a.e./L for the salt and 225 mg a.e./L for the acid (Appendix 5).

A standard chronic reproduction bioassay has been conducted in *Daphnia magna* using the monoethanolamine salt of clopyralid. The no-observed-effect concentration was 66 mg a.i./L, which is equivalent to 23.1 mg a.e./L (Dow AgroSciences 1998).

4.1.3.4. Aquatic Plants – Aquatic plants are more sensitive to clopyralid than fish or aquatic invertebrates. The EC_{50} for growth inhibition in duckweed, an aquatic macrophyte, is 89 mg/L (Dow AgroSciences 1998). At lower concentrations, however, in the range of 0.01 to 0.1 mg/L, growth of other aquatic macrophytes is stimulated (Forsyth et al. 1997). The lowest reported EC_{50} for growth inhibition of green algae is 6.9 mg/L (Dill and Milazzo 1985).

4.1.3.5. Other Aquatic Microorganisms – There are no published or unpublished data regarding the toxicity of clopyralid to aquatic bacteria or fungi.

4.2. EXPOSURE ASSESSMENT

4.2.1. Overview. Terrestrial animals might be exposed to any applied herbicide from direct spray, ingestion of contaminated media (vegetation, prey species, or water), grooming activities, or contact with contaminated vegetation. In acute exposure scenarios, exposures from direct spray for small terrestrial vertebrates could reach up to about 8.5 mg/kg under the conservative assumption of 100% absorption. Acute exposures from the consumption of contaminated vegetation could lead to doses of about 6 to 9 mg/kg under typical conditions with an upper range of 17 to 27 mg/kg. In chronic exposures, estimated daily doses for the a small vertebrate from the consumption of contaminated vegetation are in the range of 0.0002 to 0.2 mg/kg/day. The upper ranges of exposure from contaminated vegetation far exceed doses that are anticipated from the consumption of contaminated water – i.e., about 0.0004 mg/kg/day to 0.0007 mg/kg/day. Based on general relationships of body size to body volume, larger vertebrates will be exposed to lower doses and smaller animals, such as insects, to much higher doses than small vertebrates under comparable exposure conditions.

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 rates considered in this risk assessment, 0.35 lb a.e./acre. Estimates for the other routes of exposure are much less. All of these exposure scenarios are dominated by situational variability because the levels of exposure are highly dependent on site-specific conditions. Thus, the exposure estimates are intended to represent conservative but plausible ranges that could occur but these ranges may over-estimate or under-estimate actual exposures in some cases. Spray drift is based on estimates from AgDrift. The proportion of the applied amount transported off-site from runoff is based on GLEAMS modeling of clay, loam, and sand. The amount of clopyralid that might be transported off-site from wind erosion is based on estimates of annual soil loss associated with wind erosion and the assumption that the herbicide is incorporated into the top 1 cm of soil. Exposure from the use of contaminated irrigation water is based on the same data used to estimate human exposure from the consumption of contaminated ambient water and involves both monitoring studies as well as GLEAMS modeling.

Exposures to aquatic plants and animals is based on essentially the same information used to assess the exposure to terrestrial species from contaminated water. The peak estimated rate of contamination of ambient water associated with the normal application of clopyralid is 0.02 (0.005 to 0.07) mg a.e./L at an application rate of 1 lb a.e./acre. For longer-term exposures, average estimated rate of contamination of ambient water associated with the normal application of clopyralid is 0.007 (0.001 to 0.013) mg a.e./L at an application rate of 1 lb a.e./acre. For the assessment of potential hazards, these contamination rates are adjusted based on the application rates considered in this risk assessment.

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

In this exposure assessment, estimates of oral exposure are expressed in the same units as the available toxicity data. As in the human health risk assessment, these units are usually expressed as mg of agent per kg of body weight and abbreviated as mg/kg. Chronic exposures are in units of mg/kg/day. For dermal exposure, the units of measure usually are expressed in mg of agent per cm of surface area of the organism and abbreviated as mg/cm^2. In estimating dose, however, a distinction is made between the exposure dose and the absorbed dose. The *exposure dose* is the amount of material on the organism (i.e., the product of the residue level in mg/cm^2 and the amount of surface area exposed), which can be expressed either as mg/organism or mg/kg body weight. The *absorbed dose* is the proportion of the exposure dose that is actually taken in or absorbed by the animal.

The exposure assessments for terrestrial animals are summarized in Worksheet G01. As with the human health exposure assessment, the computational details for each exposure assessment presented in this section are provided scenario specific worksheets (Worksheets F01 through F16b). Given the large number of species that could be exposed to herbicides and the varied diets in each of these species, a very large number of different exposure scenarios could be generated. For this generic – i.e., not site specific or species specific – risk assessment, an attempt is made to limited the number of exposure scenarios.

Because of the relationship of body weight to surface area as well as the consumption of food and water, small animals will generally receive a higher dose, in terms of mg/kg body weight, than will larger animals. Consequently, most general exposure scenarios for mammals and birds are based on a small mammal or bird. For mammals, the body weight is taken as 20 grams, typical of mice, and exposure assessments are conducted for direct spray (F01 and F02a), consumption of contaminated fruit (F03, F04a, F04b), and contaminated water (F05, F06, F07). Grasses will generally have higher concentrations of herbicides than fruits and other types of vegetation (Fletcher et al. 1994; Hoerger and Kenaga 1972). Because small mammals do not generally consume large amounts of grass, the scenario for the assessment of contaminated grass is based on a large mammal – a deer (Worksheets F10, F11a, and F11b). Other exposure scenarios for a mammals involve the consumption of contaminated insects by a small mammal (Worksheet F14a) and the consumption of small mammals contaminated by direct spray by a medium sized mammalian carnivore (Worksheet F16a). Exposure scenarios for birds involve the consumption of contaminated insects by a small bird (Worksheet F14b), the consumption of contaminated fish by a predatory bird (Worksheets F08 and F09), the consumption of consumption of small mammals contaminated by direct spray by a predatory bird (Worksheet 16b) and the consumption of contaminated grasses by a large bird (Worksheets F12, F13a, and F13b).

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

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

For this risk assessment, three groups of direct spray exposure assessments are conducted. The first, which is defined in Worksheet F01, involves a 20 g mammal that is sprayed directly over one half of the body surface as the chemical is being applied. The absorbed dose over the first day (i.e., a 24-hour period) is estimated using the assumption of first-order dermal absorption. The estimated absorption rate for humans is used as a protective assumption – i.e., the rate is higher than the measured value in rats (Koizumi 1991, Section 3.2.4.1). An empirical relationship between body weight and surface area is used to estimate the surface area of the animal. The estimates of absorbed doses in this scenario may bracket plausible levels of exposure for small mammals based on uncertainties in the dermal absorption rate of clopyralid.

Other, perhaps more substantial, uncertainties affect the estimates for absorbed dose. For example, the estimate based on first-order dermal absorption does not consider fugitive losses from the surface of the animal and may overestimate the absorbed dose. Conversely, some animals, particularly birds and mammals, groom frequently, and grooming may contribute to the total absorbed dose by direct ingestion of the compound residing on fur or feathers. Furthermore, other vertebrates, particularly amphibians, may have skin that is far more permeable than the skin of most mammals (Moore 1964). Quantitative methods for considering the effects of grooming or increased dermal permeability are not available. As a conservative upper limit, the second exposure scenario, detailed in Worksheet F02, is developed in which complete absorption over day 1 of exposure is assumed.

Because of the relationship of body size to surface area, very small organisms, like bees and other terrestrial insects, might be exposed to much greater amounts of clopyralid per unit body weight, compared with small mammals. Consequently, a third exposure assessment is developed using a body weight of 0.093 g for the honey bee (USDA/APHIS 1993). Because there is no information regarding the dermal absorption rate of clopyralid by bees or other invertebrates, this exposure scenario, detailed in worksheet F02b, also assumes complete absorption over the first day of exposure.

Direct spray scenarios are not given for large mammals. As noted above, allometric relationships dictate that large mammals will be exposed to lesser amounts (relative to body weight) of a compound in any direct spray scenario than smaller mammals. As detailed further in Section 4.4, the direct spray scenarios for the small mammal are substantially below a level of concern. Consequently, elaborating direct spray scenarios for a large mammal would have no impact on the characterization of risk.

4.2.2.2. Indirect Contact – As in the human health risk assessment (see Section 3.2.3.3), the only approach for estimating the potential significance of dermal contact is to assume a relationship between the application rate and dislodgeable foliar residue. The study by Harris

and Solomon (1992) (Worksheet A04) is used to estimate that the dislodgeable residue will be approximately 10 times less than the nominal application rate. As noted in Section 3.2.3.3, this estimate is consistent with the dislodgeable residue data for clopyralid (Peacock and Phillips 1999).

Unlike the human health risk assessment in which transfer rates for humans are available, there are no transfer rates available for wildlife species. As discussed in Durkin et al. (1995), the transfer rates for humans are based on brief (e.g., 0.5 to 1-hour) exposures that measure the transfer from contaminated soil to uncontaminated skin. Wildlife, compared with humans, are likely to spend longer periods of time in contact with contaminated vegetation.

It is reasonable to assume that for prolonged exposures a steady-state may be reached between levels on the skin, rates of absorption, and levels on contaminated vegetation, although there are no data regarding the kinetics of such a process. The bioconcentration data on clopyralid (Section 3.2.3.5) as well as the estimated rates of dermal absorption in humans (Section 3.1.12) suggest that clopyralid is not likely to partition from the surface of contaminated vegetation to the surface of skin, feathers, or fur. Thus, a plausible partition coefficient is unity (i.e., the concentration of the chemical on the surface of the animal will be equal to the dislodgeable residue on the vegetation).

Under these assumptions, the absorbed dose resulting from contact with contaminated vegetation will be one-tenth that associated with comparable direct spray scenarios. As discussed in the risk characterization for ecological effects (Section 4.4), the direct spray scenarios result in exposure levels below the estimated NOAEL (i.e., hazard quotients below one). Consequently, details of the exposure scenarios for contaminated vegetation are not further elaborated in this document.

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

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

estimated at about 3.6 g/day or about 18% of body weight per day from the general allometric relationship for food consumption in rodents (U.S. EPA/ORD 1993, p. 3-6).

A large herbivorous mammal is included because empirical relationships of concentrations of pesticides in vegetation, discussed below, indicate that grasses may have substantially higher pesticide residues than other types of vegetation such as forage crops or fruits (Worksheet A04). Grasses are an important part of the diet for some large herbivores, but most small mammals do not consume grasses as a substantial proportion of their diet. Thus, even though using residues from grass to model exposure for a small mammal is the most conservative approach, it is not generally applicable to the assessment of potential adverse effects. Hence, in the exposure scenarios for large mammals, the consumption of contaminated range grass is modeled for a 70 kg herbivore, such as a deer. Caloric requirements for herbivores and the caloric content of vegetation are used to estimate food consumption based on data from U.S. EPA/ORD (1993). Details of these exposure scenarios are given in worksheets F10 for acute exposures as well as Worksheets F11a and F11b for longer-term exposures.

For the acute exposures, the assumption is made that the vegetation is sprayed directly – i.e., the animal grazes on site – and that100% of the animals diet is contaminated. While appropriately conservative for acute exposures, neither of these assumptions are plausible for longer-term exposures. Thus, for the longer-term exposure scenarios for the large mammal, two sub-scenarios are given. The first is an on-site scenario that assumes that a 70 kg herbivore consumes short grass for a 90 day period after application of the chemical. In the worksheets, the contaminated vegetation is assumed to account for 30% of the diet with a range of 10% to 100% of the diet. These are essentially arbitrary assumptions reflecting grazing time at the application site by the animal. Because the animal is assumed to be feeding at the application site, drift is set to unity - i.e., direct spray. This scenario is detailed in Worksheet F11a. The second sub-scenario is similar except the assumption is made that the animal is grazing at distances of 25 to 100 feet from the application site (lowering risk) but that the animal consumes 100% of the diet from this contaminated area (increasing risk). For this scenario, detailed in Worksheet F12b, AgDrift is used to estimate deposition on the off-site vegetation. Drift estimates from AgDrift are summarized in Worksheet A06 and this model is discussed further in Section 4.2.3.2.

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

For this component of the exposure assessment, the estimated amounts of pesticide residue in vegetation are based on the relationship between application rate and residue rates on different types of vegetation. As summarized in Worksheet A04, these residue rates are based on estimated residue rates from Fletcher et al. (1994).

Similarly, the consumption of contaminated insects is modeled for a small (10g) bird and a small (20g) mammal. No monitoring data have been encountered on the concentrations of clopyralid

in insects after applications of clopyralid. The empirical relationships recommended by Fletcher et al. (1994) are used as surrogates as detailed in Worksheets F14a and F14b. To be conservative, the residue rates from small insects are used – i.e., 45 to 135 ppm per lb/ac – rather than the residue rates from large insects – i.e., 7 to 15 ppm per lb/ac.

A similar set of scenarios are provided for the consumption of small mammals by either a predatory mammal (Worksheet 16a) or a predatory bird (Worksheet 16a). Each of these scenarios assume that the small mammal is directly sprayed at the specified application rate and the concentration of the compound in the small mammal is taken from the worksheet for direct spray of a small mammal under the assumption of 100% absorption (Worksheet F02a).

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

4.2.2.4. Ingestion of Contaminated Water – Estimated concentrations of clopyralid in water are identical to those used in the human health risk assessment (Worksheet B06). The only major differences involve the weight of the animal and the amount of water consumed. There are well-established relationships between body weight and water consumption across a wide range of mammalian species (e.g., U.S. EPA 1989). Mice, weighing about 0.02 kg, consume approximately 0.005 L of water/day (i.e., 0.25 L/kg body weight/day). These values are used in the exposure assessment for the small (20 g) mammal. Unlike the human health risk assessment, estimates of the variability of water consumption are not available. Thus, for the acute scenario, the only factors affecting the variability of the ingested dose estimates include the field dilution rates (i.e., the concentration of the chemical in the solution that is spilled) and the amount of solution that is spilled. As in the acute exposure scenario for the human health risk assessment, the amount of the spilled solution is taken as 200 gallons. In the exposure scenario involving contaminated ponds or streams due to contamination by runoff or percolation, the factors that affect the variability are the water contamination rate, (see Section 3.2.3.4.2) and the application rate. Details regarding these calculations are summarized in Worksheets F06 and Worksheet F07.

4.2.3. Terrestrial Plants. In general, the primary hazard to non-target 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.

4.2.3.1. Direct Spray – Unintended direct spray will result in an exposure level equivalent to the application rate. For many types of herbicide applications – e.g., rights-of-way management – it is plausible that some non-target plants immediately adjacent to the application site could be sprayed directly. This type of scenario is modeled in the human health risk assessment for the consumption of contaminated vegetation.

4.2.3.2. Off-Site Drift – Because off-site drift is more or less a physical process that depends on droplet size and meteorological conditions rather than the specific properties of the herbicide, estimates of off-site drift can be modeled using AgDrift (Teske et al. 2001). AgDrift is a model developed as a joint effort by the EPA Office of Research and Development and the Spray Drift Task Force, a coalition of pesticide registrants. AgDrift is based on the algorithms in FSCBG (Teske and Curbishley. 1990), a drift model previously used by USDA.

