



SERA TR-052-16-04a

Endothall
Human Health and Ecological Risk Assessment
FINAL REPORT

Submitted to:
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USDA Forest Service Contract: **AG-3187-C-06-0010**
USDA Forest Order Number: **AG-43ZP-D-08-0013**
SERA Internal Task No. **52-16**

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November 27, 2009

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Attachment 2: Aquathol Super K EXCEL Worksheets for Human Health and Ecological Risk Assessments.
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Attachment 4: Hydrothol 191 Granular EXCEL Worksheets for Human Health and Ecological Risk Assessments.
Attachment 5: Worker Exposure Rates and Elaborated Hazard Quotients for General Exposures

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
AChE	acetylcholinesterase
AEL	adverse-effect level
a.i.	active ingredient
BCF	bioconcentration factor
bw	body weight
calc	calculated value
CBI	confidential business information
ChE	cholinesterase
CI	confidence interval
cm	centimeter
CNS	central nervous system
cpm	count per minute
DAA	days after application
DAT	days after treatment
DER	data evaluation record
d.f.	degrees of freedom
EC _x	concentration causing X% inhibition of a process
EC ₂₅	concentration causing 25% inhibition of a process
EC ₅₀	concentration causing 50% inhibition of a process
EHE	2-ethylhexyl ester
EFED	Environmental Fate and Effects Division (U.S. EPA/OPP)
ExToxNet	Extension Toxicology Network
F	female
FH	Forest Health
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FQPA	Food Quality Protection Act
g	gram
GLP	Good Laboratory Practices
ha	hectare
HED	Health Effects Division (U.S. EPA/OPP)
HQ	hazard quotient
IARC	International Agency for Research on Cancer
IREED	Interim Reregistration Eligibility Decision
IRIS	Integrated Risk Information System
i.p.	intraperitoneal
i.v.	intravenous
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

ACRONYMS, ABBREVIATIONS, AND SYMBOLS *(continued)*

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

COMMON UNIT CONVERSIONS AND ABBREVIATIONS

To convert ...	Into ...	Multiply by ...
acres	hectares (ha)	0.4047
acres	square meters (m ²)	4,047
atmospheres	millimeters of mercury	760
centigrade	Fahrenheit	1.8°C+32
centimeters	inches	0.3937
cubic meters (m ³)	liters (L)	1,000
Fahrenheit	centigrade	0.556°F-17.8
feet per second (ft/sec)	miles/hour (mi/hr)	0.6818
gallons (gal)	liters (L)	3.785
gallons per acre (gal/acre)	liters per hectare (L/ha)	9.34
grams (g)	ounces, (oz)	0.03527
grams (g)	pounds, (oz)	0.002205
hectares (ha)	acres	2.471
inches (in)	centimeters (cm)	2.540
kilograms (kg)	ounces, (oz)	35.274
kilograms (kg)	pounds, (lb)	2.2046
kilograms per hectare (kg/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 (µg/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

Endothall is used by the Forest Service as an aquatic herbicide. Granular and liquid formulations are available as the dipotassium salt (Aquathol formulations) and as a mono-(N,N-dimethylalkylamine) salt (Hydrothol formulations) of endothall. Both Aquathol and Hydrothol formulations are used for the control of aquatic macrophytes. Hydrothol formulations are also used for the control of algae. Application rates for endothall are expressed as target concentrations. Aquathol formulations are labeled for target concentrations of 0.35 to 3.5 mg a.e./L. Hydrothol formulations are labeled for target concentrations of 0.5 to 5 mg a.e./L.

Worker exposures and the associated risks are related linearly to the target concentration and the volume of treated water. Uncertainty in the risk characterization for workers is substantial, and this uncertainty is dominated by the assumptions used in the exposure assessment for routine exposures associated with aquatic applications (Section 3.2.2.1). Because endothall is a severe skin irritation, the U.S. EPA/OPP assumes that dermal exposures will be self-limiting and the U.S. EPA/OPP considers only inhalation exposures quantitatively in the exposure assessment for workers. Unlike the U.S. EPA/OPP, the current Forest Service risk assessment does quantitatively consider dermal exposures. Nonetheless, the exposure assessments for workers in the current Forest Service risk assessment are based on lower worker exposure rates than those used for other aquatic pesticides covered in Forest Service risk assessments.

At target concentrations of 0.1 ppm, the level of concern for workers is not exceeded, even at the maximum plausible treatment volume of 150 acre-feet. Higher target concentrations may result in exposures above the level of concern. Based on the chronic RfD, all HQ values are below a level of concern for treatments of up to 150 acre-feet at target concentrations of up to 0.1 mg/L. Higher application rates lead to upper bound HQ values in the range of 1.1 to 16 over treatment volumes of 25 acre-feet to 150 acre-feet. At 5 mg/L, the maximum target concentration for Hydrothol formulations, the treatment of 10 acre-feet leads to an upper bound HQ of 1. Based on the acute RfD, the HQ values are at or below the level of concern (HQ=1) for the target concentrations of up to 5 mg/L and treatment volumes of up to 125 acre-feet. Endothall is also highly irritating to the eyes. In addition, ocular exposures in rabbits have resulted in lethality. The use of protective eyewear as well as mitigation measures for accidental contamination of the eyes should be rigorously enforced and monitored in any application of endothall.

For the general public, the only exposure scenarios of concern involve the consumption of contaminated water. Under a set of standard exposure assumptions used in most Forest Service risk assessments, accidental spills of a large amount of liquid formulations are of greatest concern. Non-accidental exposures—i.e., those that might be expected in the normal use of endothall—lead to HQs that modestly exceed the level of concern at application rates above 0.8 mg a.e./L for acute exposures and 0.5 mg a.e./L for longer-term exposures.

The ecological risk assessment for endothall suggests that adverse effects in terrestrial organisms are not likely to occur, except in the case of a severe spill, in which case canids are the most likely groups of terrestrial organisms to be adversely affected. Risks

to aquatic organisms are highly dependant of the formulation of endothall used. Effective applications of Hydrothol formulations could adversely affect sensitive species of aquatic animals as well as aquatic plants. Effective applications of Aquathol formulations will adversely affect aquatic macrophytes, while adverse toxic effects in other groups of organisms are less likely. The application of any effective herbicide to a water body with a dense population of sensitive plants could result in a decrease in oxygen concentrations in the water which could adversely affect many aquatic organisms. For both types of formulations, partial or shore-line treatments could be less hazardous to aquatic species than treatments of the entire water body might be.

1. INTRODUCTION

This document provides human health and ecological risk assessments of the environmental consequences of using endothall in Forest Service programs. Endothall is used in Forest Service programs only for aquatic weed control. Accordingly, the endothall formulations covered in this risk assessment include liquid and granular formulations of Aquathol and Hydrothol.

In addition to standard literature searches of TOXLINE and AGRICOLA, this risk assessment considers the reviews on endothall conducted for the Washington State Department of Ecology (CSI 2001) and the San Francisco Estuary Institute (Siemering et al. 2005), the risk assessment conducted by the California Environmental Protection Agency (CalEPA 1997), as well as the endothall reviews prepared by the U.S. EPA's Office of Pesticide Programs (U.S. EPA/OPP 2004a-c, 2005a-i), Office of Drinking Water (U.S. EPA/ODW 1987, 1992), and Office of Research and Development (U.S. EPA/ORD 1991). Other reviews of the open literature on endothall were consulted in the preparation of the risk assessments, including EXTOKNET 1995; Folmar 1977; Johnson 1968; Keckemet 1969; Lindaberry 1961; Mullison 1970; Pollis et al 1998; Pritchard 1988; Reinert and Rogers 1987; Simsiman et al. 1976; Siemering et al. 2005; Sprecher et al. 2002; Stratton 1987; Westerdahl and Getsinger 1988a, primarily to augment the standard literature searches of TOXLINE and AGRICOLA. With very few exceptions, full copies of the original open literature citations were obtained and information was not taken from secondary sources. The exceptions —i.e., information taken from secondary sources —are identified in the bibliography (Section 5).

The Reregistration Eligibility Decision (RED) for endothall includes a 79-page bibliography of unpublished studies (i.e., approximately 900 citations) going back to the 1950s. Since the EPA categorizes these studies as confidential business information (CBI), copies of the complete studies were not available for use in the current risk assessment. Hence, the current risk assessments are based on publically available EPA summaries, particularly the EPA reviews of endothall prepared by the Office of Pesticide Programs in support of the 2005 Reregistration Eligibility Decision (RED) on endothall (U.S. EPA/OPP 2004a-c, 2005a-i).

A Freedom of Information Act (FOIA) request was made to obtain the available EPA *cleared reviews* pertaining to endothall. Cleared reviews consist primarily of detailed summaries of registrant submitted studies (referred to as Data Evaluation Records or DERs), internal EPA analyses and reviews, and correspondence between the EPA and the registrant. A total of 87 cleared reviews (as electronic files) were kindly provided by U.S. EPA/OPP. Many of the cleared reviews are internal administrative documents from EPA, which are not cited in the current risk assessments. Following standard conventions in Forest Service risk assessments, DERs are cited as the study on which the DER is based, which are included in the reference list. Other internal documents from EPA, particularly the review by Dykstra (1978), contain brief summaries of otherwise unavailable information on endothall formulations. These documents are cited in the reference list by the name of the first author at EPA. In response to a second FOIA

request, U.S. EPA/OPP provided several additional DERs that were not previously cleared (Mallory 1991a,b,c; Mallory 1992).

In addition to reviews published in the open literature, there is a substantial amount of information on endosulfan available on the Internet—e.g., nearly 60,000 entries identified in a simple Google search. For the most part, data obtained from the Internet are not used in the current risk assessments unless the information is well documented. The most useful database found on the Internet for the current ecological risk assessment is the ECOTOX database compiled and reviewed by the EPA (U.S. EPA/ORD 2009). ECOTOX is also the main ecotoxicity database used by the Pesticide Action Network (PAN at <http://www.panna.org/>).

The human health and ecological risk assessments prepared for the USDA Forest Service are not, and are not intended to be, comprehensive summaries of all of the available information. For endosulfan, some studies from the earlier literature were excluded from consideration if the endosulfan salt was not specified or the magnitude of exposure cannot be determined (e.g., Berry et al. 1975; D'Silva et al. 1977; Gillette et al. 1952; Jiltbran 1967; Jordan et al. 1962; Kratky and Warren 1971). As discussed further in Section 4 (Ecological Risk Assessment), the potassium and amine salts of endosulfan exhibit substantially different toxicities.

The Forest Service periodically updates pesticide risk assessments 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 is likely to alter the conclusions reached in the risk assessments.

Like other Forest Service risk assessments, this document has four chapters: the introduction, program description, risk assessment for human health effects, and risk assessment for ecological effects or effects on wildlife species. Each of the two risk assessment chapters has four major sections, including an identification of the hazards associated with endosulfan 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.

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

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

body of the document. For the more cumbersome calculations, EXCEL workbooks, consisting of sets of EXCEL worksheets, are included as an attachment to the risk assessment. The worksheets provide the detail for the estimates cited in the body of this document. Documentation on the use of EXCEL workbooks is provided in SERA (2009a). Because of differences in the composition of granular and liquid Aquathol and Hydrothol formulations, discussed further in Section 2, separate EXCEL workbooks are provided for each of these formulations. These workbooks are included as Attachments 1 through 4 of this risk assessment.

2. PROGRAM DESCRIPTION

2.1. OVERVIEW

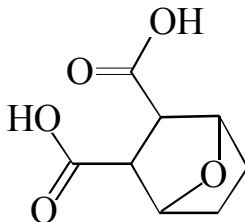
Endothall is a herbicide that is registered for aquatic and terrestrial applications. Only aquatic applications are covered in the current Forest Service risk assessment. All aquatic formulations of endothall are supplied by United Phosphorous Inc. Two sets of formulations, Aquathol and Hydrothol, are available in both liquid and granular forms. Aquathol formulations contain the dipotassium salt of endothall, and these formulations are labeled for the control of various aquatic macrophytes. The Hydrothol formulations contain an amine salt of endothall and are labeled for the control of both macrophytes and algae.

Application rates for endothall are expressed as target concentrations in units of parts per million (ppm or mg/L). For Aquathol formulations, the target concentrations range from 0.35 to 3.5 ppm a.e. The target concentrations for Hydrothol formulations vary with the intended purpose: from 0.05 to 1.5 ppm a.e. for the control of algae, from 0.5 to 3 ppm a.e. for the control of macrophytes in lakes or ponds, and from 3 to 5 ppm a.e. for the control of macrophytes in canals. In lakes and ponds, hydrothol applications greater than 1 ppm a.e. may only be made to 1/10th of the water surface area at any given time.

Endothall may be applied either to the water surface or to the subsurface. Details regarding metered applications to flowing water are not provided on the product labels. Nonetheless, descriptions of metered applications to flowing water are available in the open literature and are discussed in EPA documents supporting the 2005 Reregistration Eligibility Decision (RED) for endothall. The current Forest Service risk assessments consider the range of labeled application rates for endothall formulations—i.e., 0.35-3.5 ppm a.e. for Aquathol formulations and 0.05-5 ppm a.e. for Hydrothol formulations. The workbooks that accompany this risk assessment document are based on a target concentration of 1 ppm a.e. for all formulations. The consequences of using higher or lower target concentrations are discussed in the risk characterizations for human health (Section 3.4) and ecological effects (Section 4.4).

2.2. CHEMICAL DESCRIPTION AND COMMERCIAL FORMULATIONS

Endothall is the common name for 7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acid:



Endothall was developed as a terrestrial herbicide in the late 1940s (Tischler et al. 1948, 1950), and the effectiveness of endothall as an aquatic herbicide was discovered in 1953 (Keckemet 1969). Endothall was developed by Sharples Chemical Corporation, which is now called Cerexagri Inc (Tomlin 2004). Endothall has been produced by Pennsalt Corporation, Pennwalt Corporation, and Elf Atochem North America (Sprecher et al.

2002); however, according to the U.S. EPA Reregistration Eligibility Document (RED) for endothall (U.S. EPA/OPP 2005a), Cerexagri Inc. is the only registrant for the production of technical grade endothall in the United States.

Since the publication of the RED, Cerexagri Inc. appears to have changed to or been purchased by United Phosphorus Limited (UPL). The former web site for Cerexagri Inc. (www.cerexagri.com) is now redirected to <http://www.uplonline.com/index.php3>, and the address for United Phosphorus Limited is identical to the address listed on the EPA labels for endothall formulations offered by Cerexagri Inc. Based on a press release from United Phosphorus Limited (UPL 2006), it appears that United Phosphorus Limited purchased Cerexagri Inc in 2006. Consequently, the current risk assessments refer to the registrant for endothall as United Phosphorus Limited rather than Cerexagri Inc.

Table 1 summarizes the chemical and physical properties of endothall. Additional information about the chemical and physical properties used in this risk assessment to model endothall concentrations in the environment is discussed in Section 3.2 (Exposure Assessment). As discussed further on in this document, the endothall formulations covered in the risk assessments contain either the dipotassium salt of endothall or its mono (N,N-dimethylalkylamine) salt. Consistent with the convention used in the EPA RED for endothall (U.S. EPA/OPP 2005a), the mono (N,N-dimethyl-alkylamine) salt is referred to as the *amine salt*.

The structure of endothall and its salts is presented in Figure 1, and the comparative data on these compounds are summarized in Table 2. Note that the amine salt of endothall is based on a mixture of C8 to C18 alkyl compounds derived from coconut oil. Because the salt is a mixture of alkyls, no molecular formula or molecular weight is given in Table 2 for the amine salt.