For aerial applications, AgDrift permits very detailed modeling of drift based on the chemical and physical properties of the applied product, the configuration of the aircraft, as well as wind speed and temperature. For ground applications, AgDrift provides estimates of drift based solely on distance downwind as well as the types of ground application: low boom spray, high boom spray, and orchard airblast. Representative estimates based on AgDrift (Version 1.16) are given in Worksheet A06. For the current risk assessment, the AgDrift estimates are used for consistency with comparable exposure assessments conducted by the U.S. EPA. In addition, AgDrift represents a detailed evaluation of a very large number of field studies and is likely to provide more reliable estimates of drift. Further details of AgDrift are available at http://www.AgDrift.com/.

Estimates of drift for ground and aerial applications is given in Worksheet A06. In ground broadcast applications, clopyralid will typically be applied by low boom ground spray and thus these estimates are used in the current risk assessment.

Drift associated with backpack (directed foliar applications) are likely to be much less although studies quantitatively assessing drift after backpack applications have not been encountered. Drift distance can be estimated using Stoke's law, which describes the viscous drag on a moving sphere. According to Stoke's law:

$$v = \frac{D^2 \cdot g}{18n}$$

or

$$v = 2.87 \cdot 10^5 \cdot D^2$$

where v is the velocity of fall (cm sec^{-1}), D is the diameter of the sphere (cm), g is the force of gravity (980 cm sec^{-2}), and n is the viscosity of air ($1.9 \cdot 10^{-4}$ g sec^{-1} cm^{-1} at 20°C) (Goldstein et al. 1974).

In typical backpack ground sprays, droplet sizes are greater than 100 μ, and the distance from the spray nozzle to the ground is 3 feet or less. In mechanical sprays, raindrop nozzles might be used. These nozzles generate droplets that are usually greater than 400 μ, and the maximum distance above the ground is about 6 feet. In both cases, the sprays are directed downward.

Thus, the amount of time required for a 100 μ droplet to fall 3 feet (91.4 cm) is approximately 3.2 seconds,

$$91.4 \div (2.87 \cdot 10^5 (0.01)^2).$$

The comparable time for a 400 μ droplet to fall 6 feet (182.8 cm) is approximately 0.4 seconds,

$$182.8 \div (2.87 \cdot 10^5(0.04)^2).$$

For most applications, the wind velocity will be no more than 5 miles/hour, which is equivalent to approximately 7.5 feet/second (1 mile/hour = 1.467 feet/second). Assuming a wind direction perpendicular to the line of application, 100 μ particles falling from 3 feet above the surface could drift as far as 23 feet (3 seconds · 7.5 feet/second). A raindrop or 400 μ particle applied at 6 feet above the surface could drift about 3 feet (0.4 seconds · 7.5 feet/second).

For backpack applications, wind speeds of up to 15 miles/hour are allowed in Forest Service programs. At this wind speed, a 100 μ droplet can drift as far as 68 feet (3 seconds · 15 · 1.5 feet/second). Smaller droplets will of course drift further, and the proportion of these particles in the spray as well as the wind speed and turbulence will affect the proportion of the applied herbicide that drifts off-site.

4.2.3.3. Runoff – Clopyralid or any other herbicide may be transported to off-site soil by runoff or percolation. Both runoff and percolation are considered in estimating contamination of ambient water. For assessing off-site soil contamination, however, only runoff is considered. This approach is reasonable because off-site runoff 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. Based on the results of the GLEAMS modeling (Section 3.2.3.4.2), the proportion of the applied clopyralid lost by runoff was estimated for clay, loam, and sand at rainfall rates ranging from 5 inches to 250 inches per year.

4.2.3.4. Contaminated Irrigation Water – Unintended direct exposures of nontarget plant species may occur through the use of contaminated ambient water for irrigation. Effects on non-target vegetation have been observed with irrigation water contaminated by other herbicides (e.g., Bhandary et al. 1997; Gomez de Barreda et al. 1993).

The levels of exposure associated with this scenario will depend on the concentration of clopyralid in the ambient water used for irrigation and the amount of irrigation water that is applied. As detailed in Section 3.2.3.4, clopyralid is relatively mobile and peak contamination of ambient water may be anticipated and can be quantified (i.e., 0.02 [0.005 to 0.07] mg a.e./L at an application rate of 1 lb a.e./acre [Worksheet B06]).

The amount of irrigation water that may be applied will be highly dependent on the climate, soil type, topography, and plant species under cultivation. Thus, the selection of an irrigation rate is somewhat arbitrary. Typically, plants require 0.1 to 0.3 inch of water per day (Delaware Cooperative Extension Service 1999). In the absence of any general approach of determining and expressing the variability of irrigation rates, the application of one inch of irrigation water will be used in this risk assessment. This is somewhat higher than the maximum daily irrigation rate for sandy soil (0.75 inches/day) and substantially higher than the maximum daily irrigation

rate for clay (0.15 inches/day) (Delaware Cooperative Extension Service 1999). This variability is addressed further in the risk characterization (Section 4.4.2.2).

Based on the estimated concentrations of clopyralid in ambient water and an irrigation rate of 1 inch per day, the estimated functional application rate of clopyralid to the irrigated area is about 2×10^{-4} (4×10^{-5}–5×10^{-4}) lb a.e./acre (see Worksheet F15 for details of these calculations). This level of exposure is inconsequential relative to off-site drift and runoff [Worksheets G04 and G05].

4.2.3.5. Wind Erosion – Wind erosion is a major transport mechanism for soil (e.g., Winegardner 1996). Although no specific incidents of nontarget damage from wind erosion have been encountered in the literature for clopyralid, this mechanism has been associated with the environmental transport of other herbicides (Buser 1990). Numerous models have been developed for wind erosion (e.g., Strek and Spaan 1997; Strek and Stein 1997) and the quantitative aspects of soil erosion by wind are extremely complex and site specific. Field studies conducted on agricultural sites found that wind erosion may account for annual soil losses ranging from 2 to 6.5 metric tons/ha (Allen and Fryrear 1977). The upper range reported by Allen and Fryrear (1977) is nearly the same as the rate of 2.2 tons/acre (5.4 tons/ha) recently reported by the USDA (1998). The temporal sequence of soil loss (i.e., the amount lost after a specific storm event involving high winds) depends heavily on soil characteristics as well as meteorological and topographical conditions.

To estimate the potential transport of clopyralid by wind erosion, this risk assessment uses average soil losses ranging from 1 to 10 tons/ha·year, with a typical value of 5 tons/ha·year. The value of 5 tons/ha·year is equivalent to 500 g/m^2 (1 ton=1000 kg and 1 ha = 10,000 m^2) or 0.05 g/cm^2 (1m^2=10,000 cm^2). Using a soil density of 2 g/cm^3, the depth of soil removed from the surface per year would be 0.025 cm [(0.05 g/cm^2)÷ (2 g/cm^3)]. The average amount per day would be about 0.00007 cm/day (0.025 cm per year ÷ 365 days/year). This central estimate is based on a typical soil loss rate of 5 tons/ha·year. Since the range of plausible rates of annual soil loss is 1 to 10 tons/ha·year, the range of soil loss per day may be calculated as 0.00001 cm/day (0.00007÷5 = 0.000014) to 0.0001 cm/day (0.00007×2 = 0.00014).

The amount of clopyralid that might be transported by wind erosion depends on several factors, including the application, the depth of incorporation into the soil, the persistence in the soil, the wind speed, and the topographical and surface conditions of the soil. Under desirable conditions, like relatively deep (10 cm) soil incorporation, low wind speed, and surface conditions that inhibit wind erosion, it is likely that wind transport of clopyralid would be neither substantial nor significant. For this risk assessment, it will be assumed that clopyralid is incorporated into the top 1 cm of soil. Thus, daily soil losses expressed as a proportion of applied amount would be 0.00007 with a range of 0.00001 to 0.001. These values are encompassed by the range of off-site drift associated with ground applications, 0.0008 to 0.0187 [Worksheet G05a], and thus the risks associated with wind erosion are encompassed by the exposure scenarios and hazard quotients given in Worksheet G05a. As with the deposition of clopyralid in runoff, the deposition of the clopyralid contaminated soil from wind erosion will vary substantially with local conditions and, for this risk assessment, neither concentration nor dispersion is considered quantitatively.

4.2.4. Soil Organisms. Limited data are available on the toxicity of clopyralid to soil invertebrates (Section 4.1.2.3) as well as soil microorganisms (Section 4.1.2.5). For both groups, the toxicity data are expressed in units of soil concentration – i.e., mg clopyralid/kg soil which is equivalent to parts per million (ppm) concentrations in soil. The GLEAMS modeling discussed in Section 3.2.3.4 provides estimates of concentration in soil as well as estimates of off-site movement (runoff, sediment, and percolation). Based on the GLEAMS modeling, concentrations in clay, loam, and sand over a wide range of rainfall rates are summarized in Table 4-2. As indicated in this table, peak soil concentrations in the range of about 0.2 to 0.25 ppm are likely in relatively arid soils at an application rate of 1 lb a.e./acre. As rainfall rate increases, maximum soil concentrations are substantially reduced in sand and, to a lesser extent, in loam because of losses from soil through percolation. The potential consequences of such exposures are discussed in Section 4.4 (Risk Characterization).

4.2.5. Aquatic Organisms. The potential for effects on aquatic species are based on estimated concentrations of clopyralid in water that are identical to those used in the human health risk assessment (Worksheet B06). As summarized in Worksheet B06, the peak estimated rate of contamination of ambient water associated with the normal application of clopyralid is 0.02 (0.005 to 0.07) mg a.e./L at an application rate of 1 lb a.e./acre. For longer-term exposures, average estimated rate of contamination of ambient water associated with the normal application of clopyralid is 0.007 (0.001 to 0.013) mg a.e./L at an application rate of 1 lb a.e./acre. For the assessment of potential hazards, these contamination rates are adjusted based on the application considered in this risk assessment – i.e., 0.35 lb a.e./acre.

4.3. DOSE-RESPONSE ASSESSMENT

4.3.1. Overview. For terrestrial mammals, the dose-response assessment is based on the same data as the human health risk assessment (i.e., an acute NOAEL of 75 mg/kg/day and a chronic NOAEL of 15 mg/kg/day). These NOAEL values are detailed in Section 3.3. None of the exposure scenarios, acute or longer term, result in exposure estimates that exceed this NOAEL. A comparison of gavage studies between mammals and birds suggest that birds may be more sensitive than mammals by about a factor of 3. Based on a comparison of short-term dietary NOAELs, however, birds appear to be somewhat less sensitive with an acute dietary NOAEL of about 670 mg/kg/day, a factor of about 9 above the acute NOEL of 75 mg/kg/day for mammals. Since most of the exposure assessments developed in this risk assessment involve gradual intake during the day rather than gavage like exposures, the dietary NOEL of 696 mg/kg/day is used for the risk characterization in birds. No lifetime toxicity studies in birds have been encountered and the chronic NOAEL for mammals of 15 mg/kg/day is used in this risk assessment to assess the risks associated with longer term exposures.

The toxicity of clopyralid to terrestrial plants can be characterized relatively well and with little ambiguity. Clopyralid is more toxic to broadleaf plants than grains or grasses and is more toxic in post-emergence applications (i.e., foliar spray) than pre-emergence applications (i.e., soil treatment). For assessing the potential consequences of exposures to nontarget plants via runoff, the NOEC values for seed emergence are used for sensitive species (0.025 lb a.e./acre) and tolerant species (0.5 lb a.e./acre). For assessing the impact of drift, bioassays on vegetative vigor will be used with NOEC values of 0.0005 lb/acre for sensitive species and 0.5 lb/acre for tolerant species.

The data on toxicity to fish are limited. No chronic studies or even long-term studies on fish egg-and-fry have been encountered. The dose-response assessment uses admittedly limited data suggesting that at least some fish species may be more sensitive to clopyralid than daphnids. For acute exposures, an acute LC_{50} value of 103.5 mg/L is used to characterize risk for sensitive species and an acute LC_{50} value of 1645 mg a.e./L is used to characterize risk for tolerant fish species. Based on differences in acute toxicity between sensitive fish and daphnids, the longer term NOEC for sensitive species is based on the 23.1 mg a.e./L from daphnids but adjusted downward by a factor of 2 and then rounded to one significant digit – i.e. 10 mg/L. For sensitive aquatic plants, risk is characterized using the lowest reported EC_{50} of 6.9 mg a.e./L. Conversely, for tolerant aquatic plants, the highest reported EC_{50}, 449 mg/L, is used. The available data on aquatic plants are not sufficient to support separate dose-response assessments for macrophytes and algae.

4.3.2. Toxicity to Terrestrial Organisms.

4.3.2.1. Mammals – As summarized in the dose-response assessment for the human health risk assessment (Section 3.3), the Office of Pesticide Programs of the U.S. EPA has derived an acute RfD of 0.75 mg/kg/day and a chronic RfD of 0.15 mg/kg/day for clopyralid. The acute RfD is based on a short-term NOAEL of 75 mg/kg/day and an uncertainty factor of 100. The chronic RfD is based on a 2-year dietary NOAEL in rats of 15 mg/kg/day and an uncertainty factor of 100. All of the estimated mammalian acute exposures are below the acute NOEL of 75 mg/kg/day and all of all of the estimated mammalian chronic exposures are below the chronic

NOEL of 75 mg/kg/day. Consequently, these acute and chronic NOAELs are used directly and without elaboration.

4.3.2.2. Birds – As noted in Section 4.1.2.2, one acute gavage LD_{50} value in Mallard ducks is about a factor of 3 below a gavage dose in rats that resulted in no apparent signs of toxicity. This suggests that birds may be somewhat more sensitive to clopyralid than mammals, but the data supporting this suggestion are extremely limited.

Dietary studies suggest that the dietary LC_{50} values for both clopyralid and the monoethanolamine salt of clopyralid are above 4640 ppm in both quail (Fink 1973a) and ducks (Fink 1973a). Typically, these dietary studies in birds involve food consumption rates that are equal to about 15% of body weight per day. Thus, a dietary exposure of 4640 ppm corresponds to a daily dose of about 696 mg/kg/day. This is about a factor of nine above the acute gavage NOEL of 75 mg/kg/day for mammals. Because the mammalian NOAEL was from a gavage exposure over an 11 day period and the bird NOAEL is from a dietary study over a 5 day period, the apparent lesser sensitivity in birds – i.e., a higher NOAEL – could be due to differences in the experimental conditions.

Since most of the exposure assessments developed in this risk assessment involve gradual intake during the day – i.e., grazing activity in dietary exposures – rather than acute exposures, the dietary NOEL of 696 mg/kg/day based on the studies by Fink (1973a,b) will be used to characterize acute risks in birds and this value is rounded to 670 mg/kg/day and entered into the bottom of Worksheet G02. No chronic toxicity studies in birds have been encountered. For this risk assessment, the chronic NOAEL for mammals of 15 mg/kg/day will be used. It should be noted that a case could be made for increasing this value based on the apparent differences in the acute dietary NOAELS – i.e., 75 mg/kg/day for mammals and 670 mg/kg/day for birds. This is not explored in the current risk assessment because the use of the lower value of 15 mg/kg/day results in hazard quotients that are below the level of concern for all exposure scenarios even at the upper limit of plausible doses. Thus, the use of a higher chronic NOAEL would have no impact on the characterization of risk.

4.3.2.3. Terrestrial Invertebrates – As discussed in Section 4.1.2.3, several studies indicate that the toxicity of clopyralid to bees is on the same order of magnitude and perhaps somewhat less than the toxicity of clopyralid to mammals (i.e., acute oral or contact LD_{50} values >9000 mg/kg bw). For this risk assessment, the study by Hinken et al. (1986c) will be used for the dose-response assessment for acute contact toxicity, in which no significant increase in mortality was noted at doses of up to 0.1 mg/bee (Appendix 3). Taking an average weight of 110 mg/bee or 0.00011 kg/bee from Hinken et al. (1986c), the LD_{50} of 0.1 mg/bee corresponds to a dose of 909 mg/kg bw (0.1 mg/bee ÷ 0.00011 kg/bee = 909 mg/kg bw). This order of toxicity is comparable to the acute NOAEL value for birds of 670 mg/kg/day discussed in the previous section.

Based on a single study, the acute toxicity of clopyralid to earthworms also appears to be low (i.e., soil LC_{50} >1000 ppm soil). While these data can be used to assess acute hazard, no quantitative consideration can be given to other potential subchronic or non-lethal effects.

The report by Hassan et al. (1994) on both laboratory bioassays and field trials with clopyralid does not suggest that clopyralid is likely to be remarkably hazardous to terrestrial invertebrates. However, this publication provides only a very brief summary of what appears to be a large and complex study on many invertebrates species. Consequently, it cannot be used quantitatively to develop species specific dose/response relationships.

4.3.2.4. Terrestrial Plants (Macrophytes) – As discussed in Section 4.1.2.4, clopyralid is relatively ineffective against grasses and grains but can be highly toxic to broadleaf plants, both target and non-target. A summary of the dose-severity relationships for terrestrial plants is given in Table 4-1. This table is based on the data presented in Appendix 4. The first column of this table gives the range of application rates. The next four columns represent four severity categories: no effect, slight effect, moderate effect, and severe effect as defined in the key to Table 4-1. The definitions of these levels of severity are intended to broadly encompass the various types of observations specified in Appendix 4.

Listings of the same plant group in multiple columns indicates species differences within the group. For example, at application rates of 0.2 to 0.5 lb a.i./acre, the responses of different species of cacti are highly variable. Some species of cacti will have no effects, some will suffer high levels of mortality, and other species will show intermediate responses (Crosswhite et al. 1995). Thus, in Table 4-1 cactus species are listed in each of the four severity columns in the row associated with application rates of >0.2–0.5 lb/acre. Table 4-1 does not attempt to capture temporal relationships. For example, at an application rate of 0.28 kg a.i./ha, red maple evidenced significant visual injury at 60 to 150 days after treatment but these effects were transient and over the longer term there was no effect on growth (Smith and Skroch 1995). In Table 4-1, red maple is simply put into the severe response category for the appropriate range of application rates.

Several studies are available on a variety of different plant species in which clopyralid was applied at rates that are in the range of the typical (0.1 lb a.e./acre) to the highest application rate (1.0 lb a.e./acre). While these studies generally support the specificity of clopyralid to broadleaf plants, the likelihood of observing damage will vary within groups of plants depending on the species. For example, damage to grasses or grass-like grains at or near the upper range of the application rate may be minimal in some species of grains such as Glenlea wheat but apparent in other species such as Meepawa wheat (O'Sullivan and Kossatz 1984a,b). Similarly, near the typical application rate of 0.1 lb a.e./acre, some forbes or trees may evidence damage while others will not (e.g., Bachman et al. 1995; Pywell et al. 1996; Smith and Skroch 1995).

The extent to which these differences within various groups of plants can be attributed to simple physical differences among the various plant groups as opposed to intrinsic differences in sensitivity or persistence is unclear. In some case, such as the differential sensitivities of willow (less sensitive) and poplar (more sensitive), the differences may be due simply to greater retention of clopyralid by the more sensitive species (Clay 1991). In other cases, such as the effects seen in red maple but not in pear, myrtle, and redbud, the basis for the differing effects is unclear (Smith and Skroch 1995).

In addition, a substantial difference in the sensitivity of plants is seen depending on the stage at which clopyralid is applied (i.e., pre-emergence or post-emergence). This is best illustrated in the study by Weseloh (1987), who estimated NOAELs for various species after both pre-emergent and post-emergent applications. When applications were made prior to emergence (i.e., directly to the soil before the germination of the plant seeds) NOAELs for sensitive species such as soybeans, snap beans, tomatoes, and sunflowers was in the range of 0.028 to 0.056 kg/ha. When applied directly to the foliage (i.e., post-emergence) the NOAELs were much lower, in the range of 0.00056 kg/ha. As discussed in Section 4.1.2.4, this difference is attributable to the very rapid absorption of clopyralid after direct foliar application.

For assessing the potential consequences of exposures to nontarget plants via runoff, the NOEC for seed emergence in soy bean of 0.028 kg a.e./ha is used (equivalent to 0.025 lb a.e./acre) for sensitive species and the the NOEC for seed emergence in several species of 0.56 kg a.e./ha is used (equivalent to 0.5 lb a.e./acre) for tolerant species. The specific species associated with these NOEC values are given in Appendix 4 (Weseloh 1987). These values for sensitive and tolerant species are entered into Worksheet G04.

For assessing the impact of drift, bioassays on vegetative vigor will be used, also from the study by Weseloh (1987). For sensitive species, the NOEC of 0.00056 kg/ha (0.0005 lb/acre) for soybean, snap bean, tomato, and sunflower will be used. For tolerant species, the NOEC of 0.56 kg/ha (0.5 lb a.e./acre) for barley, corn, radish, and canola will be used. These values for sensitive and tolerant species are entered into Worksheet G05a (ground applications) and G05b (aerial application).

4.3.2.5. Terrestrial Microorganisms – The most appropriate study for assessing effects on soil microorganisms is the 10 ppm soil NOEC for clopyralid for effects on nitrification, nitrogen fixation, and degradation of carbonaceous material (McCall et al. 1979) (See Appendix 3). As discussed further in Section 4.4, this NOEC is much higher than anticipated concentrations of clopyralid in soil.

4.3.3. Aquatic Organisms.

4.3.3.1. Animals – The data on toxicity to fish are extremely and atypically limited. As noted in the previous risk assessment on clopyralid (SERA 1999), no chronic studies or even long-term studies on fish egg-and-fry were encountered in the CBI files or open literature. In the current updated risk assessment, a complete search of the CBI files for clopyralid as well as a search of all published studies was again conducted and again no longer-term studies on toxicity to fish were encountered. The only chronic toxicity study in any aquatic animal is the reproduction study in Daphnia magna (Dow AgroSciences 1998) which reports an NOEC of 23.1 mg a.e./L (Section 4.1.3.3).

In the previous risk assessment (SERA 1999), the NOEC of 23.1 mg a.e./L was used to characterize risk to all aquatic species. As discussed in the exposure assessment for aquatic species (Section 4.2.4), this chronic NOEC is substantially higher than the anticipated concentrations for acute or chronic exposures and could be used as the basis for asserting that no adverse effects are plausible in any aquatic animals.

For the current risk assessment, the dose-response assessment will be somewhat elaborated to better reflect the admittedly limited data suggesting that at least some fish species may be more sensitive to clopyralid than daphnids. As indicated in Appendix 5, the most sensitive fish species appears to be rainbow trout (*Salmo gairdneri*), with an acute LC_{50} value of 103.5 mg/L in a bioassay using acid form of clopyralid (Dow Chemical 1980e). This LC_{50} value will be used to characterize acute risks to sensitive fish species. Much higher LC_{50} values, in the range of 700 to 1645 mg a.e./L have been reported for both rainbow trout, bluegill sunfish, and fathead minnows using the monoethanolamine salt of clopyralid (Appendix 5). These differences in toxicity of the salt and acid forms of clopyralid may simply reflect the buffering effect of the monoethanolamine salt. For this risk assessment, however, the conservative assumption will be made that acute LC_{50} value of 103.5 mg/L should be applied to assessing risks for sensitive species and the upper range of 1645 mg a.e./L for the salt formulation will be applied only to presumably tolerant species.

For chronic exposures, the estimated NOEC for sensitive species will be based on the 23.1 mg a.e./L from daphnids. As noted in Appendix 5, the LC_{50} values for daphnids are about 230 mg/L (Batchelder 1980), higher than the LC_{50} value used for sensitive fish species by a factor of 2 [230 mg/L ÷ 103.5 mg/L = 2.22]. Consequently, for sensitive species the chronic daphnid NOEC of 23.1 mg a.e./L will be divided by 2 and rounded to one significant digit to estimate a chronic NOEC of 10 for sensitive fish. While a case could be made for similarly increasing the longer term NOEC for tolerant fish – i.e., apparent LC_{50} values of up to 1645 mg a.e./L – the lower experimental value of 23.1 mg a.e./L from daphnids is used directly.

4.3.3.2. Aquatic Plants – The relevant data on the toxicity of clopyralid to aquatic plants is summarized in Appendix 5. The most sensitive aquatic plant species appears to be *Selenastrum capricornutum*, with a 96-hour EC_{50} of 6.9 mg a.e./L based on a reduction in cell count relative to controls (Dill and Milazzo 1985). The more recent study by Forsyth et al. (1997), which reports NOAELs at 0.1 mg/L for two aquatic macrophytes, adds relatively little to the dose-response assessment because, based on the other earlier studies, no effects would be anticipated at

clopyralid concentrations of 0.1 mg/L. Thus, it does not seem reasonable to differentiate between aquatic macrophytes and algae. EC_{50} values for other freshwater algal species are reported as 61 and 449 mg/L (Dow AgroSciences 1998). The upper range of 449 mg/L is used to assess effects on tolerant aquatic plants.

4.3.3.3. Aquatic Microorganisms – There is no information that would permit a quantitative dose-response assessment for aquatic microorganisms.

4.4. RISK CHARACTERIZATION

4.4.1. Overview. Clopyralid is an herbicide and the most likely damage to nontarget species will involve terrestrial plants. Sensitive plant species could be adversely affected by the off-site drift of clopyralid under a variety of different scenarios depending on local site-specific conditions that cannot be generically modeled. If clopyralid is applied in the proximity of sensitive crops or other desirable sensitive plant species, site-specific conditions and anticipated weather patterns will need to considered if unintended damage is to be avoided. More tolerant plant species are not likely to be affected unless they are directly sprayed or subject to substantial drift. Because of the tendency for clopyralid to move into soil rather than to be transported by runoff and because of the greater toxicity of clopyralid by foliar deposition compared to soil contamination, off-site movement of clopyralid by soil runoff does not appear to be substantial risk to nontarget plant species. Aquatic plants do not appear to be at any substantial risk from any plausible acute or chronic exposures. In the very extreme case of an accidental spill of a large amount of the herbicide into a relatively small body of water, sensitive aquatic plants could be damaged.

No adverse effects are anticipated in terrestrial or aquatic animals from the use of clopyralid in Forest Service programs at the typical application rate of 0.35 lb a.e./acre. The same qualitative assessment holds for the maximum application rate of 0.5 lb a.e./acre except for the large bird feeding exclusively on contaminated vegetation over a 90 day period. Other more plausible scenarios – i.e., the longer term consumption of vegetation contaminated by drift or the longer term consumption of contaminated water or fish – yield hazard quotients that are in the range of 0.00005 to 0.02, far below a level of concern.

The risk characterization for both terrestrial and aquatic animals is limited by the relatively few animal and plant species on which data are available compared to the large number of species that could potentially be exposed. This limitation and consequent uncertainty is common to most if not all ecological risk assessments.

4.4.2. Terrestrial Organisms.

4.4.2.1. Terrestrial Animals – The quantitative risk characterization for terrestrial animals is summarized in Worksheet G02. The toxicity values used for each group of animals – mammals, birds, and insects – is summarized at the bottom of Worksheet G02 and refer to values derived in the dose-response assessment (Section 4.3). In this and all other similar worksheets discussed in this section, risk is characterized as the estimated dose, taken from Worksheet G01, divided by toxicity value. This ratio is referred to as the hazard quotient (HQ). All exposures summarized in Worksheet G01 are based on the typical application rate of 0.35 lb a.e./acre. At this application rate, an HQ of one or less indicates that the estimated exposure is less than the toxicity value. When this is the case, there is no basis for asserting that adverse effects are plausible.

As discussed in Section 2 (Program Description), the maximum application rate that might be used in Forest Service programs is 0.5 lb a.e./acre. Because exposure is directly related to application rate, the level of concern for the hazard quotients given in Worksheet G02 for an application rate of 0.5 lb a.e./acre is 0.7 [0.35 lb a.e./acre ÷ 0.5 lb a.e./acre = 0.7].

As indicated in Worksheet G02, the highest hazard quotient for any acute exposure is 0.3, the upper range of the hazard quotient for the consumption of contaminated insects by a small mammal. Thus, there is no basis for asserting that adverse effects are likely from the application of clopyralid at any application rate that might be used in Forest Service programs. For chronic exposures, all hazard quotients are below one. Thus, at the typical application rate of 0.35 lb a.e./acre, there is also no basis for asserting that adverse effects are likely. However, the hazard quotients for the chronic consumption of contaminated vegetation by a large bird feeding exclusively on treated vegetation (i.e., labeled "on-site" in Worksheet G02) yields a hazard quotient of 0.9. This is below the level of concern at an application rate of 0.35 lb a.e./acre but exceeds the level of concern at an application rate of 0.5 lb a.e./acre by a factor of about 1.3 – i.e., 0.9 ÷ 0.7. This scenario, as well as the similar exposure scenario for mammals consuming vegetation on-site, is essentially used in these risk assessments as a very conservative/extreme screening scenario. The scenarios assume that the vegetation is treated and that the animal stays in the treated area consuming nothing but the contaminated vegetation. Given that most forms of vegetation treated at an effective (i.e., herbicidal) application rate would likely die or at least be substantially damaged, this exposure scenario is implausible. It is, however, routinely used in Forest Service risk assessments as a very conservative upper estimate of potential exposures and risks.

The simple verbal interpretation of this quantitative risk characterization is similar to that of the human health risk assessment: the weight of evidence suggests that no adverse effects in mammals are plausible using typical or worst-case exposure assumptions at the typical application rate of 0.35 lb a.e./acre. As with the human health risk assessment, this characterization of risk must be qualified. Clopyralid has been tested in only a limited number of species and under conditions that may not well-represent populations of free-ranging non-target terrestrial animals. Notwithstanding this limitation, the available data are sufficient to assert that no adverse effects are anticipated in terrestrial animals from the use of clopyralid in Forest Service programs at the typical application rate of 0.35 lb a.e./acre. The same qualitative assessment holds for the maximum application rate of 0.5 lb a.e./acre except for the large bird feeding exclusively on contaminated vegetation over a 90 day period. Other more plausible scenarios – i.e., the longer term consumption of vegetation contaminated by drift or the longer term consumption of contaminated water or fish – yield hazard quotients that are in the range of 0.00005 to 0.02, far below a level of concern.