The endothall formulations covered in these Forest Service risk assessments are listed in Table 3. These formulations include liquid and granular formulations of the dipotassium salt of endothall—i.e., Aquathol K (liquid) and Aquathol Super K (granular)—as well as the amine salt of endothall— i.e., Hydrothol 191 (liquid) and Hydrothol 191 Granular. As noted above, the labels and material safety data sheets (MSDSs) for all endothall formulations are referenced to Cerexagri Inc., while the registration for the endothall formulations appears to be held currently by United Phosphorus Limited.

The dipotassium and amine salts of endothall are both labeled for a variety of aquatic weeds including bur reed, coontail, water stargrass, *Hydrilla*, *Hygrophila*, *Naiad*, and various species of pondweed (*Potamogeton*). Several labeled uses of endothall formulations are excluded in California. The Hydrothol formulations (i.e., the amine salts) are also labeled for the control of algae and *Elodea*. In California, the use of Hydrothol formulations for the control of algae is limited to designated genera: *Cladophora*, *Pithophora*, *Spirogyra*, and *Chara*.

Although endothall formulations are labeled for the control of numerous aquatic plant species, the primary target species for the Aquathol formulations are submerged aquatic

vegetation such as hydrilla and pondweed in the Southern and Great Lakes States; whereas, the Hydrothol formulations are used for algal control and the control of submerged vegetation in small areas such as small ponds and canals used for drainage or irrigation (U.S. EPA/OPP 2005c).

As summarized in Table 4, Aquathol K, Hydrothol 191, and Hydrothol 191 Granular do not contain listed inerts on the MSDSs for these formulations. Aquathol Super K—i.e., the granular formulation of the dipotassium salt of endothall—does list a potassium polymer of 2-propenamide as being present as 27.5% of the formulation. Little information is available on this inert; furthermore, the inert is not discussed in the EPA risk assessment or other risk assessments on endothall cited in Section 1. Material safety data sheets for the agent with the same CAS number as that listed on the MSDS for Aquathol Super K indicate that the 2-propenamide is not classified as hazardous (Ciba 2004; Southern Agricultural Insecticides, Inc. 1998). U.S. EPA/OPP regulates the use of inert ingredients, and the 2-propenamide potassium polymer is an allowable inert in nonfood use pesticide products (U.S. EPA/OPP 2009). Notably, an older granular formulation of the dipotassium salt of endothall (7.2% a.e.) contained substantial amounts of clay (Reinert et al. 1985a).

2.3. APPLICATION METHODS

The liquid formulations of endothall may be applied either to the water surface or to the subsurface. The specific types of equipment for surface or subsurface applications are not specified on the product labels and could vary substantially, depending on the conditions in and size of the area to be treated. Granular formulations of endothall are labeled only for surface applications. Again, the nature of the equipment to be used is not specified on the product labels.

U.S. EPA/OPP (2005a, p. 3 ff) discusses the general types of equipment that can be used to apply various endothall formulations. Liquid applications to the water surface may be made with low pressure hand wand sprayers or hand gun sprayers. Subsurface applications are to be made with metered hoses or pipes. Aerial applications of liquid formulations are not permitted. Granular applications may involve boats equipped with centrifugal or blower-type spreaders or helicopters equipped with spreaders.

All product labels for endothall note that endothall is a contact herbicide which should be applied only after weeds emerge. The product labels also recommend that endothall should be applied only to still or slowly flowing waters. As discussed further in Section 2.4 (Application Rates), the labeled application instructions for endothall are based on a standing body of water, which is unlike the case with fluridone, another aquatic herbicide, for which the product labels provide separate sets of instructions for applications to standing water and flowing water.

Nonetheless, the product labels for endothall do not exclude applications to streams or rivers and specifically note applications to canals. Studies involving the efficacy of injecting endothall into flowing water have been conducted; however the limited contact times associated with rapidly flowing water restricts the effectiveness of endothall

treatments (e.g., Bowmer and Smith 1984; Bowmer et al. 1995). For more rapidly flowing water, the use of continuous flow metering pumps can be used to achieve adequate control of submerged weeds (e.g., Price 1969; Sisneros et al. 1998). As noted by the previous registrant, however, there are “...no uses on any endothall product label that allows metered use in flowing water” (Cerexagri Inc. 2005, p. 9). As an alternative to metered applications, increasing treatment concentrations will decrease the exposure time required for effective control, and maximum application rates could be effective in rapidly flowing water in some circumstances (Slade et al. 2008).

2.4. MIXING AND APPLICATION RATES

The application rates for endothall are summarized in Table 2. On the product labels, all application rates are expressed as the target nominal concentrations in units of ppm (mg/L) in water. All product labels provide application instructions for the liquid or granular formulations as amounts per acre-foot of water. An acre-foot (ac-ft) is a unit of liquid volume equivalent to covering a 1-acre (43,560 ft²) area in 1 foot of water. Thus, an acre-foot is equivalent to 43,560 ft³. A cubic foot contains 28.32 liters (Budavari 1989). Thus, an acre-foot is equivalent to approximately 1,233,619.2 L [43,560 ft³ × 28.32 L/ ft³].

For liquid formulations, the following general algorithm is used to calculate the target concentration (TC in units of ppm) per acre-feet of water based on the gallons of formulation (Frm_(gal)) to apply and the concentration of the agent in the formulation, FC_(lb/gal), in units of pounds/gallon:

$$TC_{(mg/L)} = \frac{Frm_{(gal)} \times FC_{(lbs/gal)} \times 453592.27 \text{ mg/lb}}{(ac - ft \times 1,233,619.2 \text{ liters/ac - ft})} \quad \text{Eq 1}$$

The above equation can be rearranged to calculate the gallons of formulation required to treat a specified number of acre-feet, *N*, to achieve the desired target concentration:

$$Frm_{(gal)} = \frac{TC_{(mg/L)} \times (N \text{ ac - ft} \times 1,233,619.2 \text{ liters/ac - ft})}{FC_{(lbs/gal)} \times 453592.27 \text{ mg/lb}} \quad \text{Eq 2}$$

A similar general algorithm is used to calculate the target concentration for granular formulations based on the pounds of formulation to be applied (Frm_(lb)) and the proportion (P) of the agent in the formulation:

$$TC_{(mg/L)} = \frac{Frm_{(lb)} \times P_{(unitless)} \times 453592.27 \text{ mg/lb}}{(ac - ft \times 1,233,619.2 \text{ liters/ac - ft})} \quad \text{Eq 3}$$

Alternatively, the above equation can be rearranged to calculate the pounds of formulation required to treat a specified number of acre-feet to achieve the desired target concentration:

$$Frm_{(lb)} = \frac{TC_{(mg/L)} \times N_{ac-ft} \times 1,233,619.2 \text{ liters/ac-ft}}{P_{(unitless)} \times 453592.27 \text{ mg/lb}}$$

Small discrepancies will be noted in applying the above algorithms to the tables presented in the product labels. These discrepancies appear to be relatively minor rounding errors associated with the constants used to convert acre-feet to L and pounds to mg. These rounding errors are inconsequential.

A somewhat more subtle but more significant error involves differences in the units for application rates between Aquathol and Hydrothol formulations. Aquathol formulations express application rates in units of ppm a.i.; whereas, Hydrothol formulations express application rates in units of ppm a.e.

Aquathol formulations do not explicitly state that application rates are expressed as ppm a.i.—i.e., the dipotassium salt—but this is evident from the mixing directions. For example, the mixing directions on the product label for Aquathol K, the liquid formulation of the dipotassium salt of endothall, state that target concentrations of 4-5 ppm (mg/L) can be achieved by adding from 2.6 to 3.2 gallons of formulation per acre-foot of water. As specified on the product label and summarized in Table 3, Aquathol K contains 4.23 lbs of the dipotassium salt of endothall per gallon—i.e., 4.23 lbs/gallon. Substituting 4.23 lbs a.i./gallon for $FC_{(lb/gal)}$ and 2.6-3.2 gallons for $Frm_{(gal)}$ in Equation 1 yields target concentrations of 4.044-4.977 mg a.i./L, approximately equal to the 4-5 ppm (mg/L) target concentration specified on the product label.

In contrast, the product label for the Hydrothol 191 liquid formulation provides mixing directions indicating that from 2.7 to 4.0 gallons of the formulation should be added per acre-foot of water to achieve a target concentration of 2-3 ppm. As specified on the product label and summarized in Table 3, Hydrothol 191 liquid contains 2 lb a.e./gallon. Substituting 2.0 lbs a.e./gallon for $FC_{(lb/gal)}$ and 2.7-4.0 gallons for $Frm_{(gal)}$ in Equation 1 yields target concentrations of 1.985-2.942 mg a.e./L, approximately equal to the 2-3 ppm (mg/L) target concentration specified on the product label.

As summarized in Table 3, the labels for both Aquathol and Hydrothol formulations specify application rates of 0.5-5 ppm for the control of aquatic macrophytes. However, because the application directions for Aquathol formulations are given in terms of the active ingredient (a.i. or the dipotassium salt) rather than acid equivalents (a.e.), the labeled application rates for Aquathol formulations are less than those for Hydrothol formulations. As noted in Table 2, the conversion factor for going from the dipotassium salt of endothall to acid equivalents of endothall is about 0.7096. This factor is the ratio of the molecular weight of endothall acid (MW=186.2 grams/mole) divided by the molecular weight of the dipotassium salt of endothall (MW=262.4 grams/mole). When this conversion factor is applied, the labeled application rates of 0.5-5 ppm a.i. for Aquathol formulations correspond to about 0.35-3.5 ppm a.e.

The current Forest Service risk assessments take into consideration the range of labeled application rates for endothall formulations—i.e., from 0.35 to 3.5 ppm a.e. for Aquathol formulations and from 0.05 to 5 ppm a.e. for Hydrothol formulations. The four EXCEL workbooks that accompany the risk assessments are based on an application rate of 1 ppm for aquatic and granular formulations of both Hydrothol and Aquathol. The consequences of using lower or higher application rates are discussed in the risk characterization for human health effects (Section 3.4) and the risk characterization for ecological effects (Section 4.4).

As discussed in U.S. EPA/OPP (2005c), endothall formulations may be used repeatedly during a season; however, neither the maximum annual application rate nor the minimum interval between applications is specified on the product labels. For the control of algae, the product labels for Hydrothol formulations only provide the following guidance: *Repeat applications when algae reappear and reach treatment levels.* The exposure scenarios in the EXCEL workbooks that accompany the current Forest Service risk assessments are based on a single application. These workbooks, however, are structured to allow for any number of applications at a specified application interval. The impact of multiple applications is discussed in the risk characterization for human health (Section 3.4) and ecological effects (Section 4.4).

The Aquathol formulations are labeled for applications to either the entire water body or for spot or lake margin treatments. As indicated in Table 3, the maximum application rates for both types of treatments are identical—i.e., 5 ppm a.i. or 3.5 ppm a.e. The minimum application rate for spot or margin applications is 1 ppm a.e.; whereas, a lower application rate of 0.35 ppm a.e. may be used for treating an entire water body. The Hydrothol formulations may also be used to treat an entire water body but the maximum application for whole water body treatments is limited to 1 ppm a.e. Applications of Hydrothol formulations greater than 1 ppm a.e. up to a maximum of 5 ppm a.e. are limited to areas that are no greater than one-tenth of the surface area of the water body. While not specified on the product labels, the limitation of treatment areas for applications greater than 0.1 of the surface area appears to be associated with the higher toxicity of the amine salt of endothall (used in Hydrothol formulations), relative to the dipotassium salt. All Hydrothol labels do indicate that applications at rates greater than 0.3 ppm should be made only by commercial applicators because of the potential toxicity to fish. The product labels for Hydrothol formulations also indicate that applications at rates greater than 0.3 ppm a.e. may be associated with fish mortality and that applications of 1.0 ppm a.e. should be made only in marginal or sectional treatments where some fish kill is acceptable. The differences in toxicity of the amine and dipotassium salts of endothall to fish as well as other aquatic organisms are substantial, as discussed in detail in Section 4.1.3 (Hazard Identification for aquatic organisms) and Section 4.3.3 (Dose-Response Assessment for aquatic organisms).

The product labels for Aquathol formulations provide specific cautionary language concerning oxygen depletion in treated waters:

If an entire pond is treated at one time, or if the dissolved oxygen level is low at the time of application, decay of weeds may remove enough oxygen from the water causing fish to suffocate. Water containing very heavy vegetation should be treated in sections to prevent suffocation of fish. Sections should be treated 5-7 days apart.

Product labels for Aquathol K and Aquathol Super K

This type of cautionary language does not appear on Hydrothol formulations. Oxygen depletion may occur in the application of any aquatic herbicide because of the decay of plant matter. The cautionary language is omitted from Hydrothol formulations probably because whole water body treatments are not permitted at high application rates—i.e., fish may avoid localized areas of water in which oxygen levels are low.

2.5. USE STATISTICS

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

This kind of comparison cannot be made for endothall. Based on the records of Forest Service applications, endothall use has not been reported. Thus, no assessment can be made of the likely magnitude of Forest Service uses of endothall as an aquatic herbicide, relative to total national uses. The USGS does provide a pesticide use map for endothall (http://water.usgs.gov/nawqa/pnsp/usage/maps/show_map.php?year=02&map=m1948) but this map includes only terrestrial applications—i.e., agricultural uses on cotton, potatoes, and hops—which are not covered in the current Forest Service risk assessments of endothall.

U.S. EPA/OPP (2005c, p. xv ff) provides relatively detailed information on the patterns of aquatic applications of endothall in the continental United States. As illustrated in Figure 2, aquatic applications of endothall are made in Forest Service Region 5 (California), Region 6 (Washington and Oregon), parts of Region 8 (North and South Carolina as well as Florida), and parts of Region 9 (Minnesota and Michigan). In Regions 5 and 6, the major uses of endothall involve the control of algae or submersed macrophytes in lakes, reservoirs, or ponds. The primary target species in these areas are Eurasian watermilfoil, hydrilla, curlyleaf pondweed, as well as dense patches of some native pondweeds. In Region 9, endothall is applied primarily for the control of Eurasian water milfoil and submerged aquatic weeds. Somewhat more than 14,123 pounds of endothall (a.e.) were applied in Minnesota between 2000 and 2002. In Region 8, the primary use of endothall is for the control of relatively small patches (<1 acre to about 30 acres) of hydrilla in lakes or canals. While the rate of flow for canals is not specified in U.S. EPA/OPP (2005c), the EPA notes that the water flow is sufficient to allow for only a

few hours of exposure. The total used in Florida is specified as no more than 10,000 acres. The limiting factor in Florida appears to be the cost of treatment. The treatment of hydrilla in Florida canals consists of 2-3 applications per season at a rate of 3 ppm. The use patterns described in U.S. EPA/OPP (2005c) are based on all applications of endothall. It is not clear that Forest Service applications would reflect the general use patterns summarized in U.S. EPA/OPP (2005c) or that Forest Service uses would be limited to the States specified in U.S. EPA/OPP (2005c).

3. HUMAN HEALTH RISK ASSESSMENT

3.1. HAZARD IDENTIFICATION

3.1.1. Overview

In terms of potential adverse health effects in humans, endothall has two major characteristics. At the cellular level, endothall is an inhibitor of a protein phosphatase, an enzyme involved in the dephosphorylation of proteins. At the level of the whole animal, endothall is a severe irritant.

The inhibition of protein phosphatase is important because phosphorylation and dephosphorylation of proteins play a central role in regulating normal cellular function. Protein phosphorylation is a very fundamental process common to both animals and plants. Thus, the toxicity of endothall to both animals and plants may share a common mechanism. This is not to suggest, however, that effects on protein phosphorylation at the cellular level is the predominant mechanism of toxicity in mammals or the predominant hazard to humans. To the contrary, the major effect of endothall on mammals at the level of the whole animal appears to involve severe irritation or corrosion of tissue. Direct tissue damage at the portal entry has been noted consistently by all routes of exposure: gastrointestinal damage on oral exposure, skin irritation on dermal exposure, respiratory irritation on inhalation exposure, and damage to the eyes after ocular exposure. It is not clear that the cellular mechanism of endothall toxicity (i.e., protein phosphatase inhibition) is directly related to the gross irritant effects of endothall at the portal of entry.