As with most ecological risk assessments, this characterization of risk must be qualified. Clopyralid has been tested in only a limited number of species and under conditions that may not well-represent populations of free-ranging nontarget animals. Notwithstanding this limitation, the available data are sufficient to assert that adverse effects in terrestrial animals from the use of this compound in Forest Service programs do not appear to be likely.

4.4.2.2. Terrestrial Plants – A quantitative summary of the risk characterization for terrestrial plants is presented in Worksheet G04 for runoff and Worksheets G05a and G05b for drift. Analogous to the approach taken for terrestrial animals, risk in these worksheets is characterized as a ratio of the estimated exposure to a benchmark exposure (i.e., exposure associated with a defined response). For both worksheets, the benchmark exposure is a NOEC, as derived in Section 4.3.2.2, for both sensitive and tolerant species.

Clopyralid is an effective herbicide, at least for a number of different broadleaf weeds, and adverse effects on some nontarget plant species due to drift are likely under certain application conditions and circumstances. As indicated in Worksheets G05a and G05b, off-site drift of clopyralid associated with ground and aerial applications may cause damage to sensitive plant species at distances of about 300 feet from the application site. The closer that the non-target species is to the application site, the greater is the likelihood of damage. Whether or not damage due to drift would actually be observed after the application of clopyralid would depend on a several site-specific conditions, including wind speed and foliar interception by the target vegetation. In other words, in some right-of-way applications conducted at low wind speeds and under conditions in which vegetation at or immediately adjacent to the application site would limit off-site drift, damage due to drift would probably be inconsequential or limited to the area immediately adjacent to the application site. Tolerant plant species would probably not be impacted by the drift of clopyralid and might show relatively little damage unless they were directly sprayed.

As summarized in Worksheet G04, runoff does not appear to present a significant risk to non-target plant species (sensitive or tolerant) even under conditions in which runoff is favored – i.e., clay soil over a very wide range of rainfall rates.

The situational variability in the exposure assessments for runoff, wind erosion, and irrigation water does have a substantial impact on the characterization of risk for sensitive nontarget plant species. All of these scenarios may overestimate or underestimate risk under certain conditions. For example, the exposure conditions involving runoff and contaminated irrigation water are plausible for applications in which relatively substantial rainfall occurs shortly after application and in which local topographic and/or hydrological conditions favor either runoff or percolation.

As summarized in Section 4.2.3.5, daily soil losses due to wind erosion, expressed as a proportion of an application rate, could be in the range of 0.00001 to 0.001. As summarized in Worksheet G04, this is substantially less than off-site losses associated with runoff from clay but similar to off-site losses associated with drift in the range of about 200 feet to 900 feet (Worksheet G05a). As with the drift scenarios, wind erosion could lead to adverse effects in sensitive plant species. Wind erosion of soil contaminated with clopyralid is most plausible in relatively arid environments and if local soil surface and topographic conditions favor wind erosion.

The simple verbal interpretation for this quantitative risk characterization is that sensitive plant species could be adversely affected by the off-site drift of clopyralid under a variety of different scenarios depending on local site-specific conditions that cannot be generically modeled. If

clopyralid is applied in the proximity of sensitive crops or other desirable sensitive plant species, site-specific conditions and anticipated weather patterns will need to considered if unintended damage is to be avoided. More tolerant plant species are not likely to be affected unless they are directly sprayed.

4.4.2.3. Soil Organisms. As discussed in Section 4.2.4 and detailed in Table 4-2, maximum concentration of clopyralid in soil will be in the range of 0.2 to 0.25 mg clopyralid/kg soil at an application rate of 1 lb a.e./acre. At the maximum application rate of 0.5 lb a.e./acre, the estimated maximum soil concentrations would be in the range of 0.1 to 0.125 mg clopyralid/kg soil.

While the available toxicity data on soil organisms are limited, these projected maximum concentrations in soil are far below potentially toxic levels. The information on soil organisms is limited, however, consisting only of an acute LC_{50} value for earthworms reported as >1000 mg/kg soil (Section 4.3.2.3) and a report in soil microorganisms indicating an NOEC of 10 ppm soil for effects on nitrification, nitrogen fixation, and degradation of carbonaceous material (Section 4.3.2.5). Nonetheless, this information does not provide any basis for asserting that adverse effects on soil organisms are plausible.

4.4.3. Aquatic Organisms. The risk assessment for aquatic organisms is relatively simple and unambiguous. Clopyralid appears to have a very low potential to cause any adverse effects in any aquatic species. As detailed in Section 3.2.3.4.2, concentrations of clopyralid in ambient water associated with a standardized application rate of 1 lb/acre are estimated to be no greater than 0.013 mg/L over prolonged periods of time. The peak concentration of clopyralid associated with runoff or percolation, also at an application rate of 1 lb/acre, are estimated to be no more than 0.07 mg/L. While these represent the upper range of estimated exposures, they appear to be plausible under some conditions and should not be regard as implausible. In any event, as summarized in Worksheet G03, all of the hazard quotients for aquatic species are extremely low, ranging from 0.000004 (acute exposures in tolerant fish) to 0.004 (sensitive aquatic plants). Thus, even though some of the risk characterizations are based on LC_{50} values rather than NOECs, there is no basis for asserting that effects on nontarget aquatic species are likely. As detailed in Section 4.3.3.1, confidence in this risk characterization is reduced by the lack of chronic toxicity studies in fish. Nonetheless, the maximum hazard quotient for daphnids for chronic exposures is 0.0004. Thus, in order for the hazard quotient in fish to reach a level of concern, fish would have to be more sensitive than daphnids by a factor of 2500 [1÷0.0004].

The accidental spill scenario used in the human health risk assessment (Worksheet D06) results in a maximum concentration of clopyralid in water of about 16 mg/L. As discussed in Section 3.2.3.4.1 and detailed in Worksheet D06, this is an extreme scenario that is used in the human health risk assessment to characterize the need for action to protect the general public in case of a relatively large spill into a relatively small body of water that might be used for drinking. This scenario is dominated by arbitrary variability – i.e., amount of compound spilled and the size of the water body into which it is spilled. Consequently, this extreme exposure scenario is not used explicitly in the ecological risk assessment. Nonetheless, it is worth noting that the maximum estimated concentration of 16 mg/L for this scenario exceeds the EC_{50} value of 6.9 mg/L for

sensitive aquatic plants. Thus, in cases of accident gross contamination of a small body of water, effects on sensitive aquatic plants are plausible.

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Table 2-1: Identification and physical/chemical properties of clopyralid and the monethanolamine salt of clopyralid.

Property		Value	Reference
Synonyms		3,6-dichloro-2-pyridinecarboxylic acid, 3,6-dichloropyridine-2-carboxylic acid, 3,6-dichloropicolinic acid, 3,6-DCP, Dowco 290 Formulations: Reclaim, Stinger, Transline all labeled for Forestry. Other formulations (e.g. Lontrel) and mixtures available. XRM-3972 (Lontrel)	Budavari 1989 Dow AgroSciences 1998 C&P Press 1998
Molecular weight		192 (acid) 253 (salt)	Budavari 1989
CAS Number		001702-17-6 (acid) 057754-85-5 (salt)	Budavari 1989 C&P Press 2003
EPA Registration Number		62719-259	C&P Press 2003
MW		192 (acid) 253 (salt)	Budavari 1989
pK_a		2.33 2.0 2.3	Bidlack 1982 Dow AgroSciences 1998 USDA/ARS 1995
Photolysis (day^{-1})		25 [soil and water]	USDA/ARS 1995
Melting Point		151-152°C	Budavari 1989
Vapor pressure at 25°C		1.2×10^{-5} mm Hg	Budavari 1989
Water solubility		1000 mg/L	Budavari 1989
		9,000 mg/L @20°C	Baloch-Haq et al. 1993 USDA/ARS 1995
$Log_{10} K_{o/w}$	pH 5 pH 7 pH 9	-1.81 -2.63 -2.55	Dow AgroSciences 1998 USDA/ARS 1995
$K_{o/c}$ (ml/g)		10 0.4-29.8 36 (13-60)	Bidlack 1982 Dow AgroSciences 1998 USDA/ARS 1995
K_d (ml/g)		6-36	USDA/ARS 1995
Soil $t_{1/2}$ [1]		25 (8-250) days (field dissipation) 13(10-30) days (field dissipation) 26(13-39) days (aerobic) 10 to 161 days (field dissipation)	Dow AgroSciences 1998 USDA/ARS 1995 USDA/ARS 1995 Appendix 6
Soil leaching in undisturbed soil columns		0.001 to 0.006 of applied dose center of mass movement: 6-18"	Dow AgroSciences 1998

[1] Soil persistence dependent on concentration. See Section 4.1.2.5.

Table 2-2: Use of Clopyralid by the Forest Service from 2001 to 2003 by Region.

Use by Region				Proportion of Use	
Region	Pounds	Acres	lbs/acre	by lbs	by Acres
1	3134.63	9473.08	0.33	0.453	0.342
2	2503.70	9338.86	0.27	0.362	0.337
4	1120.13	8233.69	0.14	0.162	0.297
5	75.91	339.50	0.22	0.011	0.012
8	88.82	330.00	0.27	0.013	0.012
All	6923.19	27715.13	0.25		

Source: USDA (2004)

Table 3-1: Chemical and site parameters used in GLEAMS Modeling for clopyralid.

Chemical Specific Parameters

Parameter	Clay	Loam	Sand	Comment/ Reference
Halftimes (days)				
Aquatic Sediment		1000		Note 1
Foliar	2	2	2	Knisel and Davis 2000
Soil	14	25	29	Note 2
Water		261		Concha and Shepler 1994
Ko/c, mL/g	0.4	3.15	12.9	Note 3
K_d, mL/g	0.0094	0.02	0.0935	Note 3
Water Solubility, mg/L		1,000		Budavari 1989
Foliar wash-off fraction		0.95		Knisel and Davis 2000

Note 1 Halftime set to 1000 days based on Hawes and Erhardt-Zabik (1995), who observed no significant degradation of clopyralid over a one-year period in anaerobic sediments.

Note 2 Based on values from (Baloch and Grant 1991b) at 20°C and 40% moisture holding capacity for different soil types. As noted by Baloch and Grant 1991b, the soil degradation rate appears to be directly related to soil moisture (see Table 3-X).

Note 3 Take from Woodburn and French (1987). Values for sand (0.73% OC) and loam (0.63% OC) are taken directly from Woodburn and French (1987). The values for clay are based on clay loam (2.34% OC) from Woodburn and French (1987).

Site Parameters
(see SERA 2003, SERA AT 2003-02d dated for details)

Pond	1 acre pond, 2 meters deep, with a 0.01 sediment fraction. 10 acre square field (660' by 660') with a root zone of 60 inches and four soil layers.
Stream	Base flow rate of 4,420,000 L/day with a flow velocity of 0.08 m/second or 6912 meters/day. Stream width of 2 meters (about 6.6 feet') and depth of about 1 foot. 10 acre square field (660' by 660') with a root zone of 60 inches and four soil layers.

Table 3-2: Summary of modeled concentrations of clopyralid in streams (all units are µg/L or ppb per lb/acre)

Annual Rainfall (inches)	Clay		Loam		Sand	
	Average	Maximum	Average	Maximum	Average	Maximum
5	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
10	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
15	0.01691	4.50456	0.00000	0.00000	0.00001	0.00102
20	0.02429	6.98768	0.00014	0.00639	0.02983	0.60639
25	0.02842	8.50807	0.02315	0.42790	0.10405	2.65217
50	0.03317	10.55479	0.27714	7.00034	0.55788	17.99383
100	0.03215	10.40035	0.54220	21.04166	0.83234	44.46110
150	0.03111	10.08846	0.56208	26.08294	0.82007	58.39894
200	0.03045	9.88694	0.52969	27.75653	0.75643	62.00708
250	0.02999	9.74423	0.48776	27.48657	0.68788	67.43548

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

Annual Rainfall (inches)	Clay		Loam		Sand	
	Average	Maximum	Average	Maximum	Average	Maximum
5	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
10	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
15	1.55437	2.85788	0.00000	0.00000	0.00050	0.00081
20	1.40722	4.19252	0.00611	0.00904	1.38894	2.01848
25	1.26697	4.94710	0.78342	1.15098	3.74878	6.41084
50	0.84138	6.60086	5.29172	13.04550	11.31862	33.11471
100	0.57136	7.35963	7.38523	27.70456	12.55461	59.83145
150	0.48293	7.78991	6.73098	30.77489	11.08482	68.87600
200	0.44077	8.13500	5.90782	30.38532	9.68516	72.07381
250	0.41620	8.41249	5.20154	29.03485	8.53731	73.35085

Table 3-4: Clopyralid Residue Levels in Strawberries.

Application rate		Residues (ppm or mg/kg) at different days after treatment		
kg/ha	lb/acre	30	59	87
0.07	0.0624	0.00054	0.00025	0
0.14	0.125	0.00083	0.00048	0.00027
0.28	0.250	0.00193	0.00079	0.00033

Source: McMurray et al. 1996

Details of Calculation of confidence limits for halftimes on fruit.

Data from Table 5 of McMurray et al. 1996, 8 observations, fit the exponential model:

ln(residue(mg/kg) = -0.024474 days + 4.91472 lb a.e./acre - 7.0336

with an r^2 of 0.9152.

Note that at t_0 the estimated residue for 1 lb a.e./acre is $e^{4.91-7.03} = e^{-2.12} \approx 0.12$ mg/kg fruit.

There are 5 degrees of freedom [8 observations - 3 parameters] and the associated critical value for the t-distribution at 0.025 is 2.571 (Mendenhall and Scheaffer, 1973, Appendix III, Table 4, p. A31).

The standard error for the time parameter (k_e) is 0.003226.

Central Estimate of Halftime:	$\log_e(2) \div 0.024474 = 28.3$
Lower Limit of Halftime:	$\log_e(2) \div (0.024474 + (2.571 \times 0.003226)) = 21.2$
Upper Limit of Halftime:	$\log_e(2) \div (0.024474 - (2.571 \times 0.003226)) = 42.8$

Table 3-5: Chemical and site parameters used in GLEAMS Modeling for hexachlorobenzene.

Chemical Specific Parameters

Parameter	Clay	Loam	Sand	Comment/ Reference
Halftimes (days)				
Aquatic Sediment	2190	2190	2190	Note 1
Foliar	1	1	1	Note 2
Soil, upper 1 cm	7.1	7.1	7.1	Note 3
Soil, lower layers	1640	1640	1640	Note 3
Water	1533	1533	1533	Note 4
Ko/c (mL/g)	50000	50000	50000	Note 5
K_d (mL/g)	1500	750	150	Note 6
Water Solubility, mg/L	0.006	0.006	0.006	ATSDR 2002
Foliar washoff fraction	0.1	0.1	0.1	Note 2

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 Volatilization will rapidly remove hexachlorobenzene from plant surfaces. For the GLEAMS modeling, all hexachlorobenzene is assumed to be deposited on soil. Thus, the values for foliar half-time and washoff do not impact the results of the modeling.