While there is a substantial open literature on endothall, much of the most relevant information of the potential effects of endothall in humans comes from the unpublished studies submitted to the EPA in support of the registration of endothall. These studies are not available to the general public and have not been available for the preparation of the current Forest Service risk assessment. While detailed reviews, referred to as Data Evaluation Records (DERs) or *cleared reviews* are available on some of the registrant submitted studies which impact the ecological risk assessment (Section 4), no DERs or cleared reviews are available for the studies that impact the human health risk assessment. Consequently, the hazard identification for potential human health effects is based on available EPA documents, particularly the RED (U.S. EPA/OPP 2005a), the Science Chapter prepared by the Health Effects Division of OPP (U.S. EPA/OPP 2005e), and the hazard identification for endothall also prepared by the Health Effects Division of OPP (U.S. EPA/OPP 2005f). While these documents are valuable sources of information, they do not provide the detailed summaries for many studies which would be useful for assessing the potential hazards of endothall to humans. This limitation is noted frequently in the current hazard identification for this Forest Service risk assessment.

3.1.2. Mechanism of Action

Endothall is somewhat unusual for an herbicide in that the mechanism of action in animals and plants may be quite similar if not identical at the cellular level. As illustrated

in Figure 3, endothall is structurally similar to cantharidin, a natural toxin produced by blister beetles, a large group of insects from the family Meloidae (Li and Casida 1992). In the late 1980s, Matsuzawa et al. (1987) noted similar structure-activity relationships for endothall and other cantharidin analogues in acute toxicity studies of plants and mammals and suggested that the mechanism of action of these compounds may be similar for both plants and mammals. Subsequently, numerous mechanistic studies were conducted indicating that endothall, cantharidin, and a number of other structurally similar compounds inhibit a specific protein phosphatase, PP2A. This and other similar enzymes dephosphorylate many different proteins. Another group of enzymes, referred to as protein kinases, are involved in the phosphorylation of proteins. The interplay between phosphorylation and dephosphorylation of some proteins plays a fundamental role in the regulation of normal cellular function in both animals and plants (Ehness et al. 1997; Erodi et al. 1995; Ferrero-Gutierrez et al. 2008; Laidley et al. 1997; Li et al. 1993; MacKintosh et al. 1990; Thiery et al. 1999; Toivola and Eriksson 1999; Yi and Simpkins 2008).

In mammals, the role of endothall and structurally related compounds in protein dephosphorylation is associated with damage to the liver (Kawamura et al. 1990; Toivola and Eriksson 1999) and nervous system (Moreno-Delgado et al 2007; Yi and Simpkins 2008). The recent study by Ferrero-Gutierrez et al. (2008) suggests that protein phosphatase inhibitors may reduce the capacity of cells to respond to oxidative stress, a very general and fundamental mechanism of toxicity.

At the level of the whole animal, endothall is highly corrosive. This effect was observed after the suicidal ingestion of endothall in which damage to the gastrointestinal tract of the individual was evidenced by hemorrhage characteristic of ... *a very irritating and corrosive substance* (Allender 1983, p. 80). Gastrointestinal damage is also characteristic in chronic oral toxicity studies and reproduction studies in experimental mammals (Sections 3.1.5 and 3.1.9.2).

Endothall is also highly irritating to the skin and eyes (Section 3.1.11). In terms of ocular irritation, endothall is unusual in that a standard eye irritation study in rabbits (Mallory 1991a) resulted in not only damage to the eyes but also mortality in four/six rabbits. The Mallory (1991a) study is discussed further in Section 3.1.11.3.

3.1.3. Pharmacokinetics and Metabolism

3.1.3.1. General Considerations

Pharmacokinetics involves the quantitative study of the absorption, distribution, and excretion of a compound. Pharmacokinetics is important to this risk assessment because several of the most plausible exposure assessments (Section 3.2) involve dermal exposure, while most of the dose-response assessments (Section 3.3) used to interpret the consequences of dermal exposure involve oral exposure levels. Accordingly, it is necessary to understand the kinetics of both oral and dermal absorption so that dermal exposure assessments can be appropriately compared with oral dose-response assessments.

Soo et al. (1967) is the only published paper on the pharmacokinetics of endothall. In this study, adult rats were given 5 ppm unlabelled endothall in the diet for 2 weeks and were then dosed with 1 mg of ^{14}C -endothall (labeled in the C1 and C2 carbons) at single doses of 1 mg/animal. While Soo et al. (1967) do not explicitly state the method of administration of the labeled endothall, the description given in the study is consistent with gavage dosing. Based on the reported body weights—i.e., 0.25-0.26 kg for males and 0.172-0.206 kg for the females—the 1 mg dose/animal corresponded to doses ranging from 3.8 to 5.8 mg/kg bw. About 90% of the administered dose was recovered in the feces and only about 5-7% was recovered in the urine. Endothall excreted in the urine and feces appeared to be unchanged except for conjugates of endothall, not otherwise specified, recovered in the feces. This result does not suggest, however, that no endothall is metabolized. In a separate phase of the study, Soo et al. (1967) dosed male and female rats with 1 mg ^{14}C -labelled endothall and recovered 2.5-2.8% of the administered radioactivity as ^{14}C -labelled CO_2 in the expired air. This observation indicates that a small proportion of the administered endothall was completely mineralized. The complete mineralization of endothall was observed also in microorganisms and fish (Sikka and Saxena 1973; Sikka et al. 1975).

The greatest concentrations of endothall in terms of radioactivity per unit dry weight of tissue occurred in the stomach and intestine, as would be expected after a gavage exposure. The kidney was the only organ (other than the stomach and GI tract) that contained higher concentrations of endothall than those in the blood (Soo et al. 1967, Table III). As illustrated in Figure 1 and summarized in Table 2 of the current Forest Service risk assessment, endothall contains two carboxylic acid groups and is a weak acid with pKa values of about 4-6. As discussed in the risk assessment on 2,4-D (SERA 2006), weak acids are subject to active secretion the proximal tubules of the kidney, in a manner similar to excretion of paraminohippuric acid (PAH). Thus, it would be expected that the concentration of endothall would proceed from the blood to the kidneys

Soo et al. (1967) provide kinetic analyses for half-lives in the intestine (14.4 hours), stomach (2.2 hours initial, 14.4 hours terminal), kidney (1.6 hours initial, 34.6 hours terminal), and liver (21.6 hours) but do not provide an analysis of whole-body excretion rates. As discussed further in Section 3.1.3.3, whole-body excretion rates are used to assess the potential of pesticides to accumulate/biomagnify in mammals. For the current Forest Service risk assessment, the total radioactivity in different organs reported in Table III of Soo et al. (1967) was analyzed using a simple first-order excretion model. As summarized in Figure 4, these data fit the first-order model very well ($r^2=0.97$, $p=0.000016$) and yield an estimated whole-body half-life of 7.8 hours.

As a separate component of the study, Soo et al. (1967) also dosed two pregnant rats at 0.2 mg/rat of unlabelled endothall for 5 days prior to delivery followed by 0.4 mg of ^{14}C -labelled endothall after delivery. Single pups were assayed for ^{14}C on days 2, 3, 4, 6, 7, and 11 after birth, and no radioactivity was noted in any of the pups.

In addition to the published study by the Soo et al. (1967), U.S. EPA/OPP (2005e, pp. 23-24) summarizes two additional pharmacokinetic studies designated as MRID 42169502

with a date of 1990 and MRID 44263501 with a date of 1997. The later study is a registrant submission of the rat study conducted by Bounds (1997). The 1990 study, MRID 42169502, cannot be identified. A full citation for this study is not provided in U.S. EPA/OPP (2005e) or in the bibliography in the endothall RED (U.S. EPA/OPP 2005a); furthermore, there are no cleared reviews of these studies.

The summary of the 1990 study in U.S. EPA/OPP (2005e) indicates a dose-dependant increase in plasma half-lives for male rats after i.v. administration: 1.8 hours at a dose of 0.9 mg/kg bw and 13.9 hours at a dose of 4.5 mg/kg bw. No toxicity data are reported in the EPA summary of the 1990 study. As discussed further in Section 3.1.4, i.v. doses as low as 5 mg/kg bw are associated with toxic effects in rabbits and dogs.

The oral phase of the 1990 study (MRID 42169502) yields results generally similar to those of Soo et al. (1967), indicating rapid excretion primarily in the feces (89-90%) and urine (5-9%). The study by Bounds (1997) is an oral study in which rats were dosed at 9 mg/kg bw. As in the study by Soo et al. (1967), the Bounds (1997) study indicates rapid excretion (71% within 24 hours), primarily in the feces (about 48%). Using a first-order approximation, the excretion of 0.71 of the administered dose corresponds to an elimination rate (k_e) of about 1.24 day^{-1} [$k_e = -\ln(1-P)/t = -\ln(1-0.71)/1 \text{ day}$] and a half-life [$t_{1/2} = \ln(2)/k_e$] of 0.55 days or 13.4 hours, which is less than a factor of 2 greater than the first-order whole-body half-life of 7.8 hours from the Soo et al. (1967) study. Also as in the study by Soo et al. (1967), both of the MRID studies summarized in U.S. EPA/OPP (2005e) indicate that endothall is excreted unchanged in the feces.

While the oral administration studies by Soo et al. (1967) and Bounds (1997) indicate that excretion occurs primarily in the feces, this result may be an artifact of poor oral absorption, as discussed further in Section 3.1.3.2. The i.v. study summarized in U.S. EPA/OPP 2005e reports excretion as primarily urinary (67%). Similarly, U.S. EPA/OPP (2005e, 2005f) summarizes a dermal absorption study (MRID 42169503) in which urinary excretion was much greater than fecal excretion—i.e., 2.3% of the administered dose excreted in the urine vs <0.1% of the administered dose excreted in the feces. For a highly water soluble, weak acid, urinary excretion is expected to be the predominant route of elimination, discussed above. Like the 1990 study discussed above (MRID 42169502), the dermal absorption study (MRID 42169503) discussed in EPA/OPP (2005e, 2005f) cannot be identified. A full citation for MRID 42169503 is not provided in U.S. EPA/OPP documents or in the bibliography in the endothall RED (U.S. EPA/OPP 2005a), and there is no cleared review of the study. Nonetheless, the study provides the only experimental data on the dermal absorption rate of endothall, as discussed in greater detail in Section 3.1.3.2.2 (Dermal Absorption).

3.1.3.2. Absorption

3.1.3.2.1. Oral Absorption

Based on the study by Soo et al. (1967), endothall appears to be poorly absorbed after oral administration. Soo et al. (1967, Table III, p. 1020) report a total of 410,899 cpm (counts per minute of total radioactivity) for the liver, kidney, heart, lung, spleen, brain, stomach, and intestine combined at 1 hour after dosing. The nominal total dose to each

animal was 407,000 cpm. Thus, although Soo et al. (1967) do not report data for other parts of the carcass, the organs for which counts are given appear to account for the total amount of endothall administered. When the cpm values for the stomach (306,000 cpm) and intestine (96,000 cpm) at 1 hour are subtracted out, the total absorbed dose of endothall at 1 hour after dosing is about 1.2% of the total administered dose $[(306,000 \text{ cpm} + 96,000 \text{ cpm}) \div 407,000 \text{ cpm} \approx 98.8\%]$. This value, however, does not consider the amount of endothall excreted as carbon dioxide—i.e., an indicator of both absorbed and completely metabolized endothall. As noted in Section 3.1.3.1, Soo et al. (1967) also noted that about 2.5-2.8% of the administered dose was mineralized and eliminated in the expired air as CO₂ over 24-48 hours. The apparent absorption of 1.2% at 1-hour and the 24- to 48-hour elimination of CO₂ (2.5-2.8%) cannot be added in terms of a kinetically meaningful absorption rate because it is likely that the 2.5-2.8% eventually eliminated as CO₂ at least partially included some of the initially absorbed material (1.2%) in internal organs other than the stomach and gastrointestinal tract.

3.1.3.2.2. Dermal Absorption

Most of the occupational exposure scenarios and many of the exposure scenarios for the general public involve dermal 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 in animals. Thus, it is necessary to assess the consequences of dermal exposure relative to oral exposure and the extent to which endothall is likely to be absorbed from the surface of the skin.

Two types of dermal exposure scenarios are considered: immersion and accidental spills. As documented in SERA (2007a), the calculations of absorbed dose for dermal exposure scenarios involving immersion or prolonged contact with chemical solutions use Fick's first law and require an estimate of the permeability coefficient, K_p , expressed in cm/hour. For direct spray or accidental spill scenarios, which involve deposition of the compound on the surface of the skin, dermal absorption rates (proportion of the deposited dose that is absorbed per unit time) rather than dermal permeability rates are used in the exposure assessment.

Relatively little information is available on the dermal absorption of endothall. As noted in Section 3.1.3.1, U.S. EPA/OPP (2005e, p. 24; 2005f, p. 7) summarizes the results of a single dermal absorption study, MRID 42169503, which cannot be further identified. This study is described most fully in U.S. EPA/OPP (2005f), which serves as the basis for the following description of the study. Dermal applications were made at three doses, 0.0125 mg/cm², 0.0625 mg/cm², and 0.125 mg/cm² to groups of 30 rats/dose. In the EPA summary, the test material is specified as ¹⁴C-labelled endothall formulated as ... *Hydrothal 191 Aquatic Algicide and Herbicide formulation (23.4% w/w a.i. Lot No Pennwalt ALC-09L8-07)*. *Hydrothal* appears to be a typographical error, and it is likely that a *Hydrothol* 191 formulation was used. The composition of 23.4% a.i. corresponds to the liquid formulation of Hydrothol 191 considered in this risk assessment (Table 3). Thus, the material applied to the rats was essentially a solution of the mono(N,N,-dimethyl-alkylamine) salt of endothall.

The use of the amine salt in the dermal absorption study is important. As discussed further in Section 4.1 (Hazard Identification for the ecological risk assessment), the amine salt of endothall is more toxic to birds and aquatic species than either endothall acid or the dipotassium salt of endothall. U.S. EPA/OPP (2005c, pp. i-ii) suggests that the higher toxicity of the amine salt could be due to either the toxicity of the alkylamine cation or to an increased uptake of the amine salt relative to the dipotassium salt. While it is not clear that the amine salt will be more rapidly absorbed than the dipotassium salt, the use of the amine salt in a dermal absorption study provides direct data on the dermal absorption of the Hydrothol formulations and may provide a conservative estimate for the Aquathol formulations.

In the dermal study, radioactivity was monitored by serial sacrifice of five animals each at 0.5, 1, 2, 4, 10, or 24 hours. In the 0.0125 mg/cm², 0.0625 mg/cm², and 0.125 mg/cm² dose groups, dermal absorption at 24 hours was estimated at 3.9%, 2.2% and 7.3%, respectively. U.S. EPA/OPP (2005f, p. 8) notes that:

The dose related pattern of absorption was typical of a chemical which directly damages the skin. The percent of dose absorbed increased with increasing dose (see attached graph).

As discussed further in Section 3.1.11.1, endothall is a severe skin irritant; nonetheless, a graph or statistical analysis of the dose-dependency is not provided in U.S. EPA/OPP (2005f). As summarized in Figure 5 of the current Forest Service risk assessment, the correlation between dose and proportion of the absorbed endothall is low ($r^2=0.49$) and is not statistically significant ($p=0.5$). In other words, the pattern of absorption versus dose is scattered, and the apparent dose-related increase qualitatively noted by U.S. EPA/OPP (2005e) could be due to random variability. A limitation in this analysis, however, involves working with the mean values for each dose group rather than the individual animal data. This limitation, however, cannot be addressed further since the individual animal data are not reported in any of the available summaries of MRID 42169503.

Many Forest Service risk assessments use quantitative structure-activity relationships (QSAR) to estimate dermal absorption rates (SERA 2006a). These methods were used for endothall acid based on the K_{ow} of 1.91 reported by Reinert and Rogers (1984) and the molecular weight of endothall, 186.2 g/mole (Table 1). As detailed in Worksheet B06, the estimated first-order dermal absorption rate coefficient using the QSAR method is about 0.0033 hour⁻¹ with a 95% confidence interval of 0.0012-0.0088 hour⁻¹ or 0.0788 (0.0292 to 0.2123) days⁻¹. The lower bound of the QSAR estimate, 2.92% per day, is similar to the 2.2% lower bound value from MRID 42169502. The central estimate from QSAR analysis of 7.88% per day is similar to the upper bound estimate of 7.3% from MRID 42169502. The upper bound value from the QSAR estimate, about 21% per day, is about a factor of 3 greater than the upper bound estimate from MRID 42169502.

No data are available on the dermal permeability (K_p) of endothall. Using the QSAR method recommended by U.S. EPA/ORD (1992) for estimating the K_p results in an

estimated dermal permeability coefficient for endothall of 0.00021 cm/hour with a 95% confidence interval of 0.00012-0.00039 cm/hour.

The current Forest Service risk assessment uses the estimated first-order dermal absorption rate coefficients 0.0033 (0.0012-0.0088) hour⁻¹ from Worksheet B06 for dermal exposure scenarios which are based on the assumption of first-order absorption. As discussed above, the central estimate is equivalent to 7.88% per day which is virtually identical to the upper bound estimate of 7.3% from MRID 42169502. As also discussed above, the U.S. EPA/OPP (2005f) suggests a dose-dependency in dermal absorption. While the data supporting a dose-dependency is not compelling, the upper bound of the dermal absorption rate used in this Forest Service risk assessment is equivalent to about 21%, about a factor of 3 higher than the upper bound rate from MRID 42169502. The hazards that might be associated with very high dermal exposures to endothall may be partially encompassed by the upper bound rate of 21% and are considered further in the risk characterization (Section 3.4). The estimated dermal permeability rates of 0.00021 (0.00012-0.00039) cm/hour from Worksheet B05 is used for dermal exposure scenarios based on the assumption of zero-order absorption.

3.1.3.3. Excretion

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

Eq 5

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

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

As summarized in Figure 4, Soo et al. (1967) can be used to estimate a whole-body elimination rate (k_e) for endothall of about 7.8 hours⁻¹ or 0.325 days⁻¹. Using the estimate of 0.325 days⁻¹ and setting the interval between doses to 1 day (i.e., daily dosing), the increased body burden with infinite exposure relative to the body burden after a single dose would be about 3.6. This suggests that endothall has a modest potential to accumulate in mammals after repeated dosing.

3.1.4. Acute Oral Toxicity

One type of acute toxicity information involves time-specific LD₅₀ or LC₅₀ values (i.e., doses or concentrations of a toxicant that result in or are estimated to result in 50% mortality of the test species during a specified exposure or observation period). These values can be viewed as an index of acute lethal potency. In addition, acute oral LD₅₀ values are often available on both the active ingredient (a.i.) as well as formulations of the active ingredient, and a comparison of LD₅₀ values for the a.i. to the formulation can

sometimes be used to indirectly assess the role, if any, of inerts in the toxicity of formulations (Section 3.1.14).

U.S. EPA/OPP (2005f, p. 19) reports acute LD₅₀ values in male and female rats of 50.2 mg/kg bw and 44.4 mg/kg bw. Based on the specified MRID number (42289201), the study was conducted by Mallory (1991b) using technical grade endothall. Similar, but not identical, toxicity values for technical grade endothall are cited in the risk assessment by CalEPA (1997). As summarized in Appendix 1 (Table 4), Gaines and Linder (1986) published LD₅₀ values of 57 (52-64) mg/kg bw in male rats and 46 (40-56) mg/kg bw in female rats.

The RED for endothall (U.S. EPA/OPP 2005a) cites additional acute oral toxicity studies in rats (e.g., MRID 36560, MRID 36568, MRID 36580, MRID 36576, MRID 36588, MRID 36591, MRID 40959, MRID 78201, MRID 78209, MRID 78216, MRID 78220, MRID 78606, MRID 78609, MRID 113972, MRID 114491, MRID 40109202, MRID 42774001, MRID 44320104, MRID 44319605). At least two of these studies involved oral LD₅₀ determinations using Aquathol formulations (MRID 78209, MRID 44320104) and one involved an oral LD₅₀ of a Hydrothol formulation. Summaries of these acute studies are not provided in the RED and were not identified in supporting documents (U.S. EPA/OPP 2005b-i) or in the EPA cleared reviews.

Acute oral toxicity data on some endothall formulations are summarized in the internal EPA review by Dykstra (1978) and included in Appendix 1 (Table 4). For the Hydrothol granular and liquid formulation, the studies summarized by Dykstra (1978) are identical or very close to the toxicity values reported in the MSDS, as discussed below. For an Aquathol granular formulation, however, the LD₅₀ value of 1340 mg/kg bw reported by Dykstra (1978) is much higher than the LD₅₀ value of 99.5 mg/kg bw reported on the MSDS for Aquathol Super K, which is probably because the formulation covered by Dykstra (1978), referenced only as a granular Aquathol formulation, is different from Aquathol Supper K. The review by CSI (2001) does summarize results from MRID 42289101 (an LD₅₀ of 186.8 mg/kg bw for a pelletized formulation of Aquathol K), MRID 42338901 (an LD₅₀ of 99.5 mg/kg bw for Aquathol K), and MRID 42774001 (an LD₅₀ of 209.8 mg/kg bw for a Hydrothol 191 formulation).

U.S. EPA/OPP (2005b) outlines batching instructions for acute toxicity data on endothall formulations. Here, the term *batching* refers to formulations that may be supported by data on other formulations—i.e., acute toxicity data on one formulation may be used as a surrogate for another formulation. Hydrothol 191 liquid and Hydrothol 191 granular are in different batches—i.e., acute data on the liquid or granular formulation cannot be used for the other formulation. Similarly, Aquathol K and Aquathol Super K are designated as formulations for which no batching is designated—i.e., acute toxicity data must be available for each formulation.

The only other source of acute oral toxicity information comes from the material safety data sheets (MSDS) for each of the formulations. As summarized in Appendix 1 (Table 1), the acute LD₅₀ values reported on the MSDS range from 98 mg/kg bw

(Aquathol Super K) to 1540 mg/kg bw (Hydrothol 191 Granular). Adjusting for a.e. conversion, the LD₅₀ values for Aquathol Super K (43.8 mg a.e./kg bw) and the Hydrothol 191 liquid formulation (54.5 mg/kg bw) are within the range of LD₅₀ values reported for endothall acid (\approx 40 to 64 mg a.e./kg bw based on the confidence limits from Gaines and Linder 1986). The LD₅₀ for the Aquathol K liquid formulation, 28.5 mg a.e./kg bw, is less than the lower bound for the acid (\approx 40 mg a.e./kg bw) by a factor of about 1.4. The LD₅₀ of 77 mg a.e./kg bw for the Hydrothol-191 granular formulation is above the upper bound for the endothall acid (64 mg a.e./kg bw) by a factor of about 1.2.

Based on the acute toxicity study by Mallory (1991b), U.S. EPA/OPP (2005a) classifies endothall as Category I for acute oral toxicity. As discussed in SERA (2007, Section 3.1.4), Category I applies to compounds for which the oral LD₅₀ is less than or equal to 50 mg/kg bw; moreover, this category designates the most toxic compounds in EPA's classification system.

As discussed in Section 3.1.3.2.1 (Oral Absorption), endothall appears to be poorly absorbed after oral dosing, although the data are not sufficient to estimate an oral absorption rate. As summarized in Appendix 1 (Tables 8 and 9), some data are available on the toxicity of endothall after intravenous (i.v.) and intraperitoneal (i.p.) dosing. For compounds that are poorly absorbed, it would be expected that i.v. or i.p. dosing would be much more toxic than oral dosing. Although the i.v. and i.p. toxicity data available on endothall are not directly comparable to the oral toxicity data, endothall does appear to be more toxic on parenteral administration than on oral administration. In the pharmacokinetic study by Soo et al. (1967), rats were given oral doses of 3.8-5.8 mg/kg bw and no overt adverse effects were noted. In contrast, i.v. doses as low as 5 mg/kg bw were reported to cause signs of toxicity in rabbits and dogs (Goldstein 1952; Strensek and Woodward 1951). Kawamura et al. (1990) report an intraperitoneal LD₅₀ of 14 mg/kg bw in mice, which is more than 3 times lower than the oral LD₅₀ in rats—i.e., 44.4 mg/kg bw (Mallory 1991b).

The only information on the acute oral toxicity of endothall in humans comes from the report by Allender (1983) of a suicidal ingestion of endothall. In this incident, a 54 kg male consumed approximately 7-8g of disodium endothall. Using the conversion factor of 0.71 a.e./a.i. (Table 3), this corresponds to doses of about 92-105 mg a.e./kg bw [7000-8000 mg a.i. \times 0.71 a.e./a.i. \div 54 kg]. This range of doses is about 3.5 times greater than the reported oral LD₅₀ value for the dipotassium salt of endothall—i.e., 28.5 mg a.e./kg bw. Thus, the death of this individual is consistent with the acute toxicity data in experimental mammals.

3.1.5. Subchronic or Chronic Systemic Toxic Effects

There are apparently no subchronic or chronic mammalian toxicity studies of endothall in the open literature. The U.S. EPA/OPP RED for endothall lists a number of subchronic and chronic toxicity studies (U.S. EPA/OPP 2005a); however, there are no cleared reviews of these studies, and their summaries must be taken from publically available EPA documents. Table 4.1b of the Science Chapter on endothall prepared by the Health Effects Division (HED) of U.S. EPA/OPP (2005e) briefly summarizes subchronic and

chronic studies in mice, rats, and dogs. This summary along with additional information from the HED Hazard Identification (U.S. EPA/OPP 2005f) is tabulated in Appendix 1 (Table 10) of the current Forest Service risk assessment.

Two 90-day feeding studies are available, one in rats (Trutter 1994a) and the other in dogs (Trutter 1994b). Chronic toxicity studies are available in dogs (Shellenberger 1990a), mice (Shellenberger 1990b), and rats (Plankenhorn 1990). In all studies, the LOAEL is defined by a decrease in body weight. Although body weight decrease is a common endpoint for LOAELs in toxicity studies, it may be an indirect effect not associated with the primary mechanism of toxicity. While the subchronic studies are not described in detail in U.S. EPA/OPP (2005e), U.S. EPA/OPP (2005f) provides additional information on observations from the chronic toxicity studies. In the chronic studies in mice, rats, and dogs, a common observation involves damage to the gastrointestinal tract—i.e., gastric epithelial hyperplasia in dogs, thickening of the wall of the glandular stomach and prolapsed rectum in mice, and thickening of the wall of the stomach in rats.

Another consistent pattern in the subchronic and chronic toxicity studies involves an increased sensitivity of dogs, relative to rats and mice. In the subchronic studies, the LOAEL in dogs is 27.5 mg/kg bw/day, somewhat less than the NOAEL in rats of 39 mg/kg bw/day and substantially less than the LOAEL in rats of 118 mg/kg/day. Taking the subchronic LOAELs as approximate equitoxic doses, dogs are over 4 times more sensitive than the rats [$118 \text{ mg/kg/day} \div 27.5 \text{ mg/kg bw/day} \approx 4.29$]. A similar pattern is seen in the chronic studies, with LOAELs of 6.5 mg/kg bw/day in dogs (Shellenberger 1990a), 45 mg/kg/day in mice (Shellenberger 1990b), and 16 mg/kg/day in rats (Plankenhorn 1990). As discussed in Section 3.1.3. (Pharmacokinetics and Metabolism), endothall is a weak acid and may be excreted by proximal tubules of the kidney. As noted in the Forest Service risk assessment on 2,4-D (SERA 2006), dogs are more sensitive than other species to the effects of 2,4-D due to their limited capacity to excrete organic acids. While somewhat speculative, the increased sensitivity of dogs to endothall may be related to the limited capacity of dogs to excrete weak acids.

An additional unpublished chronic toxicity study in dogs is included in the EPA risk assessment of endothall (U.S. EPA/ODW 1992) and in the U.S. EPA/ORD (1991) Integrated Risk Information System (IRIS). The dog study is referenced differently in various EPA documents: Keller (1965) in U.S. EPA/ODW (1992), Pennwalt Agchem (1965) in U.S. EPA/ORD (1991), and Eibert (1966) in U.S. EPA/OPP (2005a). The latter reference is adopted in the current Forest Service risk assessment. Based on the summary of Eibert (1966) in U.S. EPA/ODW (1992), groups of three male and three female dogs were given dietary concentrations of 100, 300, or 800 ppm endothall, as the disodium salt, for 2 years. These doses corresponded to 2, 6, or 16 mg a.e./kg bw/day. In the two higher dose groups, dogs evidenced increased relative weights of the stomach and small intestine. No effects were noted at the dose of 2 mg/kg bw/day. These study results are consistent with the higher sensitivity of dogs based on the chronic studies in rats and mice. As discussed further in Section 3.1.9.2 (Reproduction Studies), a multigeneration reproduction study in rats noted adverse effects in parental rats at a dose of 2 mg/kg bw/day.

3.1.6. Effects on Nervous System

U.S. EPA/OPP evaluates the potential neurotoxicity of pesticides with a relatively standard battery of acute, subchronic, and chronic toxicity studies in mammals. If effects are noted in these studies which suggest that the pesticide may be neurotoxic, U.S. EPA/OPP requires additional and more specialized neurotoxicity studies. For endothall, the Hazard Identification Assessment Review Committee (HIARC) of the U.S. EPA/OPP determined that specialized neurotoxicity studies are not required for endothall:

The HIARC concluded that there is not a concern for neurotoxicity resulting from exposure to Endothall. No clinical signs or symptoms of neurotoxicity were detected in any of the available, guideline studies.

U.S. EPA/OPP (2005f, p. 3)

Based on a review of the summaries of standard toxicity studies included in U.S. EPA/OPP (2005f) and other supporting documents, the above conclusion is clearly justified. Two studies in the open literature (Laidley et al. 1997; Yi and Simpkins 2008) suggest that protein phosphatase inhibitors, including endothall, may damage nerve cells *in vitro*. These mechanistic studies, however, do not contradict the EPA observations that the nervous system is not a primary target and neurotoxicity is not observed after *in vivo* exposures to endothall.

3.1.7. Effects on Immune System

Various tests have been developed to assess the effects of chemical exposures on several types of immune responses, including assays of antibody-antigen reactions, changes in the activity of specific types of lymphoid cells, and assessments of changes in the susceptibility of exposed animals to resist infection from pathogens or proliferation of tumor cells. Except for studies on skin sensitization (Section 3.1.11.2), however, specific studies concerning the effects of pesticides on immune function are not required for pesticide registration, and no such studies are available on endothall.