Note 3 For the top 1 cm, the halftime is based on the study by Beall (1976), as discussed in the text. ATSDR (2002) gives reported halftimes for hexachlorobenzene in soil ranging from 3 to 6 years. For lower soil layers, the mid-point, 4.5 years is used – 4.5 years×365 = 1642.5 ≈ 1640 days.

Note 4 ATSDR (2002) gives reported halftimes for hexachlorobenzene in surface water ranging from 2.7 to 5.7 years. The average, 4.2 years or about 1533 days, is used.

Note 5 Knisel and Davis (2000) give a $K_{o/c}$ of 50,000. ARS (1995) reports a Ko/c of 30,649 based on a Kd of 462.8 in a soil with 2.6% OM.

Note 6 Calculated as $K_d = K_{o/c} \times OC$. The $K_{o/c}$ is taken as 50,000 from Knisel and Davis (2000) and the proportion of OC in sand, loam, and clay is estimated as 0.003 for sand, 0.015 for loam, and 0.030 for clay.

Table 3-6: Summary of modeled concentrations of hexachlorobenzene in soil (all units are mg/kg or ppm per lb/acre)

Annual Rainfall (inches)	Clay		Loam		Sand	
	Average	Maximum	Average	Maximum	Average	Maximum
5	0.027	0.665	0.023	0.588	0.023	0.588
10	0.030	0.665	0.026	0.588	0.026	0.588
15	0.030	0.665	0.026	0.588	0.026	0.588
20	0.030	0.665	0.026	0.588	0.027	0.588
25	0.030	0.665	0.026	0.588	0.027	0.588
50	0.028	0.665	0.026	0.588	0.027	0.588
100	0.023	0.665	0.026	0.588	0.028	0.588
150	0.019	0.665	0.024	0.588	0.030	0.588
200	0.012	0.665	0.021	0.588	0.031	0.588
250	0.007	0.665	0.017	0.588	0.031	0.588

Table 3-7: Summary of modeled concentrations of hexachlorobenzene in streams (all units are µg/L or ppb per lb/acre)

Annual Rainfall (inches)	Clay		Loam		Sand	
	Average	Maximum	Average	Maximum	Average	Maximum
5	0	0	0	0	0	0
10	0	0	0	0	0	0
15	0.0036	0.58	0	0	0	0
20	0.0140	2.29	0	0	0	0
25	0.0294	4.83	0	0	0	0
50	0.162	27.4	0	0	0	0
100	0.470	88.9	0.05	8.77	0	0
150	0.794	165	0.15	26.8	0	2.0e-05
200	0.905	221	0.27	52.0	0	4.0e-05
250	0.943	268	0.38	80.5	1.1e-03	0.18

Table 3-8: Summary of modeled concentrations of hexachlorobenzene in a pond (all units are µg/L or ppb per lb/acre)

Annual Rainfall (inches)	Clay		Loam		Sand	
	Average	Maximum	Average	Maximum	Average	Maximum
5	0	0	0	0	0	0
10	0	0	0	0	0	0
15	0.09	0.15	0	0	0	0
20	0.32	0.50	0	0	0	0
25	0.62	0.94	0	0	0	0
50	2.77	3.62	0	0	0	0
100	6.82	8.52	1.02	1.58	0	0
150	10.9	15.9	2.69	5.38	1.0e-05	2.0e-05
200	12.2	21.8	4.59	11.18	3.0e-05	4.0e-05
250	12.6	27.2	6.26	17.81	2.1e-02	1.0e-01

Table 4-1. Summary of dose-severity relationships in terrestrial plants.[1]

Application Rate (lb a.e./acre)	Severity[2]			
	None	Slight	Moderate	Severe
>0.5	Barley, canola, soybean, sweet corn, raddish, wheat sp.	Wheat sp.	Strawberries	Onion, soybeans, snap bean, tomato, sunflowers
>0.2–0.5	Ash, beech, birch, cacti sp., cherry, *Juniperus*, oak, pear, sycamore willows	Alder, asparagus, cacti, *Contoneaster*, eastern redbud, strawberries, spruce	Cacti, *Lagerstroemia*, poplar,	Cacti, cranberries, red maple
>0.05–0.2	Ash, beech, birch, cherry, forbes, grasses, oak, onion, snapbean, sycamore	Alder, cotton, forbes, grasses, spruce, strawberries		Potatoes
>0.01–0.05	Cotton, tomato, soybean, sunflower [pre-emergence]		Kumara, tomatoes	Potatoes
>0.001–0.01			Potatoes	
>0.0001–0.001	Soybean, snap bean, tomato, sunflower [post-emergence]			

[1]See Appendix 4 for data and citations.

[2]KEY: Slight – No or minimal visual damage; detectable decrease in growth.
Moderate – Some visual damage; mortality unlikely.
Severe – Obvious visual damage and substantial (>10%) mortality.

Table 4-2 Summary of modeled concentrations of clopyralid in soil (all units are mg herbicide/kg soil or ppm modeled at an application rates of 1 lb a.e./acre).

Annual Rainfall (inches)	Clay		Loam		Sand	
	Average	Maximum	Average	Maximum	Average	Maximum
5	0.01927	0.25577	0.03560	0.26314	0.03539	0.25656
10	0.01690	0.26516	0.02557	0.25728	0.02249	0.22372
15	0.01613	0.25320	0.02267	0.23636	0.02347	0.20680
20	0.01608	0.24488	0.02111	0.22057	0.02033	0.19590
25	0.01602	0.23804	0.01916	0.20843	0.01736	0.18692
50	0.01576	0.22050	0.01233	0.17313	0.00971	0.15329
100	0.01545	0.20831	0.00764	0.14070	0.00510	0.11093
150	0.01526	0.20383	0.00603	0.12431	0.00347	0.08617
200	0.01513	0.20126	0.00522	0.11432	0.00265	0.07026
250	0.01502	0.19935	0.00473	0.10761	0.00216	0.05950

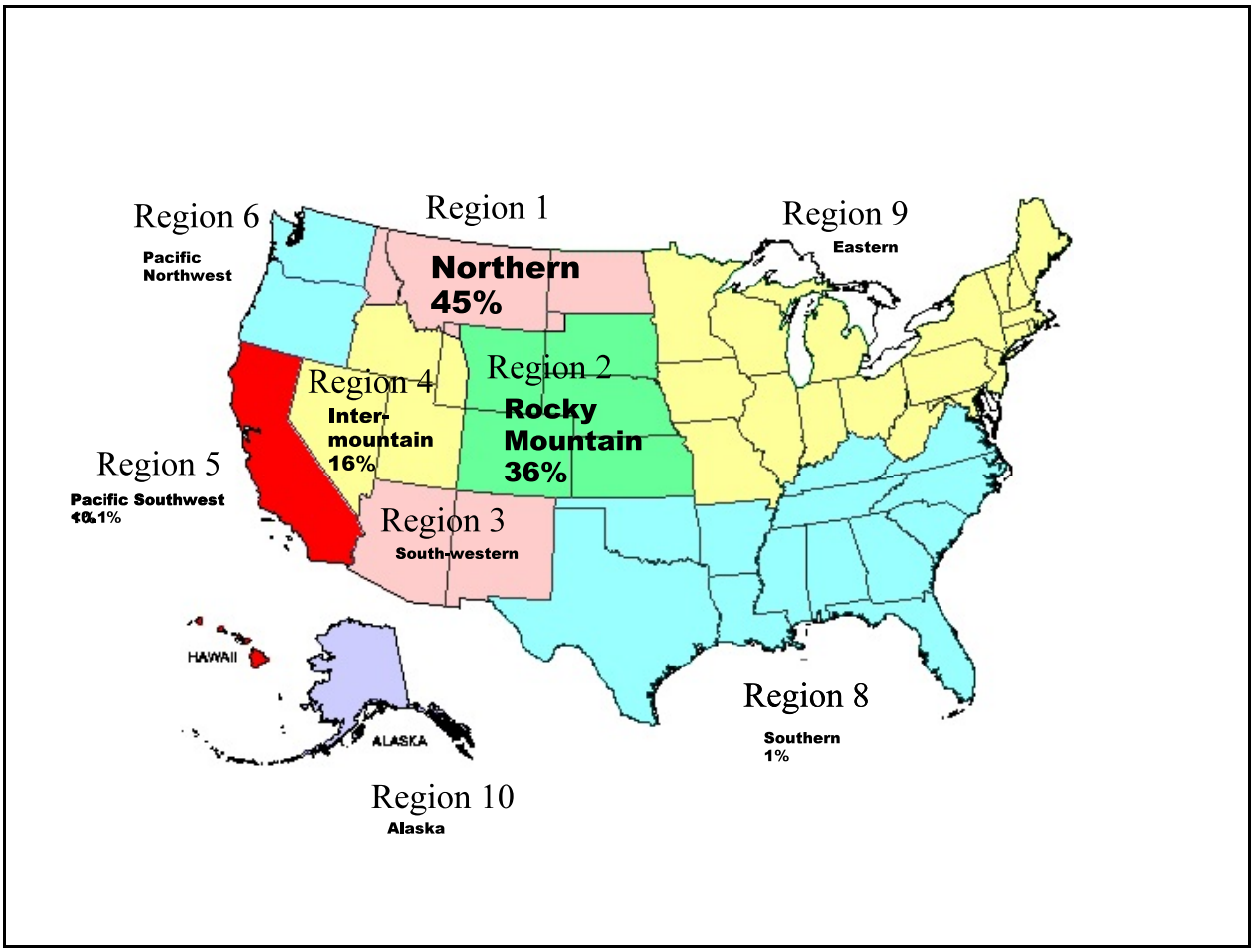

Figure 2-1. Use of clopyralid by the USDA Forest Service in various regions of the United States from 2001 to 2003 based on percentages of total use [See Table 2-2 for data].

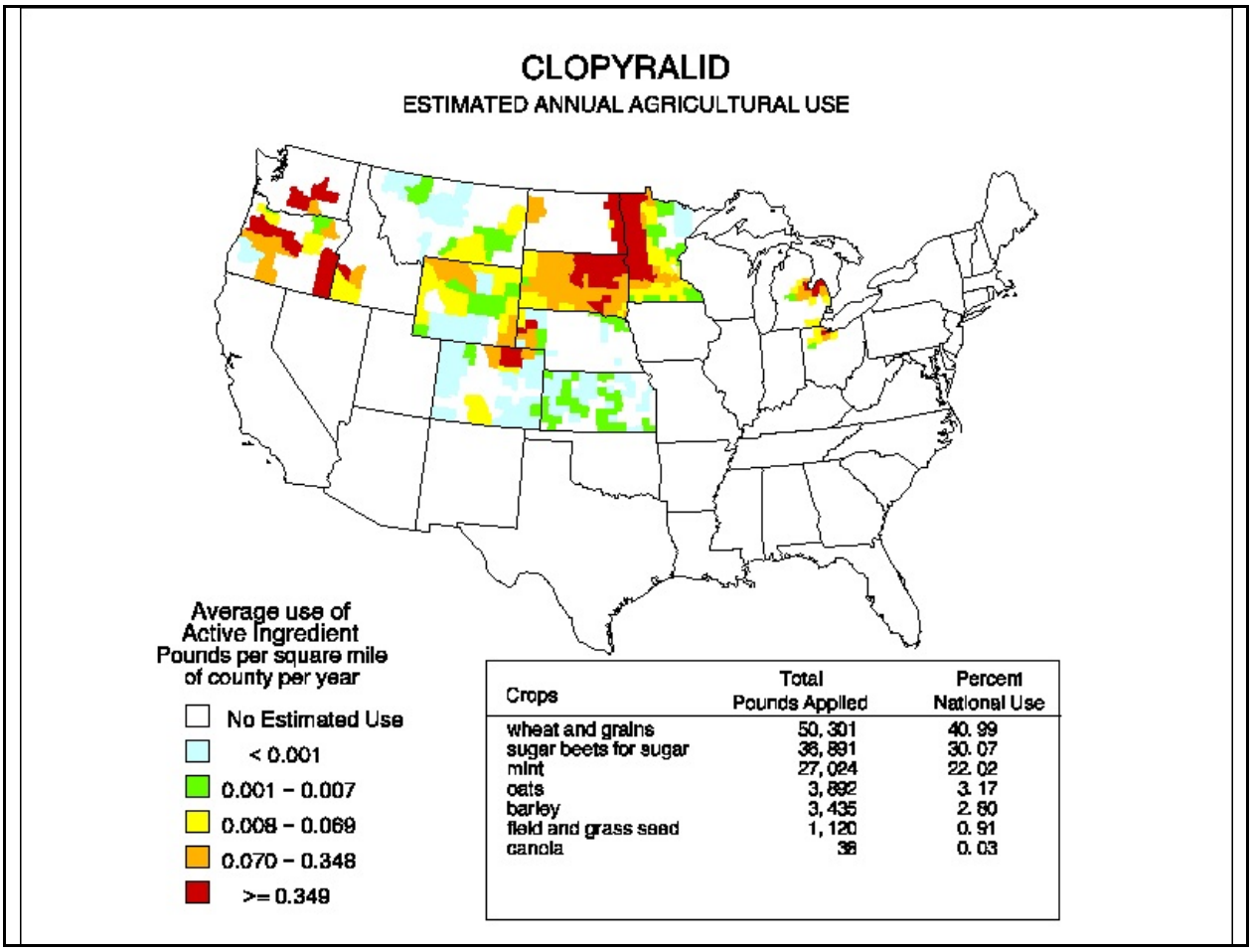

Figure 2-2. Agricultural use of clopyralid in the United States for 1992 (USGS 1998).

APPENDICES

Appendix 1: Toxicity of clopyralid to mammals.
Appendix 2: Toxicity of clopyralid to birds after oral administration.
Appendix 3: Toxicity of clopyralid to terrestrial invertebrates.
Appendix 4: Toxicity of clopyralid to non-target terrestrial plants.
Appendix 5: Toxicity to fish, aquatic invertebrates, and aquatic plants.
Appendix 6: Field studies on the fate of clopyralid in soil.

Appendix 1. Toxicity of Clopyralid to Mammals.