Despite the lack of specific studies concerning the immunologic effects of endothall, limited information on the subject is available from the standard subchronic and chronic studies (Section 3.1.5). Typical subchronic or chronic animal bioassays conduct morphological assessments of the major lymphoid tissues, including bone marrow, major lymph nodes, spleen and thymus (organ weights are sometimes measured as well), and blood leukocyte counts. These assessments can detect signs of inflammation or injury indicative of a direct toxic effect of the chemical on the lymphoid tissue. Changes in morphology of lymphoid tissue and blood, indicative of a possible immune system stimulation or suppression, can also be detected.

In the EPA hazard identification for endothall (U.S. EPA/OPP 2005f), potential effects on immune function are not addressed specifically. As summarized in Appendix 1 (Table 10), enlarged spleens were observed in some mice in the chronic toxicity study by Shellenberger (1990b); however, this finding appears to be incidental, and no dose-response relationship is noted for this effect in U.S. EPA/OPP (2005f). In the subchronic dermal toxicity study conducted with technical grade endothall (Section 3.1.12), the

investigators noted an increase in leukocyte counts; however, the increase may have been associated with infection due to severe skin damage rather than a direct effect on immune function.

3.1.8. Effects on Endocrine System

Changes in endocrine function may be associated with several endpoints that can have an impact on normal growth and development. Assessment of the direct effects of chemicals on endocrine function are most often based on mechanistic studies on estrogen, androgen, or thyroid hormone systems (i.e., assessments on hormone availability, hormone receptor binding, or post-receptor processing). In addition, changes in structure of major endocrine glands—i.e., the adrenal, hypothalamus, pancreas, parathyroid, pituitary, thyroid, ovary, and testis—may also be indicative of effects on the endocrine system. Disruption of the endocrine system during development may give rise to effects on the reproductive system which may be expressed only after maturation.

Consequently, multigeneration exposures are recommended for toxicological assessment of suspected endocrine disruptors. The one available multigeneration reproduction study on endothall is discussed in Section 3.1.9.2.

As noted in U.S. EPA/OPP (2005e, p. 35), the available toxicity data on endothall suggest *...no estrogen, androgen, and/or thyroid mediated toxicity*. As discussed in Section 3.1.5, body weight loss was observed in all of the subchronic and chronic toxicity experimental animal studies; nonetheless, this endpoint is extremely general and commonly observed in animals exposed to toxic levels of pesticides and other agents. As a single endpoint, decreased body weight does not suggest a direct effect on endocrine function.

3.1.9. Reproductive and Developmental Effects

3.1.9.1. Developmental Studies

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

Typically, the EPA requires developmental toxicity studies in both rats and rabbits. For endothall, however, only a rat developmental study (Trutter 1993a) is available. Based on the summary of this study in U.S. EPA/OPP (2005f), groups of 25 pregnant rats were given gavage doses of 0, 6.25, 12.5, or 25.0 mg/kg/day from day 6 to 15 of gestation. No effects on offspring were noted at any dose level. At the highest dose, the only effect observed in dams was a decrease in body weight—i.e., the same endpoint common in subchronic and chronic toxicity studies (Section 3.1.5).

While noting that the lack of a rabbit developmental study is a concern, the RED for endothall expresses no substantial concern for developmental effects:

...the weight of evidence suggests that endothall will be of no developmental concern. This evidence includes the results of a developmental toxicity study with rats, where endothall did not induce developmental toxicity at any of the doses tested. Effects that were observed in developmental toxicity studies (decreased pup weight gain) are not considered to be developmental toxicity effects.

-U.S. EPA/OPP 2005a, p. 8

In other words, consistent with the discussion in Section 3.1.5 (Subchronic or Chronic Systemic Toxic Effects) of the current Forest Service risk assessment, body weight is a general response to pesticide exposure in toxicity studies and does not necessarily suggest a direct impact on development.

While the developmental study by Trutter (1993a) is the only developmental study discussed in U.S. EPA/OPP (2005e,f), the bibliography for the RED (U.S. EPA/OPP 2005a) does include several other developmental studies (MRIDs 36593, 69051, 73371, 78611, 84606, 85940, 86623, 114534, 118952, 119989). A much earlier risk assessment conducted by the U.S. EPA Office of Drinking Water (U.S. EPA/ODW 1987) summarizes the results of another developmental study in rats which it cites as Science Applications, Inc (1982). This study is also summarized in greater detail in the internal U.S. EPA/OPP review by Burin (1983). This study appears to be identical to MRID 119989 cited in U.S. EPA/OPP (2005a).

The study by Science Applications, Inc (1982) dosed pregnant rats at 0, 8, 16, or 24 mg a.e. /kg bw/day on days 6 to 19 of gestation. Mortalities in dams were observed at the two higher dose levels: 2/25 dams in the 16 mg a.e./kg bw group and 10/25 in the 24 mg a.e./kg bw group. The mortalities, however, were not associated with signs of toxicity prior to death or any tissue abnormalities on necropsy. Based on maternal toxicity, the NOAEL was 8 mg/kg bw/day. U.S. EPA/ODW (1987) states that no adverse effects were noted on offspring at any dose level. The more detailed review by Burin (1983) indicates that various skeletal abnormalities indicative of slow development were noted at the two higher dose-levels and were associated with maternal toxicity. Burin (1983) also notes that behavioral tests conducted on the offspring did not indicate signs of dose-related effects.

3.1.9.2. Reproduction Studies

Reproduction studies involve exposing one or more generations of the test animal to the test substance. The general experimental method involves dosing the parental (P) generation (i.e., the male and female animals used at the start of the study) to the test substance prior to, during, and after mating, as well as through weaning of the offspring (F1). In a 2-generation reproduction study, this procedure is repeated with male and female offspring from the F1 generation to produce another set of offspring (F2). During these types of studies, standard observations for gross signs of toxicity are made.

Additional observations often include the length of the estrous cycle, assays on sperm and other reproductive tissue, and number, viability, and growth of offspring.

The EPA requires only one acceptable multi-generation reproduction study for pesticide registration, and only one two-generation reproduction study on endothall (Trutter 1993b) was submitted. In terms of the human health risk assessment, this two-generation study is critical because it forms the basis for both the short-term RfD and chronic RfD for endothall (Section 3.3). Although a cleared review of the study is not available, U.S. EPA/OPP (2005f) provides a full and detailed summary of the Trutter (1993b) study.

Trutter (1993b) exposed groups of male rats and female rats to dietary concentrations of 0, 30, 150, or 900 ppm of Endothall Turf Herbicide, a disodium salt formulation containing 19.9% a.i. Since the parental animals and their offspring grew over the period of exposure, food consumption and daily doses were variable. During the pre-mating period, daily doses were 0, 2, 10.2, or 64 mg/kg bw/day for males and 0, 2.3, 11.7, or 78.7 mg/kg bw/day for females. During the gestation period, the doses to the female rats were 0, 1.8, 9.4, or 60 mg/kg bw/day. During the lactation period, when female rats will substantially increase food and water consumption, the daily doses were substantially higher—i.e., 0, 3.1, 17.3, or 104.7 mg/kg bw/day.

Proliferative lesions of the gastrointestinal tract were observed in male and female parental rats at all dose levels. Thus, in terms of this reproduction study, a NOAEL for systemic toxicity in adults is not defined. As noted above, the lowest dietary concentration (30 ppm) is associated with doses of about 2 mg/kg bw/day. This LOAEL is a factor of 4 below the chronic rat NOAEL of 8 mg/kg bw/day from the study by Plankenhorn (1990) and a factor of about 20 below the subchronic rat NOAEL of 39 mg/kg bw/day from the study by Trutter (1994a). Based on effects observed in offspring, the NOAEL is 9.4 mg/kg bw/day with a LOAEL of 60.0 mg/kg/day, based on decreased pup body weights. This NOAEL is comparable to the NOAEL of 8 mg/kg bw/day from the study by Plankenhorn (1990).

3.1.10. Carcinogenicity and Mutagenicity

In terms of a quantitative significance to the human health risk assessment, carcinogenicity is an issue only if the data are adequate to support the derivation of a cancer potency factor. A cancer potency factor is typically derived based on a dose-related increase in malignant tumors from a chronic toxicity study that encompasses a significant portion of the test animals' lifespan. As summarized in Appendix 1 (Table 10), two such bioassays were conducted on endothall: the chronic (79-week) study in mice (Shellenberger 1990b) and the chronic (2-year) study in rats (Plankenhorn 1990). The EPA reviewed both studies in detail (U.S. EPA/OPP 2005f). Neither the chronic study in rats nor the chronic study mice reported significant or dose-related increases in the incidence of malignant tumors. In addition, none of the mutagenicity screening assays submitted to the EPA noted any mutagenic activity. Based on lack of carcinogenic or mutagenic activity, U.S. EPA/OPP (2005f, p. 16) classifies endothall as: *Not likely to be carcinogenic to humans*. This determination is also reflected in the RED for endothall (U.S. EPA/OPP 2005a, p. 5).

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

3.1.11.1. Skin Irritation

As with most types of studies required for pesticide registration, U.S. EPA/OPPTS has outlined specific guidelines for acute assays of skin irritation (U.S. EPA/OPPTS 1998b). Typically, rabbits are used as the test organisms, and the severity of dermal irritation is observed over a 14-day period. Depending on the severity and persistence of the dermal response, the compound is classified into one of four categories defined by the EPA with Category I being the most severe irritant and Category IV being the least severe irritant.

Several acute skin irritation studies conducted between 1967 and 1997 are referenced in the U.S. EPA/OPP (2005a) RED for endothall (i.e., MRIDs 36567; 36573; 36577; 36586; 37848; 52457; 78208; 78217; 78214; 78604; 78614; 84475; 96293; 116272; 133024; 40109204; 42289104; 42289204; 42338904; 42774003; 43242303; 43343502; 44319609; 44320107; 92057004).

The only acute dermal irritation study specifically cited in the endothall RED or other supporting documents (e.g., U.S. EPA/OPP 2005e,f) is MRID 42289204, which is a skin irritation study conducted by Mallory (1992) in which rabbits were exposed to technical grade endothall. Except to classify the study as *Unacceptable*, the EPA documents do not provide further information about the study. The classification of *Unacceptable* indicates that the EPA ruled that the study did not follow EPA protocol or that the study was, for some other reason, classified as unsound. A DER for the Mallory (1992), however, indicates that the study is classified as *Guideline*, a term synonymous with acceptable and that endothall was not a primary skin irritant in rabbits at a dose of 500 mg/animal. The acceptability of this study is also indicated in a memorandum from a toxicologist in U.S. EPA/OPP (Marish 1993). The reasons for the discrepancies in the evaluations of the Mallory (1992) study are not clear.

Dykstra (1978) summarizes studies on Aquathol K liquid and granular formulations (Appendix 1, Table 6); however, it is not clear that the studies were conducted on the Aquathol formulations covered in this risk assessment. The equivalence of the formulations is questionable because the studies report only slight dermal irritation in one study involving an Aquathol liquid formulation and no irritation in a study involving an Aquathol liquid and an Aquathol granular formulation.

As summarized in Section 3.1.3.2.2 (Dermal Absorption), U.S. EPA/OPP (2005e, p. 24; 2005f, p. 7) reports severe skin irritation in a dermal absorption study in rats (MRID 42169503). As discussed further in Section 3.1.12 (Systemic Toxic Effects from Dermal Exposure), a standard 21-day dermal toxicity study in rats (Margitich and Ackerman 1994) also noted severe skin irritation. Based on this information, U.S. EPA/OPP (2005a) classifies endothall as a Category I skin irritant.

In an internal EPA review of the older literature on endothall, Coberly (1966) notes that 1 and 4% concentrations of sodium endothall causes... *light to moderate erythema of the skin*... in humans. Formulations of sodium endothall are not covered in the current

Forest Service risk assessment; nonetheless, this brief statement by Coberly (1966) is the only report of the dermal irritation in humans exposed to endothall.

Relatively little information on the dermal irritancy of endothall is available in the open literature. As summarized in Appendix 1 (Table 5), Goldstein (1952) reported only mild dermal irritancy in the abraded skin of rabbits after dermal exposure to endothall (NOS) as 1% powder. At higher concentrations—i.e., 10-20% powder—severe skin lesions were observed.

3.1.11.2. Skin Sensitization

The bibliography of registrant-submitted studies in the EPA RED for endothall (U.S. EPA/OPP 2005a) notes several studies on skin sensitization (MRIDs 69052, 70572, 73370, 116272, 44319610, 44320108) dated between 1971 and 1997. Based on a study identified as MRID 4187190, which is not listed in the RED bibliography, U.S. EPA/OPP (2005a) classifies endothall as a skin sensitizer. MRID 4187190 is also cited but not discussed in U.S. EPA/OPP (2005e,f) and is used to classify endothall as a skin sensitizer. Dykstra (1981a, p. 3) summarizes the results of a guinea pig sensitization study using Hydroul, a formulation of the di-amine salt of endothall, in which no skin sensitization was observed.

Skin sensitization is not discussed in the California EPA review of endothall (CalEPA 1997). The CSI (2001) review of endothall notes responses in skin sensitization studies are mixed. Presumably, this statement refers to the skin sensitization studies cited in the EPA RED. The review by CSI (2001) concludes:

Based on the results of the skin sensitization investigations, allergic skin reactions would not be expected from persons contacting endothall treated bodies of water because of the low product use rates, water dilution factor and degradation of the chemical in the aquatic environment.

CSI, 2001, p. 11

Although the CSI interpretation given above may apply to members of the general public, workers will be exposed to relatively concentrated solutions of endothall (Table 3), as discussed further in the risk characterization for workers (Section 3.4.2).

3.1.11.3. Ocular Effects

As with dermal irritation and other acute endpoints, U.S. EPA/OPP has a categorization scheme for eye irritation which ranges from Category I (most irritating) to Category IV (least irritating). Based on the Mallory (1991a) study conducted with technical grade endothall, U.S. EPA/OPP (2005a,e,f) classifies endothall as a Category I eye irritant. Mallory (1991a) is a standard eye irritation study in which doses of about 100 mg were instilled into right eye of three male and three female rabbits each weighing between 2.5 and 3.3 kg. No eyes were washed after treatment. The doses to each rabbit ranged from about 30 mg/kg bw [$100 \text{ mg} \div 3.3 \text{ kg} \approx 30.30 \text{ mg/kg bw}$] to 40 mg/kg bw [$100 \text{ mg} \div 2.5 \text{ kg}$]. The left eye of each rabbit served as a control. Within 1 hour of treatment, severe eye irritation was noted in all rabbits.

Mallory (1991a) is a somewhat unusual study in that mortality and signs of systemic toxicity were observed in the treated rabbits. Within 5 hours of dosing, all rabbits exhibited signs of systemic toxicity, including lethargy, lack of coordination, and labored breathing. Overnight, after the day of dosing, four of six rabbits died (all three males and one female). On postmortem examination, all dead rabbits had fluid in the peritoneal cavity, two rabbits had red fluid in the bladder (probably indicative of kidney toxicity), and one rabbit had a discolored liver. The two surviving rabbits were sacrificed at 24-hours after dosing, at which time one of the surviving rabbits evidenced lethargy and lack of coordination.

As summarized in Appendix 1 (Table 8), intravenous doses ranging from 25 to 50 mg/kg bw are lethal to rabbits (Strensek and Woodward 1951). As discussed in Section 3.1.4 (Acute Oral Toxicity), the oral LD₅₀ for endothall in rats is also about 50 mg/kg bw. Thus, it seems plausible that the ocular installation of 100 mg of endothall in the eyes of rabbits might be lethal.

Dykstra (1978) provides additional information on several other eye irritation studies using technical grade endothall as well as granular and liquid formulations of Aquathol and Hydrothol. These studies are summarized in Appendix 1 (Table 7). The study using technical grade endothall is similar to the above study by Mallory (1991a) in that mortality was noted over night after the rabbits were dosed. However, mortality was seen in only 3/6 rabbits rather than 4/6 rabbits. Further, Dykstra (1978) indicates that mortality was noted only in rats whose eyes were not washed within 20 to 30 seconds after endothall instillation. Thus, it seems that the study on technical grade endothall summarized by Dykstra (1978) is different from the Mallory (1991a) study. The RED for endothall (U.S. EPA/OPP 2005a), however, does not list a second study on eye irritation with technical grade endothall.

One other eye irritation study with endothall summarized by Dykstra (1978) notes lethality in treated rabbits. As summarized in Appendix 1 (Table 7), this study involved the instillation of 0.1 ml of Hydrothol 191 liquid, equivalent to a dose of about 10 mg a.e./kg bw. As in the study with technical grade endothall, exposure resulted in the mortality of three of six rabbits; however, unlike the results of the Mallory (1991a) study conducted with technical grade endothall, mortality did not occur until 72 hours after dosing.

3.1.12. Systemic Toxic Effects from Dermal Exposure

Significant information regarding the dermal toxicity of endothall is not available in the open literature. As summarized in Appendix 1 (Table 5), the published studies (Gaines and Linder 1986; Goldstein 1952) do not specify the nature of the material tested—i.e., endothall acid, salt, or formulation. The EPA typically requires both acute and 21-day dermal toxicity studies on pesticides and pesticide formulations and has developed standard protocols for these studies (<http://www.epa.gov/opptsfrs/home/guidelin.htm>).

In a limit test for dermal toxicity in rabbits, Mallory (1991c) reports that no mortality occurred over a 14-day observation period following a single dermal dose of 2000 mg/kg bw. The only adverse effect observed in individual rabbits was diarrhea in one female rabbit on days 7-10 after dosing. Average body weights in rabbits were slightly reduced on day 7 after dosing in both males (98.6% of pretreatment weights) and females (93.4% of pretreatment weights) but body weights were normal by day 14. Based on the bibliography of registrant studies included in the endothall RED (U.S. EPA/OPP 2005a), additional acute dermal toxicity studies were submitted on the disodium salt of endothall (MRID 58720), liquid and granular Aquathol formulations (MRIDs 36575, 78215, 44320105, 7737847, 42338902) as well as liquid and granular Hydrothol formulations (MRIDs 36579, 78219, and 78200). Neither the RED nor other supporting EPA documents summarize the results of these acute dermal toxicity studies.

As summarized in Appendix 1 (Table 2), the MSDS for the endothall formulations covered in this risk assessment include dermal LD₅₀ values. This information is presumably taken from the acute dermal toxicity studies cited in U.S. EPA/OPP (2005a). For the two granular formulations, Aquathol Super K and Hydrothol 191 Granular, the LD₅₀ values are expressed as >2000 mg formulation/kg bw and >10,000 mg formulation/kg body. The *greater than* (>) designation indicates that less than 50% of the animals died at the specified dose. In terms of acid equivalents, the LD₅₀ values for the granular formulations are >894 mg a.e./kg bw for Aquathol Super K and >500 mg a.e./kg bw for Hydrothol 191 Granular. Both liquid formulations are more toxic than the granular formulations. The dermal LD₅₀ for Aquathol K is 572 mg a.e./kg bw and the corresponding value for Hydrothol 191 is 112 mg a.e./kg bw. The greater toxicity of the liquid formulations relative to the granular formulations is not unusual and may reflect the decreased absorption of endothall from the matrices of the granular formulations. While confidence limits for the LD₅₀ values are not reported, the LD₅₀ for the liquid Hydrothol formulation is a factor of about 5 less than that of the Aquathol formulation. As discussed in Section 3.1.3.2.2, the higher toxicity of the Hydrothol formulation relative to the Aquathol formulation suggests that the amine salt of endothall may be more rapidly absorbed than the dipotassium salt of endothall.

In addition to the acute dermal toxicity studies, two 21-day dermal toxicity studies were conducted, one on the amine salt of endothall (Margitich and Ackerman 1994) and the other study on Aquathol K (Margitich and Ackerman 1992). The study on the Aquathol K formulation is cited in the RED (U.S. EPA/OPP 2005a) but is not otherwise detailed in the RED or supporting documents (U.S. EPA/OPP 2005e,f). The 21-day dermal study on the amine salt, however, is described in some detail in U.S. EPA/OPP (2005f). As discussed in Section 3.1.11.1 (Skin Irritation), the study on the amine salt by Margitich and Ackerman (1994) is one of the studies used to classify endothall as a Category I skin irritant.

The study by Margitich and Ackerman (1994) involved a formulation of endothall consisting of 30.3% endothall amine or 11.6% endothall acid, which does not correspond directly to any of the formulations included in the current Forest Service risk assessment (Table 3). The compound was applied daily to rats at doses of 30, 100, and 300 mg

amine salt/kg bw/day. These doses correspond to acid equivalent doses of about 11.4, 38.2, and 115 mg a.e./kg bw/day [11.6%/30.3% x 30, 100, and 300 mg amine salt/kg bw/day].

No mortalities were noted at the lowest dose. Signs of toxicity at the lowest dose included weight loss in female rats and decreased body weight gains in male rats (27.6% below controls) and female rats (84.5% below controls). At the mid and highest dose, mortalities were 1/10 and 3/10, respectively. Signs of systemic toxicity included significant weight loss and severe morbidity. Because of the latter effect, all animals in the high dose group were sacrificed by day 16. Additional observations of toxicity included liver and kidney toxicity, an increase in white blood cells and a decrease in red blood cells. In addition to the signs of systemic toxicity, skin irritation—i.e., reddening, swelling, cracking and necrosis—was observed at all dose levels.

3.1.13. Inhalation Exposure

The hazard identification for inhalation exposures is particularly important to the current risk assessment. As discussed further in Section 3.2.2.1 (General Exposures in Workers), the EPA elected to consider only the inhalation route of exposure in the occupational exposure assessment (EPA/OPP 2005a,e,f).

U.S. EPA/OPP (2005a) cites two standard acute inhalation studies conducted with technical grade endothall (MRIDs 42221501 and 42408701) as well as additional toxicity studies conducted with Aquathol and Hydrothol, the endothall formulations covered in the current Forest Service risk assessment (MRIDs 36561, 36592, 78202, 78610) and some more recent studies conducted with the Aquathol formulation (MRIDs 42407101 and 42407102). The only acute inhalation toxicity study discussed in the RED and supporting documents, however, is MRID 42169501 (U.S. EPA/OPP 2005a,e,f). The EPA does not provide a citation for this study, and the EPA supporting documents (U.S. EPA/OPP 2005e,f) simply indicate acute inhalation LC₅₀ values of 1.27 mg/L in female rats, 2.2 mg/L in male rats, and 1.51 mg/L based on male and female rats combined. Based on these results, U.S. EPA/OPP (2005a) classifies endothall as Category III with respect to inhalation toxicity.

CSI (2001) and CalEPA (1997) provide some additional details of the study involving technical grade endothall, which is referenced by EPA as MRID 42221501. These reviews indicate that the signs of toxicity included lethargy, labored breathing, discharges from the nose and eyes of the exposed rats, and signs of respiratory tract irritation. The summary provided by CalEPA (1997) reports that 1.678 and 2.472 mg/L were lethal to rats. The summary by CSI (2001) indicates that 1 of 10 animals died after exposure to 0.446 mg/L. Dykstra (1978, p. 30) summarizes an inhalation study conducted with a Hydrothol granular formulation in which the LC₅₀ was 5.32 mg/L, which is identical to the LC₅₀ reported on the MSDS for Hydrothol 191 granular.

As indicated in Appendix 1 (Table 3), the inhalation LC₅₀ values for Aquathol K, Hydrothol 191 (liquid), and Hydrothol 191 granular are quite similar, ranging from 0.16 to 0.27 mg/L. Although inhalation toxicity studies with granular Aquathol formulations

appear to have been conducted (MRIDs 36592, 78202, 42407101), there is no information about the results of these studies. Relative to the LC₅₀ of 1.51 mg/L for technical grade endothall (U.S. EPA/OPP 2005e,f), the LC₅₀ values for the formulations suggest that they are more toxic than technical grade endothall by factors of about 5.6-9.4.

3.1.14. Inerts and Adjuvants

3.1.14.1. Inerts

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

As summarized in Table 4, the only other ingredient specifically listed in the MSDS for the endothall formulations covered in the current risk assessment is 2-propenamide, polymer with potassium, CAS No. 31212-13-2, which comprises 27.5% of Aquathol Super K. This inert is approved by the EPA (U.S. EPA/OPP 2009) for use in pesticides that are not applied to food products. Very little additional information is available on this compound. The CAS number for the polymer is not listed as a food additive in Clydesdale (1997). An MSDS for this agent (Aquatrols 2005) indicates that the oral LD₅₀ is >5,000 mg/kg bw but that no information is available on other acute endpoints.

The lack of detailed information on other ingredients in pesticide formulations is a common issue in pesticide risk assessments. The identity of the other ingredients is often regarded as proprietary information. While the U.S. EPA/OPPTS (2003, p. 5-2) encourages expanded inert statements on product labels that specifically identify the inert ingredients, doing so is not a requirement. Even when information on other ingredients is disclosed, the toxicity information on these ingredients is often very limited, as is the case with the 2-propenamide polymer in Aquathol Super K.

Because the paucity of information on inerts, Forest Service risk assessments often attempt to characterize the potential hazards of inerts by comparing the toxicity information on pesticide formulations with corresponding information on the active ingredient. As summarized in Section 3.1.3, the acute oral LD₅₀ values for endothall and endothall formulations are quite similar in terms of acid equivalents. In terms of dermal toxicity (Section 3.1.12), however, the liquid formulation of the amine salt (Hydrothol 191) appears to be more toxic than either technical grade endothall or the liquid formulation of the dipotassium salt (Aquathol K). It is unclear whether this difference reflects the toxicity of the amine moiety or the more rapid dermal absorption of the amine salt relative to the potassium salt. As discussed further in Section 4.1.3., a similar pattern is apparent in the toxicity of the dipotassium and amine salts of endothall to aquatic organisms. In terms of inhalation toxicity (Section 3.1.13), the available data indicate that the Aquathol and Hydrothol formulations are more toxic than technical grade endothall by factors ranging from 6 to 10. These comparisons, however, are based on only brief summaries of toxicity values reported in the MSDS for the formulation. The

role of inerts in what appears to be a greater degree of toxicity associated with endothall formulations compared with technical grade endothall cannot be determined.

3.1.14.2. Adjuvants

For many pesticides, the issue of adjuvants—i.e., materials added to a pesticide formulation prior to application—is similar to issues associated with the assessment of *inerts*. This is not the case, however, with endothall. The product labels for endothall do not recommend the use of adjuvants, which is consistent with observations by Keckemet (1969) and Sprecher et al. (2002) that adjuvants are not required in the aquatic applications of endothall.

3.1.15. Impurities and Metabolites

3.1.15.1. Metabolites

As summarized in Section 3.1.3.1, only limited data are available on the metabolism of endothall. Because radiolabelled CO₂ was detected in the expired air of mammals after dosing with ¹⁴C-endothall, it is reasonable to assert that some fraction of endothall may be mineralized by mammals. Extensive mineralization of endothall was observed also in microorganisms and fish (Sikka and Saxena 1973; Sikka et al. 1975). In mammals, however, the majority of the endothall dose is excreted either unchanged or as a conjugate. Combined with mechanistic data indicating the endothall is the active agent in the toxicity of endothall at the receptor level (Section 3.1.2), there is no basis for asserting that endothall metabolites substantially affect the toxicity of endothall to mammals.

3.1.15.2. Impurities

Virtually no chemical synthesis yields a totally pure product. Technical grade endothall, like other technical grade products, undoubtedly contains some impurities. To some extent, concern for impurities in technical grade endothall is reduced by the fact that the toxicity studies on endothall were conducted with the technical grade product or a formulated end-use 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.

3.1.16. Toxicological Interactions

There is no information available on the interactions of endothall with other compounds, and most inferences that could be made are speculative. As discussed in Section 3.1.3.1, endothall inhibits protein phosphatase which may disrupt normal cellular function. Cantharidin and a number of other structurally similar compounds also act by this mechanism. For such compounds, it is likely that interactions with endothall would be additive.

3.2. EXPOSURE ASSESSMENT

3.2.1. Overview

Details of the exposure assessments for workers and members of the general public are provided in the four EXCEL workbooks that accompany this risk assessment. These workbooks contain sets of worksheets on endothall that provide details for each exposure scenario discussed in this risk assessment. In addition, the workbooks include summary worksheets for worker exposures (Worksheet E01) and exposures to members of the general public (Worksheet E02). The documentation for these worksheets is provided in SERA (2009a).

Endothall exposure for workers and members of the general public depends on the target concentration. For the current risk assessment, all exposure assessments are based on the unit target application of 1 ppm. The consequences of using lower or higher target concentrations are discussed in the risk characterization (Section 3.4).

Since data are not available on worker exposure rates for aquatic applications of endothall, the current risk assessment is based on a study from PHED (Pesticide Handler Data Base) in which the dermal deposition rate was about 6.9 $\mu\text{g/lb}$ handled and the inhalation exposure rate was about 1.7 $\mu\text{g/lb}$ handled. The U.S. EPA/OPP considered dermal exposure to be self-limiting and did not include the dermal route in the exposure assessments for workers. The current Forest Service risk assessment takes a somewhat more conservative approach and explicitly considers both dermal and inhalation routes of exposure. Based on these assumptions, the dose to workers at a target concentration of 1 ppm in a standard application (the treatment of 100 million liters of water or about 81 acre-feet) is about 0.0086 (0.0073-0.012) mg/kg bw. Accidental dermal exposures to liquid formulations could be much higher—i.e., up to about 1.7 mg/kg bw.

Endothall may be applied directly to surface water to which members of the general public may have access. Furthermore, restrictions are not imposed on public access to treated bodies of water, meaning that members of the general public are likely to be exposed to endothall, if the treated body of water is in an area they frequent. Based on consumption of water treated at the target concentration of 1 mg/L (1 ppm), acute exposure levels of endothall for members of the general public could be much higher than non-accidental exposures for workers—i.e., absorbed doses of about 0.08 (0.05-0.11) mg/kg bw/day. Accidental exposures associated with a sizeable spill of endothall will be highly variable depending on the formulation with the highest estimated doses reaching about 32 mg/kg bw. Again, these estimates are much higher than estimated accidental exposure levels for workers. Information on the persistence of endothall in water is highly variable since the persistence will be influenced primarily by microbial activity. Thus, estimates of longer-term concentrations of endothall in water span a factor of over 80, ranging from 0.005 to about 0.42 mg/L.

3.2.2. Workers

3.2.2.1. General Exposures

In most Forest Service risk assessments, the exposure assessments for workers are based on a standard set of exposure scenarios involving applications of terrestrial herbicides and insecticides. Although these exposure assessments vary according to the available data for each chemical, the organization and assumptions used in the exposure assessments are standard and consistent. As documented in SERA (2007a), 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 various application methods, default exposure rates are typically estimated for three different types of applications: directed foliar (backpack), boom spray (hydraulic ground spray), and aerial. As discussed in Section 2.4, the application of endothall to ponds or lakes as well as to streams or canals involves application methods that are quite different from the application methods considered in most Forest Service risk assessments. Accordingly, the standard methods used in most Forest Service risk assessments do not apply to aquatic applications of endothall.