Animal	Dose	Response	Reference
ORAL			
		Acute Oral Toxicity Studies	
Rats, Fischer-344, 6/sex/dose level, 2-week observation period.	XRM-3972 Herbicide Formulation (Lontrel 360), not otherwise specified (NOS).	In male and female rats LD_{50} > 5000 mg/kg. No deaths at highest dose (5000 mg/kg). Lethargy was noted in all rats treated with XRM-3972, no other treatment-related lesions.	Carreon and New 1981 MRID No. 00147690 **Applicable to Transline (Dow AgroSciences 2003)**
Rat, Fischer-344, males and females, NOS.	Clopyralid, penta process.	LD_{50} >5000 mg/kg (no deaths at highest dose tested).	Dow AgroSciences 1998.
Rat, Fischer-344, males, NOS.	Clopyralid, electro-chemical process.	LD_{50} 3738 mg/kg	Dow AgroSciences 1998.
Rat, Fischer-344, females, NOS.	Clopyralid, electro-chemical process.	LD_{50} 2675 mg/kg	Dow AgroSciences 1998.
Rats, Fischer-344, 5/sex/dose level, Lontrel TE technical (clopyralid, 3,5-dichloro-2-pyri-dinecarboxylic acid), 2-week observation period.	500, 2000, or 5000 mg/kg Lontrel TE (25% suspension in water) by single-dose oral gavage.	At 500 mg/kg all rats survived and were grossly normal; clinical signs included fecal soiling in 1/5 male rats at 1–3 hours after dosing and urine soiling in 1/5 female rats at 7 hours to 2 days after dosing; At 2000 mg/kg 1/5 males and 1/5 females died on day 2 (excessive gas was observed in the GI tract of both animals, attributed to mouth breath and swallowing air); all other treated rats survived the 14-day observation period; clinical signs included fecal soiling in 1/5 males at 1–3 hours after dosing and urine soiling and chromorhinorrhea in 1/4 surviving males on day 2 after dosing; all surviving rats showed no signs of residual effects; At 5000 mg/kg 4/5 male rats and 5/5 female rats died by day 2;	Gilbert and Crissman 1995 MRID No. 44114101

Appendix 1. Toxicity of Clopyralid to Mammals (listed alphabetically by author) *(continued)*.

Animal	Dose	Response	Reference
ORAL *(continued)*			
		the surviving male rat was grossly normal; clinical signs at the high-dose level included decreased activity, lacrimation, and lateral recumbence; gross findings in the non-surviving rats were non-specific and primarily in the stomach.	
Rats, Fischer, 5/sex.	Gavage, 5000 mg/kg of Lontrel T. (95.4% clopyralid). 14-day observation period.	No mortality, signs of toxicity, or changes in body weight. No gross tissue lesions.	Jeffrey et al. 1987b MRID No. 41641301
Rats, 4/sex, NOS.	Clopyralid, electro-chemical process DOWCO 290 (99.2% pure).	LD_{50} >5000 mg/kg males (no deaths). LD_{50} = 4300 mg/kg (3390–5440 mg/kg) females. No clinical signs or symptoms of toxicity were reported.	Rampy et al. 1973 MRID No. 00061381
Rats, Fischer-344, 6/sex/dose level, 2-week observation period.	Clopyralid (DOWCO 290).	Acute oral LD_{50} from a pertinent formulation in male and female rats >5000 mg/kg. All rats had diarrhea. One rat out of 6 died at 5000 mg/kg. No deaths at 2500 mg/kg.	Saunders et al. 1983 MRID No. 00127275
Reproduction/Teratology Studies, Oral			
Rats, Fischer-344, 28 to 30 dams/dose level for F_0 and F_1 generations. All F_1 and F_2 litters culled to 8 pups (4/sex) if possible.	Dietary exposures adjusted to provided targeted clopyralid doses of 0, 150, 500, and 1500 mg/kg/day over 2-successive generations.	Reduced pup weight and increased relative liver weight at 1500 mg/kg/day in F_{1a} and F_{1b} pups. No effects on growth or morphology, viability of pups, or fertility or reproductive performance.	Dietz et al. 1983 MRID No. 00138155
Rats, CD, male and female, 11 liters/dose group for all generations.	Dietary exposures adjusted to provided targeted clopyralid doses of 0, 5, 15, or 50 mg/kg/day to 3 generations of CD rats.	Adults were unaffected by treatment at all doses. No deleterious effects on reproduction, gross, or micro-scopic pathology, body weight, mortality, or behavior were attributed to dietary exposure to clopyralid.	Gorsline et al 1975a,b MRID Nos. 00081593, 00028862

Appendix 1. Toxicity of Clopyralid to Mammals (listed alphabetically by author) *(continued)*.

Animal	Dose	Response	Reference
ORAL *(continued)*			
Rabbits, New Zealand white, 6–7 months old, 3.5–4.5 kg. Two groups were tested. The first involved 16/group. A second group with 10–18 per group were added after 3 weeks because of the low number of litters with pups.	Gavage clopyralid doses of 0, 50, 110, and 250 mg/kg bw on days 7–19 of gestation. Numbers of does at end of study were 19, 15, 17, and 15 mg/kg bw, going from control to high dose. Cesarean section performed on day 28.	At 50 and 110 mg/kg, no significant treatment related difference in maternal or fetal parameters. 250 mg/kg: labored breathing in about 1/3 of the does. No apparent or reportedly significant effects on maternal body weight over 28-day period [Tables 9 and 10]. Six does sacrificed early because of mortality or toxicity. Significant decrease in fetal body weights.	Hanley et al. 1990a MRID No. 41649801
Rabbits, New Zealand white, 3.5–4.5 kg. Two groups were tested. The first involved 16/group. A second group with 10–18 per group were added after 3 weeks because of the low number of litters with pups.	Gavage clopyralid doses of 0, 110, 250, and 350 mg/kg bw in corn oil on days 7–19 of gestation. Cesarean section performed on day 20.	At 110 mg/kg no significant treatment related difference in maternal or fetal parameters. At 250 mg/kg signs of maternal toxicity. At 350 mg/kg authors report a decreased maternal body weight. This does not appear to be supported in Table 5 and 6. Death of three does before the end of study. No evidence of embryo toxicity at any dose level (i.e., no significant, substantial, or systematic differences in pregnancy rates, numbers of corpora lutea, implantations, litter size, or resorption rates).	Hanley et al. 1990b MRID No. 41649802
Rats, Fischer-344, 30 litters/dose, all litters culled to 8 pups (4/sex) if possible.	Dietary exposures adjusted to provided targeted clopyralid doses of 0, 150, 500, or 1500 mg/kg/day to 2 generations of F344 rats.	At 1500 mg/kg/day saw reduced body weight in parents and weanling age offspring; also increase in absolute live weight of weanling rats, but not parents. NOAEL = 500 mg/kg/day.	Jersey et al. 1982 MRID No. 00127277

Appendix 1. Toxicity of Clopyralid to Mammals (listed alphabetically by author) *(continued)*.

Animal	Dose	Response	Reference
ORAL *(continued)*			
Rat, Fischer-344, 29 or 30 females per dose group and 35 control females.	Daily average doses of 0, 15, 75, or 250 mg/kg/day clopyralid in cotton-seed oil by gavage on gestation days 6–15. Two additional groups of 15 rats were dosed at 250 mg/kg/day on gestation days 6–15.	Maternal toxicity at 250 mg/kg/day included reduced weight gain, decreased food and water consumption, and reduced absolute liver weight. Among litters from 250 mg/kg/day exposure group, 3 fetuses form one litter were polydactyl and 1 fetus from another litter had a hemivertebra. The incidence of these malformations was not statistically significant. No major malformations were observed among litters from 2 groups of 15 dams. NOAEL for dams was 75 mg/kg/day with a LOAEL of 250 mg/kg/day based on decreased weight gain.	John et al. 1981 MRID No. 00127279
Rabbits, New Zealand white, 14 control dams, 12 dams at 110 mg/kg/day and 11 dams at 250 mg/kg/day.	Gavage doses of 0, 110, or 250 mg/kg/day clopyralid in corn oil on days 6–18 of gestation.	No signs of toxicity in dams or fetuses at 250 mg/kg/day. 250 mg/kg/day was identified as the maximum tolerated dose, due to CNS depression and ataxia to 750 and 1000 mg/kg/day and reduced food consumption at 500, 750, and 1000 mg/kg/day.	Smith et al. 1960b MRID No. 00081591
Rabbits, New Zealand white, 15 dams/dose level.	Gavaged doses of 0, 110, or 250 mg/kg/day of clopyralid (96% pure) in corn oil on gestation days 6–18.	No maternal toxicity noted. Examination of fetuses on gestation day 29 found no embryotoxicity or fetotoxicity at any dose tested.	Smith et al. 1974a MRID No. 00061375
Mice, Swiss Albino (CR), 30 females and 15 males/dose level.	Dietary exposures of clopyralid at 0, 35, 100, or 350 ppm for 18 months.	Treatment produced no deleterious effects on reproduction, body weight, survival, or gross or microscopic pathology.	West et al. 1976 MRID No. 00081592

Appendix 1. Toxicity of Clopyralid to Mammals (listed alphabetically by author) *(continued)*.

Animal	Dose	Response	Reference
ORAL *(continued)*			
		Subchronic Oral Studies	
Rat, Fischer-344, NOS.	Dietary exposures adjusted to provide doses of clopyralid at 0, 300, 1500, 2500 mg/kg/day for 90 days.	At 2500 mg/kg/day, decreased body weights associated with decreased food consumption. Increased kidney and liver weights at all dose levels in males and at the upper two dose levels in females.	Dow AgroSciences 1998.
Beagle dogs, 4/sex/dose level.	Dietary exposures adjusted to provide doses of clopyralid at 0, 15, 50, 150 mg/kg/day in the diet for 6 months.	No toxicity at any dose tested. The authors could not reproduce the bladder injury noted in Humiston et al. (1976b).	Hart and McConnell (1975a,b) MRID Nos. 00081590, 00061384
Beagle dogs, 4/sex/dose level.	Dietary exposures adjusted to provide doses of clopyralid at 0, 15, 50, 150 mg/kg/day in the diet for 6 months.	No change in diet consumption, appearance, demeanor, body weight, hematology, clinical chemistry, or urinalysis. No change in absolute or relative organ weights in males. In females, relative liver weight was increased for all 4 high-dose (150 mg/kg/day) dogs as compared to controls. Among male dogs changes in urinary bladder (cystitis, urethritis, and prostatitis) were noted among dogs receiving clopyralid (0/4 control; 1/4 at 15 mg/kg/day; 2/4 at 50 mg/kg/day; 1/4 at 150 mg/kg/day). The etiology of the bladder effects is unknown. No other gross or histological organ pathology was noted.	Humiston et al. 1976b MRID No. 00061383

Appendix 1. Toxicity of Clopyralid to Mammals (listed alphabetically by author) *(continued)*.

Animal	Dose	Response	Reference
ORAL *(continued)*			
Rats, Sprague-Dawley, 40/sex/dose level.	Dietary exposures adjusted to provide doses of clopyralid at 0, 15, 50, 150 mg/kg/day in the diet for 2 years.	Decreased body weight in females at 150 mg/kg/day. No compound-related toxicity or increase in cancer incidence at any dose tested. Additional data analysis of Humiston et al. (1977) concluded that "Dietary administration of DOWCO 290 herbicide [clopyralid] for up to 2 years to female rats in the study did not produce an oncogenic effect in either the thyroid gland or the pituitary gland" (Jersey 1985).	Humiston et al. 1977 MRID No. 00061376
Mice, B6C3F1, 10/sex/dose level.	Dietary exposures adjusted to provide doses of clopyralid at 0, 200, 750, 2000, or 5000 mg/kg/day for 13 weeks.	At 5000 mg/kg/day both male and female mice exhibited a reduction in body weight throughout the study, though this reduction was <10% after 13 weeks of clopyralid exposure. All male and female mice fed 5000 mg/kg/day clopyralid also had a slight increase in relative liver weight which was accompanied by increased size and tinctural properties of the centrilobular cells of the liver. The histological change in the centrilobular cells of the liver was also seen in 8/10 female mice receiving 2000 mg/kg/day, but not the males. The authors concluded that the hepatic changes were reversible, compensatory changes. NOAEL for males was 2000 mg/kg/day and for females was 750 mg/kg/day.	McCollister et al. 1983 MRID No. 00127276

Appendix 1. Toxicity of Clopyralid to Mammals (listed alphabetically by author) *(continued)*.

Animal	Dose	Response	Reference
ORAL *(continued)*			
Rats, Fischer-344, 15/ex/dose level.	Dietary exposures adjusted to provide doses of clopyralid at 0, 5, 15, 50,or 150 mg/kg/ day for 90 days.	Appearance, mortality, body weight, food consumption, hematology, urinalysis, clinical chemistry, organ weights (absolute and relative), gross and histologic examination of tissues were not affected by ingestion of clopyralid at any dose tested. Sporadic reduction on food consumption of female rats was judged to be unrelated to clopyralid treatment.	Olson et al. 1973 MRID No. 00061382
Chronic Oral Studies			
Rats, Fischer-344, 70/sex/dose level.	Dietary exposures adjusted to provide doses of clopyralid at 0, 15, 150, and 1500 mg/kg/day bw for 2 years.	At 1500 mg/kg/day, increased relative liver and kidney weights with changes in pathology or clinical chemistry relating to these endpoints. Also, decreased food consumption and body weight. At 150 mg/kg/day, hyperplasia and thickening of the epithelium of the anterior surface of the gastric limiting ridge (increased cells in the stratum spinosum). No treatment related effects at 15 mg/kg/day.	Barna-Lloyd et al. 1986 MRID No. 00162393
Beagle dogs, 6/sex/dose level.	Dietary exposures adjusted to provide doses of clopyralid at 0, 100, 320, or 1000 mg/kg/day for 12 months.	Dietary exposure to clopyralid had no effect on body weight, food consumption, clinical condition, urinary parameters, or eyes. [See notes below]	Breckenridge et al. 1984 MRID No. 00158256

Additional Notes on Breckenridge et al. 1984: At 320 and 1000 mg/kg/day a statistically significant reduction in red blood cells count, hematocrit, and hemoglobin concentration was noted for males and females. Bone marrow examination at study termination showed no deleterious changes. At 320 and 100 mg/kg/day, a dose-related reduction in serum protein and serum albumin/globulin was seen. Because these changes in serum protein were small in magnitude, their toxicological significance is uncertain. Increased liver weight was observed at 320 and 1000 mg/kg/day: absolute liver weight at 320 mg/kg/day; and absolute and relative liver weight at 1000 mg/kg/day. The authors concluded that dietary exposure of Beagle dogs to clopyralid produced systemic toxicity at 1000 mg/kg/day and minimal effects at 320 mg/kg/day. NOAEL = 100 mg/kg/day.

Appendix 1. Toxicity of Clopyralid to Mammals (listed alphabetically by author) *(continued)*.

Animal	Dose	Response	Reference
ORAL *(continued)*			
Mice, Charles River, 50 males and 50 females in control group, 60 males and 60 females in low- and mid-dose group, 52 males and 50 females in high-dose group.	Dietary exposure of clopyralid at 0, 35, 100, and 350 ppm to parents for 13 weeks and to progeny for 18 months.	No effects on body weight, reproduction, survival, or pathology.	West and Willigan 1976 MRID No. 00061377
Mice, B6C3F1, 50/sex/dose level.	Dietary exposures adjusted to provide doses of clopyralid at 0, 100, 500, and 2000 mg/kg/day bw for 24 months.	Decreased mean body weight (10–12%) in male mice at 2000 mg/kg/day bw. No other effects attributable to treatment based on standard clinical observations and pathology.	Young et al. 1986 MRID No. 00157783
DERMAL			
Guinea Pigs, Hartley albino, NOS.	Penta and electro-chemical processes, 10% solution.	No skin sensitization.	Dow AgroSciences 1998.
Rabbits, New Zealand white, 1 male and 5 females.	Clopyralid (96.2% XRM-3792 Herbicide Formulation Lontrel 360, NOS) 0.5 g applied to the clipped (intact and abraded) back for 24 hours.	Redness and edema noted at application site of all rabbits.	Carreon and New 1981 MRID No. 147690

Appendix 1. Toxicity of Clopyralid to Mammals (listed alphabetically by author) *(continued)*.