The literature on endothall does not include data regarding absorbed doses in workers involved in aquatic applications. This situation is similar to that encountered in recent Forest Service risk assessments on fluridone (SERA 2008a) and rotenone (SERA 2008b). In the fluridone and rotenone risk assessments, a study on worker exposure rates associated with aquatic applications of 2,4-D (Nigg and Stamper 1983) was used as a surrogate study for worker exposure. The study involved the application of a liquid formulation of 2,4-D by airboat handguns to control water hyacinths. The absorbed doses of 2,4-D were assayed in four workers as total urinary elimination over a 24-hour period. The estimated occupational exposure rates for the 2,4-D workers were 0.0009 (0.0004-0.002) mg/kg body weight per lb handled.

The U.S. EPA/OPP typically uses a very different method for estimating worker exposure, which is based on deposited or exposed doses rather than absorbed doses (PHED Task Force 1995) as well as assumptions concerning the proportion of the pesticide absorbed by dermal and inhalation routes of exposure. While the methods used in EPA and Forest Service occupational exposure assessments are very different, both methods generally lead to similar risk characterizations, and both methods generally assume that the predominant source of exposure is by the dermal route.

For endothall, however, the EPA determined that dermal exposures should not be considered for workers. The rationale for this approach is as follows:

...Risk Assessment Review Committee (RARC) determined that endothall should be regulated as a severe dermal irritant and not on systemic effects, and recommended against conducting a dermal risk assessment because the severe localized irritation effects of endothall on the skin would be self-limiting as to dermal exposures.

- U.S. EPA/OPP (2005e, p. 2)

In the EPA occupational exposure assessment for endothall (U.S. EPA/OPP 2005j, p. 35), the exposure rates for liquid and granular formulations of endothall are taken as 1.8 and 1.7 µg/lb handled, respectively.

The exposure rate of 1.7 µg/lb handled is identical to the exposure rate for inhalation exposures in applications of granular formulations with open mixing and loading cited in the PHED Exposure Guide (Keigwin 1998, p. 18). For this scenario, the PHED dermal exposure rate for workers wearing coveralls over a single layer of clothing as well as gloves is 3.4 µg/lb handled. In the normal application of the PHED method, it is likely that the EPA would use a dermal absorption factor of 0.073 for endothall taken from the PHED Science Chapter (U.S. EPA/OPP 2005e). Thus, the absorbed dermal dose rate would be estimated at about 0.25 µg/lb handled [3.4 µg/lb handled x 0.073]. For workers wearing a single layer of clothing with gloves but no coveralls, the estimated dermal exposure rate is 6.9 µg/lb handled, corresponding to an absorbed dose rate of about 0.5 µg/lb handled [6.9 µg/lb handled x 0.073]. As noted by Keigwin (1998, p. 17), confidence in the estimate for workers wearing coveralls (i.e., PPE) is classified as *Low* due to the low number of replicates for many body parts. Confidence in the estimate for a single layer of clothing with gloves is classified as *Medium*.

The exposure rate of 1.8 µg/lb handled is referenced to MRID 44972201, an *ORETF study of LCO Handgun Spray Mixer/Loader/Applicator Liquid Flowable* (U.S. EPA/OPP 2005j, p. 17). The LCO acronym designates *lawn care operators* (U.S. EPA/OPP 2005j, p. 16). The ORETF acronym presumably refers to the *Outdoor Residential Exposure Task Force*. In other words, the exposure assessments for aquatic applications of endothall are based on terrestrial applications that the EPA judges to be acceptable surrogates for aquatic applications (U.S. EPA/OPP 2005j).

The exposure rates used by EPA are based on a 60-kg worker and thus correspond to exposure rates of 0.00003 mg/kg bw/lb handled [0.0018 mg/lb handled ÷ 60 kg] and 0.000028 mg/kg bw/lb handled [0.0017 mg/lb handled ÷ 60 kg]. The difference between the EPA exposure rates for liquid and granular formulations is insubstantial. For the current Forest Service risk assessment, only the higher exposure rate of 0.00003 mg/kg bw/lb handled is considered. Since U.S. EPA/OPP assumes 100% absorption for inhalation exposures, 0.00003 mg/kg bw/lb handled essentially represents an absorbed dose rate similar to those used in Forest Service risk assessments. Relative to the exposure rate for aquatic applications of 2,4-D from Nigg and Stamper (1983), however, the exposure rate used by the EPA is lower by 30 (13.3-66.7) [0.0009 (0.0004-0.002) mg/kg body weight per lb handled ÷ 0.00003 mg/kg bw/lb handled].

As discussed in Section 3.1.11.1, the subchronic dermal toxicity study considered by the EPA in making this assessment (i.e., MRID 43465201) is based on doses of 30-300 mg/kg bw in rats in which both dermal irritation as well as systemic toxic effects were observed at all doses. Based on this and other available studies, there is little doubt that endothall in concentrated solutions will be irritating to the skin. For more dilute solutions, it is likely that a threshold for irritation could be reached. This possibility is

clearly suggested in the early study by Goldstein (1953) in which rabbits dermally exposed to a 1% granular application of endothall displayed only mild skin lesions but severe skin lesions were evident at concentrations of 10-20% endothall. As discussed in Section 2.4, the application instructions for endothall do not call for dilution of liquid formulations or for the preparation of liquid field solutions of granular applications. Thus, as indicated in Table 3, workers will be handling 26.8 % a.e. or 23.36% a.e. solutions for the liquid formulations or 44.7% or 5% a.e. granules for granular formulations.

Concern may be expressed with the EPA occupational exposure assessment for endothall because it is not standard and because it is not the most conservative approach that could be applied. In addition as discussed in Section 3.1.11.1, some studies indicate that endothall may not be a severe skin irritant—e.g., Mallory (1992) and the summary of some early studies by Dykstra (1978). Conversely, the studies considered by U.S. EPA/OPP indicate that concentrated preparations of endothall can be highly irritating to the skin. Thus, the assumption that workers would avoid dermal exposures to endothall formulations has merit.

For the current Forest Service risk assessment, neither the standard approach used in past Forest Service risk assessments involving aquatic applications nor the approach used by U.S. EPA/OPP (2005j) appears to be appropriate. The use of the Nigg and Stamper (1983) on 2,4-D can be applied reasonably to fluridone (SERA 2008a) and rotenone (SERA 2008b) because both fluridone and rotenone cause only minimal skin irritation – i.e., these pesticides are classified by the U.S. EPA as Category IV skin irritants, the least hazardous category for skin irritation – and the various salts and esters of 2,4-D are also classified as only slightly irritating – i.e., all but the DEA salt (Category III) are classified as Category IV for skin irritation (U.S. EPA/OPP 2005k). As discussed above and detailed in Section 3.1.11.1, this is not the case for endothall with the available data indicating that endothall may cause severe skin irritation. In other words, the assertion by U.S. EPA/OPP (2005j) that workers may handle endothall differently than other agents appears to be reasonable and it would not be appropriate to an occupational study on a compound that is not a skin irritant (i.e., Nigg and Stamper 1983) to estimate exposures for a compound such as endothall, which is a severe skin irritant.

While the standard Forest Service approach for aquatic applications cannot be reasonably applied to endothall, the assertion by U.S. EPA/OPP (2005j) that only inhalation exposures need to be considered appears to be extreme. While there is little doubt that workers will handle a severe skin irritant more carefully than a compound that is not a skin irritant, no data are available indicating that dermal exposure will or could be completely eliminated. In the Science Chapter prepared by the Health Effects Division of U.S. EPA/OPP (2005e), a brief summary of incident reports associated with endothall does indicate that irritant effects to the eyes, skin, and respiratory tract were reported but that no reports of serious illnesses associated with exposure to endothall are available. The lack of reports of serious illness suggests that workers may avoid dermal exposure but the reports of dermal irritation suggests that dermal exposures will not be avoided completely.

In the absence of any direct data on worker exposure to endothall, the current Forest Service risk assessment uses the data from PHED, consistent with the approach taken by U.S. EPA, but considers dermal as well as inhalation exposure. As discussed above, the inhalation exposure rate of 1.7 µg/lb handled is associated with a dermal exposure rate of 6.9 µg/lb handled (Keigwin 1998, p. 18). The other study cited by U.S. EPA/OPP (2005j, p. 17), MRID 449722, gives an almost identical inhalation exposure rate, 1.8 µg/lb handled. The EPA summary of this study, however, does not give the corresponding dermal exposure rate; thus, MRID 449722 cannot be further considered.

The dermal and inhalation exposure rates from Keigwin (1998) are associated with a 60 kg worker. Thus, the inhalation exposure rate of 1.7 µg/lb handled is equivalent to about 0.00003 mg/kg bw per lb handled [$0.0017 \text{ mg/lb} \div 60 \text{ kg} = 0.000028333 \text{ mg/kg bw per lb}$] and the dermal exposure rate of 6.9 µg/lb handled is equivalent to 0.000115 mg/kg bw per lb handled [$0.0069 \text{ mg/lb} \div 60 \text{ kg}$]. Following the standard procedures used by U.S. EPA, complete absorption is assumed for inhalation exposures. Thus, the inhalation exposure rate of 0.00003 mg/kg bw per lb handled is directly analogous to absorbed dose rates typically used in Forest Service risk assessments. For dermal exposures, the deposited dose must be converted to an absorbed dose. As detailed in Section 3.1.3.2.2 (Dermal Absorption), the first-order dermal absorption rates for endothall are taken as 0.0033 (0.0012-0.0088) hour⁻¹, which is equivalent to 0.0788 (0.0292 to 0.2123) day⁻¹. Using these estimates of dermal absorption, the deposited dermal dose rate of 0.000115 mg/kg bw per lb handled corresponds to absorbed dermal dose rates of 0.0000091 (0.0000034 to 0.000024 mg/kg bw per lb a.i. handled [$0.000115 \text{ mg/kg bw per lb handled} \times 0.0788 (0.0292 \text{ to } 0.2123) \text{ day}^{-1}$]). Adding the inhalation exposure rate of 0.00003 mg/kg bw per lb handled, the combined exposure rates for workers are taken as 0.000039 (0.000033 to 0.000054) mg/kg bw per lb a.i. handled.

The other factor that has an impact on worker exposure is the amount of the pesticide to be handled. For endothall, this amount depends on the application rate in ppm (mg/L) as well as the size of the water body to be treated. Each of these values is highly variable and specific to Forest Service applications of endothall. In a generic risk assessment, there is no satisfactory way to encompass this variability; however, for this risk assessment, Worksheet A01 of the EXCEL workbooks allows the user to specify the application rate and the volume of water to be treated. With this information, the amount handled by the worker is calculated and used to derive hazard quotients, as discussed further in Section 3.4.2.

As discussed in Section 2.4, the treatment rate of 1 ppm is in the central range of labeled application rates for endothall. The use of higher treatment rates which span the range of labeled application rates is discussed in the risk characterization (Section 3.4.2).

The volume of water to be treated is also highly variable; accordingly, U.S. EPA/OPP (2005j, p. 15) uses different treatment volumes for applications to canals versus bodies of standing water. For canals, the highest treatment volume is based on a 10-mile length of canal that is 20-feet wide and 5-feet deep. These parameters correspond to a treatment

volume of 5,280,000 ft³ [5280 feet/mile x 10 miles x 5 feet x 20 feet] or about 121 acre-feet [5,280,000 ft³ ÷ (43,560 ft³/acre-foot = 121.212 acre-feet]. For ponds and lakes, the treatment volume is based on a 30-acre surface area and a water depth of 5 feet—i.e., 150 acre-feet or about 6,534,000 ft³. Although endothall is not labeled for metered applications, U.S. EPA/OPP (2005j, p. 15) provides an estimate of water volumes that might be treated in metered applications. The maximum amount is based on a water flow of 200 ft³/sec for a period of 2 hours, corresponding to a treatment volume of 1,440,000 ft³ [200 ft³/sec x 2 hr x 60 sec/min x 60 min/hr] or about 33 acre-feet [1,440,000 ft³ ÷ 43,560 ft³/acre-foot].

The workbooks that accompany the current Forest Service risk assessment are structured to accept only a single input in liters for the volume of water treated. In these workbooks, a treatment volume of one hundred million liters (100,000,000 L) is used, equivalent to 3,531,073 ft³ [100,000,000 L ÷ 28.32 L/ft³] or about 81 acre-feet [3,531,073 ft³ ÷ 43,560 ft³/acre-foot = 81.062 acre-feet]. As discussed further in Section 3.4.2, however, a broad range of treatment volumes—i.e., from 1 acre-foot to 300 acre-feet—is considered in the risk characterization for workers.

3.2.2.2. Accidental Exposures

Forest Service risk assessments typically model two types of accidental exposures, those involving direct skin contact with a pesticide solution and those associated with accidental spills of the pesticide onto the surface of the skin (SERA 2007a). As discussed in previous subsection, U.S. EPA/OPP does not consider dermal absorption in estimating occupational exposures. While the current Forest Service risk assessment defers to EPA in this judgment for the general worker exposure assessment (i.e., exposure levels anticipated for routine applications of endothall), this does not preclude the possibility of accidental dermal exposure. Thus, for liquid formulations of endothall, the standard Forest Service accidental exposure scenarios are used.

For the liquid formulations of endothall, four accidental dermal exposure scenarios are given, two involving contaminated gloves based on zero-order absorption (i.e., the concentration of the pesticide in the contaminated gloves is essentially constant) and two involving accidental spills on the surface of the skin based on first-order absorption (i.e., a constant proportion of the pesticide is absorbed per unit time). The accidental glove scenarios are based on exposures periods of 1 minute (Worksheet C02a) and 1 hour (Worksheet C02a). The accidental spill scenarios are based on spills onto unprotected hands (Worksheet C03a) and the lower legs (Worksheet C03b) with an exposure period of 1 hour. These are standard exposure scenarios used in most Forest Service risk assessments.

For many pesticides, the accidental dermal exposure scenarios are based on concentrations in field solutions—i.e., the concentration after the formulation is diluted prior to application. For endothall, however, the liquid formulations are not diluted prior to application (Section 2.4). Consequently, the concentration to which workers will be exposed to in the accidental dermal exposure scenarios is identical to the concentration of endothall in the liquid formulations. As summarized in Table 3, the concentration of

endothall in Aquathol K is greater than the concentration of endothall in Hydrothol 191 (liquid). Thus, the absorbed doses for workers handling the liquid Aquathol formulation (3 lb a.e./gallon) is greater than that for the liquid Hydrothol formulation (2 lb a.e./gallon) by a factor of 50%. The specific estimates of doses in workers are summarized in Table 5. The highest doses are associated with wearing contaminated gloves for 1 hour—i.e., upper bound doses of about 1.7 mg/kg bw for Aquathol K and about 1.1 mg/kg bw for Hydrothol 191 (liquid).

For granular formulations of endothall, however, no accidental exposure scenarios are quantified. As discussed in Section 3.1.12, the limited acute toxicity data available on liquid and granular formulations of endothall clearly indicate that granular formulations are much less toxic than liquid formulations with respect to dermal exposure. It is likely granular formulations are less toxic due to decreased bioavailability—i.e., the binding of endothall to the granular matrices in the granular formulations. Thus, it seems reasonable to assert that accidental dermal contact with granular formulations will pose a much lower risk than accidental dermal contact with liquid formulations. The lack of dermal absorption data on the granular formulations, however, precludes any reliable estimates of exposures.

Another worker exposure scenario of concern involves ocular exposure. This exposure scenario is a concern in any pesticide application, particularly for pesticides that may cause severe eye irritation. For endothall, the accidental contamination of the eyes is a particular concern both because endothall is a severe eye irritant and because an ocular irritation study in rabbits noted lethality in four of six animals after ocular instillations (Section 3.1.11.3). Quantitative exposure assessments are not developed for accidental ocular exposures. Nonetheless, this exposure scenario is addressed semi-quantitatively in the risk characterization for workers (Section 3.4.3.3).