Animal	Dose	Response	Reference
DERMAL *(continued)*			
Rabbits, New Zealand white, 2/sex.	24-hour percutaneous absorption test of 5000 mg/kg.	Percutaneous absorption LD_{50} >5000 mg/kg with no deaths at highest dose tested (5000 mg/kg). All rabbits were lethargic, but no treatment related lesions were noted at 2 weeks after treatment.	Carreon and New 1981 MRID No. 147690
Rabbits, New Zealand, 2.04–2.4 kg, male and female, 7 males and 5 females.	Clopyralid (96.2%) 5000 mg/kg to the clipped, but non-abraded back for 24 hours. Observed for 14 days.	No mortality. Erythema in 6 animals and edema in 7 animals. Normal by day 10 of test.	Gilbert 1995a MRID No. 44114102
Guinea pigs, 10 Hartley males in 3-dose induction group and subsequent single-dose challenge group; 5 Hartley males in single-dose naive group; same number of controls for each group.	Induction Phase: 3 weekly 6-hour applications of 0.4 g Lontrel TE technical (clopyralid) 96.2% pure to the left side, clipped free of hair (controls exposed by same protocol to 0.4 mL neat DER 331 epoxy resin).	There were no observations of erythema or body weight changes 48 hours after treatment in any of the animals exposed to Lontrel TE, which indicates that the compound did not cause delayed contact hypersensitivity in guinea pigs.	Gilbert 1995b MRID No. 44114106
	Challenge Phase: single 6-hour application of 0.4 g Lontrel TE technical to the right side, clipped free of hair (controls exposed by same protocol to 0.4 mL neat DER 331).	Slight to moderate erythema, suggesting a hypersensitivity response was observed in 5/10 control animals 48 hours after exposure to 0.4 mL DER 331; none of the naive animals exposed to DER 331 showed signs of irritation; body weight effects were not observed in any of the animals exposed to DER 331.	
Rabbits, New Zealand white, weighing 2.24–2.69 kg, 2 males and 4 females.	Clopyralid (96.2%) 0.5 g applied to the clipped, but non-abraded back for 4 hours. Application sites graded for erythema and edema at 30 minutes and 24, 48, and 72 hours.	No dermal irritation was observed and there was no effect on body weight.	Gilbert 1995c MRID No. 44114105

Appendix 1. Toxicity of Clopyralid to Mammals (listed alphabetically by author) *(continued)*.

Animal	Dose	Response	Reference
DERMAL *(continued)*			
Guinea pig, Hartley albino, 10 males.	A 75% solution of XRM-3972 in dipropylene glycol monomethyl-ether was applied the skin of 10 guinea pigs for 3 weeks. Two weeks later a challenge application of 75% XRM-3972 was applied (in same vehicle). Guideline 81-6. XRM-3972 is 31.5% clopyralid.	1/10 guinea pigs developed erythema. Authors concluded that XRM-3972 is not a potential skin sensitizer.	Jeffrey 1986 MRID No. 40035101 **Applicable to Transline (Dow AgroSciences 2003)**
Guinea pigs, albino, 10 males.	Three applications of 0.4 mL of 10% solution of clopyralid (purity not specified) on shaved and intact shoulder skin.	No erythema or edema.	Jeffery 1987a MRID No. 41641306
Rabbits, New Zealand, 5/sex, 2.8 to 3.1 kg.	Single dermal application of 2000 mg/kg clopyralid applied to the back. Plastic wraps used for first 24 hours to prevent ingestion. Observed for 14 days.	No mortality. Erythema and edema at application site that reversed after 3 days. Seen in all animals except one male that only displayed erythema. All animals recovered by end of study. Signs of dermal irritation subsided within 72 hours. No treatment related lesions on group pathology exam. No deaths occurred, LD_{50} >2000 mg/kg/day.	Jeffrey et al. 1987a MRID No. 40246301 **Applicable to Transline (Dow AgroSciences 2003)**
Rabbits, New Zealand white, 3/sex, 2.6–3.3 kg.	5000 mg of clopyralid (purity not specified) applied to intact skin of back.	No evidence of dermal irritation.	Jeffrey 1987b MRID No. 41641305
Rabbits, New Zealand white, 5/sex.	Clopyralid (DOWCO 290) 0.5 g applied to the clipped, but non-abraded back for 4 hours. Application sites graded for erythema and edema at 30 minutes and 24, 48, and 72 hours.	LD_{50} >2000 mg/kg. No skin irritation or systemic toxicity noted.	Saunders et al. 1983 MRID No. 00127275

Appendix 1. Toxicity of Clopyralid to Mammals (listed alphabetically by author) *(continued)*.

Animal	Dose	Response	Reference
DERMAL *(continued)*			
Rabbits, New Zealand white, 5/sex/dose level.	Fifteen applications of clopyralid at 0, 100, 500, and 1000 mg/kg over a 21-day period. Applied as a powder under a moistened gauze to the shaved back of each animal.	Localized skin effects at the application site. Slight erythema in 2 males at both 500 and 1000 mg/kg/day and one female at 500 mg/kg/day. Mild diffuse epidermal hyperplasia accompanied by inflammation was seen in some rabbits from all treatment groups. The authors indicated that this possibly resulted from mechanical irritation by the test material. No signs of systemic toxicity or pathological lesions attributable to exposure to clopyralid. NOAEL >1000 mg/kg/day.	Vedula et al. 1990 MRID No. 41790701
Guinea pig, Hartley-Dunkin albino, 10/sex/dose level.	Clopyralid 12.5, 25, 50, or 100% w/v in distilled water. Standard protocol with application on days 1, 8, and 15 with challenge on day 29.	No contact hypersensitivity was noted from skin application.	Vosvenieks 1982 MRID No. 00141550

Appendix 1. Toxicity of Clopyralid to Mammals (listed alphabetically by author) *(continued)*.

Animal	Dose	Response	Reference
EYES			
Rabbits, New Zealand white, 6 rabbits (NOS) exposed to 0.1 mg, 3 rabbits (NOS) exposed to 0.1 mg and washed after 30 seconds.	Draize eye testing of XRM-3972 Herbicide Formulation (Lontrel 360), NOS.	Acute eye instillation resulted in moderate discomfort and scattered, diffuse areas of opacity covering much or in some cases the entire cornea in 3/6 rabbits. All signs of irritation were resolved in 48 hours. Instillation followed by washing resulted in only moderate discomfort—no signs of irritation or corneal opacity. Skin application resulted in slight (5/6 rabbits) or moderate (1/6 rabbits) redness, and edema (6/6 rabbits).	Carreon and New 1981 MRID No. 00147690 **Applicable to Transline (Dow AgroSciences)**
Rabbits, adults, New Zealand, albino, 3/sex, 2.53–3.01 kg. Observations at 1 hour as well as 1, 2, 4, 7, 14, and 21 days after instillation.	100 mg of Lontrel TE (96.2% clopyralid) in right conjunctival sac without washing.	Slight to moderate conjunctival redness, diffuse to marked corneal opacity, and slight to marked chemosis in all 6 animals within 24 hours. In one rabbit, congestion of the iris was apparent on day 21.	Gilbert 1995d MRID No. 441141004
Rabbits, adults, New Zealand, albino, 3/sex, 2.0–3.3 kg. Observations at 1 hour as well as 1, 2, 4, 7, 14, and 21 days after instillation.	0.1 g in right conjunctival sac without washing.	Slight to marked redness, chemosis, and discharge. Reddening of the iris with moderate to marked opacity of the cornea. Opacity persisted to 21-days post-treatment.	Jeffery 1987c MRID No. 41641304
Rabbits, New Zealand White, 6 males exposed to 0.1 mg, 3 females exposed to 0.1 mg and washed after 30 seconds.	Penta and electro-chemical processes DOWCO 290.	Slight to marked redness and chemosis. Reddening of the iris and corneal opacity in all animals. Signs of irritation were apparent at 21 days after treatment.	Saunders et al. 1983 MRID No. 00127275

Appendix 1. Toxicity of Clopyralid to Mammals (listed alphabetically by author) *(continued)*.

Animal	Dose	Response	Reference
INHALATION			
Rats, Fischer-344, 7-weeks old, 5/sex, Lontrel T [95.4% clopyralid], 2-week observation period.	Time-weighted average (TWA) nominal concentration of 0.2 mg/L for 4 hours. Mass median aero-dynamic diameter of 13.45 µ. Actual concentration was less because material settled in the glass works and chamber.	During exposure, a few animals had red stains around nares and one salivated. Red stains around nares also noted in all females and 3 males after exposure. By test day 6, all animals appeared normal. No mortality, clinical effects, or gross pathology after exposure.	Streeter et al. 1987 MRID No. 41641303
Rats, Fischer-344, 6/sex.	Single 6-hour period to liquid aerosol containing XRM-3972 at TWA concentration of 3.0 mg/L (the highest attainable concentration) (MMAD = 1.99 µ; GSD = 2.48). XRM-3972 is 31.5% clopyralid.	No deaths occurred. Eye and nasal irritation, altered respiration, salivation, perineal wetness, and urine soiling were noted. No clinical signs were apparent on the day after exposure and only slight (1–2%) body weight loss, which rapidly recovered. Corneal opacities were noted in 3/6 males and 1/6 females—permanence of this effect was not reported.	Gushow et al. 1986 MRID No. 40035102 **Applicable to Transline (Dow AgroSciences 2003)**
Rats, Fischer-344 [CDF (F-344)/CrlBR (Inbred)], Group I: 10 rats (5/sex/dose level), 8-to 9-weeks old, weighing 165–193 g (males) and 123–136 g (females); 2-week observation period.	Group I: nose only exposure to nominal concentration of 5.5 mg/L (gravimetric concentration of 1.0 mg/L) for 4 hours. Group II: nose only exposure to nominal concentration of 1.2 mg/L (gravimetric concentration of 0.38 mg/L) for 4 hours.	No mortality in either group; all rats had generally normal body weights during 14-day observation period; labored breathing was the only substantial effect observed during exposure period; 2 hours after exposure clinical signs included red or clear nasal discharge, chromodacryorrhea, dried red material on the face, and labored breathing; – *Notes continued below.*	Hoffman 1995 MRID No. 44114103

Continued notes on Hoffman 1995 – ... 1 day after exposure, most of the rats had recovered completely and remained normal during the remainder of the 14-day observation period; in Group I (1.0 mg/L), there were no abnormal macroscopic postmortem observations; in Group II (0.38 mg/L), 4/10 rats had discolored lungs. According to the investigators: "Although Group II exposure was at a lower exposure level (total mass) than Group I, the two exposures were comparable on the basis of concentration of particles most likely to provide alveolar deposition and inflammatory response (≤1.0 micron in size). Therefore the observations only in the lungs of Group II animals were probably not treatment related."

Appendix 1. Toxicity of Clopyralid to Mammals (listed alphabetically by author) *(continued)*.

Animal	Dose	Response	Reference
Rats, Fischer-344, NOS.	Electrochemical process	4-hour nose-only LC_{50} = 0.38 mg/L (highest attainable concentration).	Dow AgroSciences 1998. *Appears to summarize Hoffman 1995, Group II. See above.*
Rats, Fischer-344, NOS.	Penta process	4-hour nose-only LC_{50} = 1 mg/L (highest attainable concentration).	Dow AgroSciences 1998.*Appears to summarize Hoffman 1995, Group I. See above.*

Appendix 2. Toxicity of Clopyralid to Birds after Oral Administration.

Animal	Dose/Endpoint	Response	Reference
Quail, Bobwhite eggs, 6 replicates of 6 eggs in 2-treatment groups.	Sprayed at 0 [control] or 0.56 kg a.e./ha. In a field environment.	No effect on viability, hatchability, or body weight. Also no effect PHA-P wing-web r anti-SRBC antibody titer.	Dabbert et al. 1997
Quail, Bobwhite, NOS.	Eight-day dietary LC_{50} 3,6-dichloro-picolinic acid dissolved in corn oil (DOWCO 290) for 5 days in the diet (plus 3 days on untreated food).	>4640 ppm. No signs of toxicity were reported. No mortality at highest dose tested.	Fink 1973a MRID No. 00073640
Ducks, Mallard, NOS.	Eight-day dietary LC_{50} of 3,6-dichloro-picolinic acid dissolved in corn oil (DOWCO 290) for 5 days in the diet (plus 3 days on untreated food).	>4640 ppm. No signs of toxicity were reported. No mortality at highest dose tested.	Fink 1973b MRID No. 00073641
Ducks, Mallard, NOS.	Acute oral LD_{50} of 3,6-dichloropicolinic acid (DOWCO 290) single exposure.	1465 mg/kg (95% CI 1220–1760 mg/kg). Dose-related effects observed, including lethargy, reduced reaction to external stimuli, lower limb weakness, loss of coordination and righting reflex. At doses >1000 mg/kg convulsions were observed. Also, dose-related reduction in body weight and food consumption.	Fink et al. 1980 MRID No. 00059970

Appendix 3. Toxicity to Terrestrial Invertebrates and Microorganisms.

Organism	Exposure	Response	Reference
DIRECT CONTACT			
Worker honey bee (*Apis mollifera*), 10 replicates/dose, 10 bees/replicate.	100 µg/bee 3,6-di-chloropicolinic acid (DOWCO 290) in acetone applied to ventral thorax for 48 hours.	Contact LD_{50} >100 µg/bee, 13% mortality at highest dose tested.	Cole 1974a,b MRID Nos. 00081595, 00059971
Honey bee (*Apis mellifera*), 1- to 7-days old, mean individual weight 110 mg, 4 replicates/dose, 50 bees/replicate.	0, 13, 22, 36, 60, and 100 µg/bee Lontrel 35A herbicide concentrate (3,6-di-chloropicolinic acid, monoethanolamine salt, 35% a.e.) for 48 hours.	48-hour mortality: control = 4/100 solvent control = 2/100 13 µg/a.i. per bee = 5/100 22 µg/a.i. per bee = 3/100 36 µg/a.i. per bee = 5/100 60 µg/a.i. per bee = 8/100 100 µg/a.i. per bee = 6/100 NOTE: None of the responses in the exposed groups are statistically significant from control mortality at a p-value of <0.05. 48-hour LD_{50} = >100 µg/bee NOEL = 100 µg/bee	Hinken et al. 1986c MRID No. 40151612
Spiders (Theridion impressum). 30 wild immature spiders for each chemical.	Direct application of 2 mL of clopyralid (Lontrel) at the recommended application rate (0.35 L), diluted in water. Only one dose tested.	Acute (96-hour) lethality of less than 10%. Authors concluded that clopyralid was “harmless”. **NOTE**: The actual dose used cannot be determined from the information presented in the publication. See Table 1 in Pekar et al. 2002).	Pekar et al. 2002
ORAL			
Worker honey bee (*Apis mellifera*), 10 replicates/dose, 10 bees/replicate.	100 µg/bee 3,6-di-chloropicolinic acid (DOWCO 290) in 20% sucrose solution instilled via feeding tube.	48 hour oral LD_{50} >100 µg/bee, 20% mortality at highest dose tested.	Cole 1974a,b MRID Nos. 00081595, 00059971

SOIL			
Earthworm, NOS.	14-day static LC_{50} using technical clopyralid.	>1000 mg/kg soil, NOS.	Dow AgroSciences 1998
Terrestrial microorganisms.	Soil administration of 1 or 10 ppm clopyralid (DOWCO 290, 96.9% pure).	No change in soil microbial parameters tested (nitrogen fixation, nitrification, degradation of cellulose, starch, protein, and leaf material).	McCall et al. 1979 MRID No. 00059960

Appendix 4. Toxicity to Non-target Plants.

Plant	Exposure	Response	Reference
Six species of landscape plants: 4 species of *Juniperus*, *Lagerstroemia indica*, and *Cotoneaster dammeri*.	Backpack applications at 0.14, 0.28, and 0.56 kg/ha [0.125, 0.25, and 0.5 lb a.i./acre].	Visual damage [10–16 on a 100-point scale] to *Lagerstroemia* at 3 and 6 weeks after application. Extent of visual damage was not dose-related or progressive. Less severe damage [5–9 on a 100-point scale] to *Cotoneaster* at 3 weeks with apparent partial recovery at 6 weeks [0–3 on a 100-point scale]. No damage to Juniper species. No effects on growth rates of any species.	Bachman et al. 1995
Willows (two varieties) and poplar	Track sprayer, 0.2 and 0.4 kg a.i./ha.	No marked effect on willow varieties. About 50% growth inhibition in poplar. Difference probably due to greater amount of spray retained on poplar.	Clay 1991
Strawberries	Backpack sprayer at 0.1 or 0.2 kg a.e./ha.	Some leaf distortion but no effect on yield when applied to established plants.	Clay and Andrews 1984
Cacti, five species, seed-grown nursery plants or grafts. All were related to but not classified as endangered species.	Hand sprayer, 0.25 and 0.5 lb a.i./acre.	No effect on survival of *Echinocatus grusonii or Echinocereaus engelmannii* at either application rate. A modest but not strongly dose-related effect on vigor in *Echinocatus grusonii*. Increased vigor in *Echinocereaus engelmannii*. No dose-related effect on survival or vigor in *Mammillaria thornberi*. In *Pediocatus papyracanthus*, mortalities of 60 and 80% and a dose/related reduction in vigor after 6 months at low- and high-rates, respectively. In *Corphantha hesteri*, 40% mortality as well as comparable decreases in vigor at both application rates.	Crosswhite et al. 1995

Appendix 4. Toxicity to Non-target Plants (listed alphabetically by author) *(continued)*.

Plant	Exposure	Response	Reference
Cotton	0.01, 0.05, 0.1, and 0.25 lb a.i./acre.	No effects at 0.01 lb a.i./acre. When applied to pre-bloom cotton plants, 0.05 lb/acre or higher reduced yields from 35–45%.	Jacoby et al. 1990
Variety of forestry trees: ash, beech, birch, cherry, Japanese larch, oak, red alder, Sitka spruce, and sycamore; all are 2-year old potted grown plants.	0.1 and 0.3 kg a.i./ha by laboratory track sprayer.	No visible signs of damage or effects on fresh weight. Transient and not clearly dose-related changes in shoot fresh weight in alder and Sitka spruce. Some transient distortion of Japanese larch needles.	Lawrie and Clay 1994
Potatoes	0.0001, 0.001, 0.01, and 0.1 kg a.i./ha in year 1. Replanting done in years 2 and 3. Application by broadcast sprayer at 30% or 70% canopy crop cover. Soil type not specified.	In year 1, damage only at highest application rate. In year 2, there was severe damage, tuber malformation, and reduced yield, at both 0.1 and 0.01 kg a.i./ha. No damage was apparent in year 3.	Lawson et al. 1992
Potatoes, kumara, and tomatoes, mature vegetative to early flowering stage.	0.0001, 0.001, 0.01, 0.1, 0.5, and 1.0 kg a.i./ha. Broadcast spray.	In potatoes, reduced yield and severe foliar damage at 0.01 kg/ha and reduced yield at 0.001 kg/ha. In kumara, reduced yield at 0.01 kg/ha. In tomatoes, some foliar damage and reduced yield at 0.01 mg/kg.	Lucas and Lobb 1987
Sweet corn (*Zea mays*)	0.2, 0.3, 0.6, or 1.1 kg/ha by backpack sprayer.	No substantial or dose/related effects on stalk curvature, stunting, or yield.	Masiunas and Orfanedes 1991
Galt and Klondike barley	0.1 to 0.9 kg a.e./ha using motorized plot sprayer.	No effect at any application rates.	O'Sullivan and Kossatz 1984a
Glenlea and Neepawa wheat; 3- and 6-leaf stages and boot stage.	0.1 to 0.9 kg a.e./ha using motorized plot sprayer.	No effect on Glenlea wheat. Effects on Neepawa wheat at 0.6 kg/ha and above depending on plant stage at the time of application.	O'Sullivan and Kossatz 1984b
Cranberries	0.21 or 0.42 kg a.i./ha by broadcast sprayer.	At 0.21 kg/ha, moderate to severe damage only if applied to pre-bloom stage. At 0.42 kg/ha, damage to both pre-bloom and fruit set stages.	Pattern et al. 1994

Appendix 4. Toxicity to Non-target Plants (listed alphabetically by author) *(continued)*.

Plant	Exposure	Response	Reference
Seventeen species of forbs and 4 species of grasses.	0.2 kg a.i./ha by AZO pedestrian sprayer.	Decrease rooted frequency and flowering in several species with visible signs of damage in several forbs.	Pywell et al. 1996
Landscape trees: pear, myrtle, redbud, and red maple. Observations over a 2-year period.	0.28 kg a.i./ha. Directed backpack spray.	Significantly decreased trunk diameter and total weight in Eastern redbud. Significant visual injury to red maple of 60 to 150 days after treatment but no effect on tree diameter or weight by the end of the study.	Smith and Skroch 1995
Three varieties of pine seedlings. Loblolly pine (*Pinus taeda L.*), slash pine (*P. elliottii Engelm. var. elliottii*), and longleaf pine (*P. palustris Mill.*).	Post emergence field study of clopyralid on nursery seedlings. Application rate was 0, 210, 420, or 840 g a.e./ha.	These southern pines are tolerant of clopyralid in the 210 to 840 g a.e./ha. Transient epinasty was occasionally observed in both lobolly and slash pines. South (2000) concluded that clopyralid could be used to control weeds at southern pine nurseries.	South 2000
Alien and native graminoids and alien and native forbs. Split plot design (broadleaf treatment and seedling treatment) studied over 3 years.	Yearly (June) application of clopyralid at 0.28 kg a.e./ha; topsoil.	Clopyralid treatment decreased mean canopy coverage of alien forbs (untreated = 23.4%; treated = 4.2%) and increased canopy coverage or native graminoids slightly (from 4.05 untreated to 6.3% treated). Clopyralid reduced mean coverage of native forbs (untreated = 8.9%; treated = 3.9%) and increased coverage of alien graminiods (untreated = 20.2%; treated = 29.4%). In seedlings, clopyralid increased native graminoid coverage by 2.8–4.6 times, which was lover than alien graminoid cover. Clopyralid treatment produced no effects on seedling forbs (alien and native varieties).	Tyser et al. 1998

Appendix 4. Toxicity to Non-target Plants (listed alphabetically by author) *(continued)*.

Plant	Exposure	Response	Reference
Potato (*S. tuberosum*)	Field investigations of simulated drift of clopyralid (alkanolamine salt) at 0, 4, 8, 16, or 32 g a.i./ha.	Foliar injury and reduced marketable tuber yield was observed in potatoes exposed to clopyralid at 16 g a.i./ha of application rate. The data suggest that the injury may persist in tubers from sprayed fields grown in unsprayed filed the following year due to herbicide residues contained in the tubers.	Wall 1994
Onion, corn, wheat, barley, soybean, snap bean, radish, tomato, canol, and sunflow. Assays on germinating seeds, emerging seedlings, and emerged plants.	Rates of 0.056, 0.112, 0.56, 5.6, 56, and 560 g/ha. (Equivalent to 0.000056, 0.000112, 0.00056, 0.0056, 0.056, and 0.560 kg/ha.) Clopyralid applied as the potassium salt, 75% weight percent acid equivalent. Applications by greenhouse track sprayer. Sandy loam soil.	At 0.56 kg/ha, adverse effects on sunflower germination (all determinations made 3–4 days after treatment). When applied as a pre-emergence spray to soil at 0.56 kg/ha, toxic to onion, soybean, snap bean, tomato, and sunflower but not other species [observations made 10 and 14 days after treatment]. NOEL for emergence for onion is 0.14 kg/ha. NOEL for emergence for tomato and sunflower is 0.035 kg/ha. NOEL for emergence for soybean is 0.028 kg/ha. NOEL for emergence for snap bean is 0.056 kg/ha. As a post-emergent foliar spray, 0.00056 kg/ha was the NOAEL for soybean, snap bean, tomato, and sunflower (observations made up to 42 days post-spray). Barley, corn, radish, and canola were unaffected at 0.56 kg/ha.	Weseloh 1987 MRID No. 40081401

Appendix 5. Toxicity to Fish, Aquatic Invertebrates, and Aquatic Plants. [All concentrations in a.e. unless otherwise specified.]

Organism	Exposure	Response	Reference
Fish			
Sunfish, Bluegill (*Lepomis macrochirus macrochirus* Rafinesque).	3,6-dichloropicolinic acid (DOWCO 290) for 96 hours.	96-hour LC_{50} = 125.4 mg/L	Dow Chemical 1980e MRID No. 00059968
Trout, Rainbow (*Salmo gairdneri* Richardson).	3,6-dichloropicolinic acid (DOWCO 290) for 96 hours.	96-hour LC_{50} = 103.5 mg/L	Dow Chemical 1980e MRID No. 00059968
Minnow, Fathead, NOS.	Monoethanolamine salt (a.i.) of clopyralid (35% a.e.).	96-hour LC_{50} >2900 mg a.i./L (>1015 mg a.e./L)	Dow AgroSciences 1998.
Sunfish, Bluegill, NOS.	Monoethanolamine salt (a.i.) of clopyralid (35% a.e.).	96-hour LC_{50} = 4700 mg a.i./L (1645 mg a.e./L)	Dow AgroSciences 1998.
Trout, Rainbow, NOS.	Monoethanolamine salt (a.i.) of clopyralid (35% a.e.).	96-hour LC_{50} = 2000 mg a.i./L (700 mg a.e./L)	Dow AgroSciences 1998.
Aquatic Invertebrates			
Daphnia magna	Two definitive static water LC_{50} tests were conducted with technical grade clopyralid (DOWCO 290, 96.9% pure).	48-hour LC_{50} = 232 mg/L (214–254 mg/L) 48-hour LC_{50} = 225 mg/L (208–245 mg/L)	Batchelder 1980 MRID No. 00059972
Daphnia magna	Monoethanolamine salt (a.i.) of clopyralid (35% a.e.).	96-hour LC_{50} = 1000 mg a.i./L (350 mg a.e./L).	Dow AgroSciences 1998.
Daphnia magna	Monoethanolamine salt (a.i.) of clopyralid (35% a.e.).	NOEC for reproduction of 66 mg a.i./L (23.1 mg a.e./L).	Dow AgroSciences 1998.
Aquatic Macrophytes			
Duckweed, NOS.	14 days	EC_{50} = 89 mg/L	Dow AgroSciences 1998.

Appendix 5. Toxicity to Fish, Aquatic Invertebrates, and Aquatic Plants (listed alphabetically by author). [a.e. unless otherwise specified] *(continued)*

Organism	Exposure	Response	Reference
Potamogeton pectinatus and *Myriophyllum sibiricum*	12-ha pond. 1 m square enclosures in 50–70 cm deep water. Concentrations of 0.01 mg/L and 0.1 mg/L.	No adverse effects. Growth and flowering of both species were stimulated at 0.01 mg/L. At both 0.01 and 0.1 mg/L, tuber production by *Potamogeton pectinatus* was also stimulated.	Forsyth et al. 1997

Appendix 5. Toxicity to Fish, Aquatic Invertebrates, and Aquatic Plants (listed alphabetically by author). [a.e. unless otherwise specified] *(continued)*

Organism	Exposure	Response	Reference
Unicellular Algae			
Selenastrum capricornutum	96-hour exposures	EC_{50} for growth inhibition was 6.9 mg/L based on cell count and 7.3 mg/L based on total volume.	Dill and Milazzo 1985 MRID No. 40081402
Green alga, NOS	72 hours	EC_{50} = 449 mg/L	Dow AgroSciences 1998.
Green alga, NOS	72 hours	EC_{50} = 61 mg/L	Dow AgroSciences 1998.

Appendix 6. Field Studies on the Fate of Clopyralid in Soil.

Treatment	Location	Results	Reference
Clopyralid, 0.5 lbs a.e. and picloram 0.5 lb a.e./acre. Observations over a 4-month period.	Bremond TX, loamy fine sand to fine sand soil. Irrigation used to supplement rainfall. Average monthly rainfall/irrigation of 2.87 to 4.44 inches.	Rapid dissipation in soil: $t_{1/2}$ of 10 days. Dissipation $t_{1/2}$ on vegetation of about 8 days. Initial concentration on plants of about 40 ppm as read from Figure 6. (Table of plant residues is not provided.) No residues in ground water at limit of detection (1 ppb). Maximum level in soil on day 9 probably due to wash-off.	Oliver et al. 1988 MRID No. 40676201
Clopyralid, XRM-4703 (clopyralid 0.5 lb a.e./acre) and picloram at 0.5 lb a.e./acre.	Highly permeable loamy fine sand to fine sand soil in high rainfall region. Irrigation used to supplement rainfall.	Soil $t_{1/2}$ of about 10 days. Only trace levels by day 79. Residues largely in upper 36 inches of soil. No residues detected in ground water. No detectable levels at days 128 or 189.	Petty and Knuteson 1991 MRID No. 42415401
Clopyralid at 278 g a.e./ha (0.25 lb a.e./acre).	California, natural rainfall supplemented with irrigation.	Soil $t_{1/2}$ of 19 days. Field $t_{1/2}$ in grass/thatch of 48 days.	Roberts et al. 1996 MRID No. 44184701
Clopyralid (99% pure) at 1, 5, 10, 50, 100, or 500 µg/kg in soil.	Cultivated and uncultivated soil high humic acid.	Soil $t_{1/2}$ 57 days in cultivated soil. Soil $t_{1/2}$ 161 days in uncultivated, high humic acid soil.	Schutz et al. 1996
^{14}C-labeled clopyralid at 280 g/ha.	Applied to a small plots of soil.	After 312 days in field, 24% of radioactivity remained mostly associated with soil organic matter. No soil metabolites or degradation products were detected.	Yackovich et al. 1993 MRID No. 42815001