3.2.3. General Public

3.2.3.1. General Considerations

3.2.3.1.1. General Considerations

Endothall can be used to control unwanted vegetation in water bodies used by the general public for recreational activities, like fishing or swimming, and as a source of drinking water. Early recommendations from an internal review with U.S. EPA/OPP (Akerman 1975) suggested that the maximum target application rate should be no more than 0.2 mg/L in surface waters that may be used for drinking water. Currently, however, the product labels for endothall do not limit public access to treated bodies of water and do not limit applications near potable water intakes. Thus, as in the U.S. EPA drinking water assessment (U.S. EPA/OPP 2004b), peak exposures for members of the general public are based on the nominal application rate.

Because of the conservative exposure assumptions used in the current risk assessment, the number of individuals who might be exposed to endothall does not have a substantial impact on the characterization of risk presented in Section 3.4. As detailed in SERA (2007a, Section 1.2.2.2), the exposure assessments developed in this risk assessment are

based on ***Extreme Values*** rather than a single value. Extreme value exposure assessments, as the name implies, bracket the most plausible estimate of exposure (referred to generally as the central estimate) with extreme lower and upper bounds of plausible exposure estimates.

This Extreme Value approach is essentially an elaboration on the concept of the *Most Exposed Individual* (MEI), sometimes referred to as the *Maximum Exposed Individual* (MEI). As these terms also imply, exposure assessments that use the MEI approach attempt to characterize the extreme but still plausible upper limit on exposure. This approach to exposure assessment is commonly used by government agencies, including the U.S. EPA, and other organizations. In the current risk assessment, the upper bounds on exposure are all based on the MEI.

In addition to this upper bound MEI value, the Extreme Value approach used in this risk assessment also provides central and lower bound estimates of exposure. While not germane to the assessment of upper bound risk, it is worth noting that the use of the central estimate and especially the lower bound estimate is not intended to lessen concern. To the contrary, the central and lower estimates of exposure are used to assess the feasibility of mitigation—e.g., measures taken to limit exposure. The implementation of the Extreme Value approach in the exposure assessment is part of an integrated approach designed to encompass plausible upper limits of risk for the most exposed and most sensitive individuals, regardless of the specific probabilities or number of exposures, as well as more likely and lower estimates that could occur by happenstance or as the result of mitigation measures.

3.2.3.1.2. Summary of Assessments

The two types of exposure scenarios developed for the general public include acute exposure and longer-term or chronic exposure. As summarized in Worksheet E03, acute exposure scenarios are classified as either accidental or non-accidental. Specific accidental scenarios are developed for the consumption of contaminated water or fish after an accidental spill. The longer-term or chronic exposure scenarios parallel the acute exposure scenarios for the consumption of contaminated water and fish.

Most Forest Service risk assessments also include scenarios for the consumption of contaminated vegetation or fruit as well as the direct spray of a small child and a woman. These scenarios are not included in the current risk assessment which only considers aquatic applications of endosulfan. Section designations for these excluded scenarios are given below as a matter of convenience for individuals who regularly use many different Forest Service risk assessments—i.e., the section designations in all Forest Service risk assessments are consistent or nearly so.

The exposure scenarios developed for the general public are summarized in Worksheet E03. As with the worker exposure scenarios, the details about the assumptions and calculations involved in these exposure assessments are given in the worksheets that accompany this risk assessment (Worksheets D01–D11). 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 spray scenarios are not relevant to aquatic applications of endothall.

3.2.3.3. Dermal Exposure from Contaminated Vegetation

Scenarios involving dermal contact with contaminated vegetation are based on data from terrestrial applications and these scenarios are not relevant to aquatic applications of endothall.

3.2.3.4. Contaminated Water

3.2.3.4.1. Peak Expected Concentrations

In terrestrial applications of pesticides, estimates of plausible concentrations in contaminated water can be elaborate and include modeling of runoff and leaching of the pesticide from contaminated soil, unintentional direct spray from aerial applications, or drift from either ground or aerial applications. For direct applications to water, most of these considerations are not relevant.

The estimated concentration in water is set to the target concentration. As discussed in Section 2.4, the target concentration of 1 ppm (1 mg a.e./L) is used in the EXCEL workbooks that accompany this risk assessment. As summarized in Table 3, the labeled application rates range from 0.35 to 3.5 ppm a.e. for Aquathol formulations and from 0.05 to 5 ppm a.e. for Hydrothol formulations. The consequences of using this range of application rates are discussed further in the risk characterization for members of the general public (Section 3.4.3).

Applications of endothall to water are likely to be inexact—i.e., there will be uncertainty and perhaps some error in estimating the volume of water to be treated; moreover, the application devices used may also be associated with a margin of error. For endothall, the differences between nominal and monitored application rates are reportedly relatively minor. Maini (1992) noted that peak concentrations of granular and liquid Hydrothol 191 were relatively close to the target application rate after a reasonable period of time was allowed for diffusion to occur. In two of the three applications reported by Maini (1992), one with a liquid formulation and the other with a granular formulation, peak concentrations were monitored 1 day after application. In applications of a granular formulation of an amine salt of endothall, peak concentrations of endothall were only about 15% over the nominal application rate (Frank and Comes 1967). While this degree of imprecision is more obvious for aquatic applications, uncertainties and errors in actual, as opposed to nominal, application rates are inherent in all pesticide applications.

3.2.3.4.2. Longer-Term Expected Concentrations

While there are relatively few uncertainties in assessing the plausible peak concentrations of endothall in water, the longer-term concentrations of endothall in water are likely to be highly variable. Most exposure assessments conducted in Forest Service or EPA documents typically assume first-order degradation and dissipation. Under this assumption, the concentration of a pesticide in water (C_t) at time, t , is:

$$C_t = C_0 \times e^{-kt} \quad \text{Eq 6}$$

where C_0 is the concentration at time zero—i.e., the initial target concentration. As discussed in SERA 2007a (Section 3.2.3.6), the time-weighted average concentration (C_{TWA}) between time-zero and time t is simply the integral of the above equation for first-order dissipation divided by the interval, t :

$$C_{TWA} = C_0 (1 - e^{-kt}) / (k t). \quad \text{Eq 7}$$

For endothall, some studies report relatively rapid degradation that follows a pattern which is reasonably consistent with first-order kinetics. Field half-lives of 3.3 (1.9-4.9) days are reported by Maini (1992) and much shorter half-lives of 0.1-0.23 days are reported by Reinert and coworkers (Reinert and Rogers 1985; Reinert et al. 1988). The shorter half-lives are probably dominated by the dissipation of endothall. As summarized in Table 2, studies on the aquatic metabolism of endothall generally indicate metabolic half-lives in the range of 4-12 days. In a review of a dietary assessment of endothall submitted to EPA, Reinert (1983) indicates that 12 days may also be a reasonable estimate of the first-order half-life of endothall in some natural waters. [Note: The Reinert (1983) who prepared the EPA document is not the same individual as the Reinert involved in the open literature studies.]

Contrary to the results from the studies discussed above, which are at least roughly consistent with first-order degradation/dissipation, several other studies report that endothall will degrade very slowly after application over a period of a weeks, after which the degradation is extremely rapid (Ameel et al. 1997; Holmberg and Lee 1976; Simsiman and Chesters 1975). Simsiman and Chesters (1975) offer the most plausible explanation for the biphasic pattern noted in some field studies concerning the application of endothall. When endothall is applied to areas of dense aquatic vegetation, it rapidly kills the treated plants, and the decay of the dead vegetation results in severe oxygen depletion, which, in turn, results in a loss of microbial activity.

As noted in the early work of Sikka and coworkers (Sikka and Rice 1973; Sikka and Saxena 1973), the degradation of endothall in water is highly dependant on microbial activity. While Sikka and coworkers do not provide a statistical analysis of degradation rates, the approximate half-life for the degradation of a 2 ppm solution of endothall in water appears to be about 5-6 days (Sikka and Rice 1973, p. 845, Figure 3). These half-lives are somewhat longer than those noted by Maini (1992), which is to be expected. The half-lives from Maini (1992) are field values encompassing both degradation and dissipation; whereas, the studies by Sikka and coworkers are laboratory studies that consider only degradation.

The EPA drinking water assessment for endothall (U.S. EPA/OPP 2004b) uses an aquatic half-life of 30 days, based on a registrant submitted study by Reynolds (1992). Similar to the study by Sikka and Rice (1973), the study by Reynolds (1992) is a laboratory study of aquatic degradation that reports an experimental half-life of 10 days. In U.S. EPA/OPP (2004b) the experimental half-life is multiplied by a factor of 3 to account for situations in which the persistence of endothall might be greater than that observed in the laboratory study. Thus, the factor of 3 is analogous to a safety or uncertainty factor.

For the current Forest Service risk assessment, the half-lives for endothall in water are taken as 3 days with a range from 0.3 to 30 days. The central estimate of 3 days is taken from the study by Maini (1992) and may reflect applications in which oxygen depletion is not severe but dissipation is limited. The lower bound of 0.3 days is adapted from the studies by Reinert and coworkers (Reinert and Rogers 1985; Reinert et al. 1988) and may reflect applications in which dissipation is the predominant mechanism in the decrease of endothall concentrations in water. The upper bound of 30 days is taken from U.S. EPA/OPP (2004b). While this upper bound value may be highly conservative in most applications of endothall, it may better reflect applications in which oxygen is depleted, microbial activity is minimal for an extended period of time, and substantial dissipation of endothall does not occur.

As summarized in Worksheet B04b in the EXCEL workbooks that accompany this risk assessment, the resulting longer-term concentrations in water are estimated at 0.048 (0.0048-0.421) mg/L using an application rate of 1 ppm and a duration 90 days. These concentrations are used in the human health and ecological risk assessment to evaluate the consequences of longer-term exposures to endothall in water.

3.2.3.4.3. Accidental Spills

The accidental spill scenario is presented for the acute consumption of contaminated water after an accidental spill into a small pond (0.25 acres in surface area and 1 meter deep). 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. Because this scenario is based on the assumption that exposure occurs shortly after the spill, no dissipation or degradation is considered.

The accidental spill scenarios are generally based on spills of a field solution, specifically 100 (20-200) gallons of the pesticide after dilution to the concentration recommended for application. As discussed in Section 2.4, liquid solutions of endothall are not mixed or otherwise diluted prior to application. Thus, for the liquid formulations, the accidental spill scenario is based on spills of 100 (20-200) gallons of the formulation. For granular formulations that are not pre-mixed, the assumption is made that 40 (16-80) pounds of the active ingredient are spilled into the small pond. This approach is used under the assumption that greater quantities of less-concentrated granular formulations would be

required for efficacy; thus, greater amounts of less-concentrated granular formulations might be spilled. As a consequence of this approach, the accidental spill scenarios for both granular formulations—i.e., Aquathol Super K and Hydrothol 191 Granular—are identical.

The specifics of the accidental spill scenarios are given in Worksheet D05 of the EXCEL workbooks that accompany this risk assessment, and the estimated water concentrations of endothall are summarized in Table 6. The highest endothall concentrations are associated with the accidental spill of Aquathol K—i.e., 140 (28-280.1) mg/L (Table 6). The concentrations for Hydrothol 191 (liquid) are somewhat lower—i.e., 90.8 (18.2-181.7) mg/L. The concentrations involving the use of granular formulations are substantially lower than those for either of the liquid formulations—i.e., 18.1 (7.3-36.3) mg/L. These differences are essentially artifacts of the different assumptions used for aquatic applications of granular and liquid formulations.

3.2.3.5. Oral Exposure from Contaminated Fish

Three sets of exposure scenarios are presented for the consumption of contaminated fish: one set for acute exposures following an accidental spill (Worksheets D08a and D08b), one set for acute exposures based on the target application rate (Worksheets D09c and D09d), and the other set for chronic exposures based on estimates of longer-term concentrations in water (Worksheets D09a and D09b). The two worksheets in each of the three sets are intended to account for consumption rates of caught fish among both the general population and subsistence populations. Details of these exposure scenarios are provided in Section 3.2.3.5 of SERA (2007).

The pesticide concentrations in water are based on the same values used to assess contaminated water consumption (3.2.3.4). In addition to estimated pesticide concentrations in water, scenarios involving the consumption of contaminated fish require information about the bioconcentration factor (BCF) in fish.

As summarized in Table 1, the reported bioconcentration factors for endothall range from close to zero (Serns 1977) to 10 (Isenssee 1976). U.S. EPA/OPP (2005c, p. xii) cites bioconcentration factors of 0.35 for whole fish and 0.08 for the edible portion of fish. The EPA values are cited to MRID 4264001. This MRID is not otherwise identified in U.S. EPA/OPP (2005c) or in the RED (U.S. EPA/OPP 2005a); furthermore, a cleared review of this study is not available. An internal review of early studies submitted to the EPA notes BCF values in whole fish ranging from about 0.004 to 0.1 from water treated with 4 ppm endothall (Ney 1974, p. 3).

Sikka et al. (1977) report somewhat lower BCF values for endothall (0.09 whole body, 0.023 edible) in bluegills. Serns (1977) reports even lower BCF values (0.008 edible) for bluegills. The relatively high bioconcentration factor in fish reported by Isenssee (1976)—i.e., a BCF of 10 in whole mosquito fish—is based on a microcosm study. In this type of study, it is likely that microorganisms in the microcosm mineralized a substantial proportion of the endothall and that the ¹⁴C-levels in fish reflected endothall that had been mineralized and incorporated in the carbon pool.

The current risk assessment uses the BCF factors reported in U.S. EPA/OPP (2005c): 0.35 for whole fish and 0.08 for the edible portion of fish. Compared with the lower BCF values reported by Sikka et al. (1977) and Serns (1977), the BCF values used by the EPA are likely to offer plausible upper bounds of endothall residues in fish.

3.2.3.6. Dermal Exposure from Swimming in Contaminated Water

Conceptually and computationally, the exposure scenario for swimmers is virtually identical to the contaminated gloves scenario used for workers (Section 3.2.2.2)—i.e., a portion of the body is immersed in an aqueous solution of the compound at a fixed concentration for a fixed period of time. The major differences in the two scenarios involve the concentration in water and the surface area of the body that is exposed. For the worker wearing contaminated gloves, the assumption is made that both hands are exposed to the pesticide at the concentration of the compound in the solution that is being applied. For endothall, this is the concentration in the formulation. For the swimmer, the assumption is made that the entire body surface area is exposed to the expected peak concentrations in ambient water—i.e., the target concentration for endothall used in the application. While the swimmer will not be immersed for 1 hour, the entire body surface is used both as a conservative approximation (i.e., the MEI) and to consider intermittent episodes during which the whole body might be immersed or at least wet.

As with the corresponding worker exposure scenario, the 1-hour period of exposure is somewhat arbitrary, and longer periods of exposure are plausible. The 1-hour period, however, is not completely arbitrary but is intended as a unit exposure estimate. In other words, the exposure and consequently the risk will increase linearly with the duration of exposure, as indicated in Worksheet D11. Thus, a 2-hour exposure would lead to a hazard quotient that is twice as high as that associated with an exposure period of 1 hour. In cases in which this or other similar exposures approach a level of concern, further consideration is given to the duration of exposure in the risk characterization (Section 3.4.3).

3.2.3.7. Oral Exposure from Contaminated Vegetation

Scenarios involving the consumption of contaminated vegetation are based on terrestrial applications to fruit or vegetables. These scenarios are not relevant to aquatic applications of endothall.

3.3. DOSE-RESPONSE ASSESSMENT

3.3.1. Overview

The dose-response assessments for human health effects are summarized in Table 7. Forest Service risk assessments typically adopt both acute and chronic RfD values from the U.S. EPA, unless there is a compelling basis to do otherwise. The U.S. EPA's Office of Pesticide Programs (U.S. EPA/OPP) has not derived an acute RfD for endothall. Nonetheless, the Office of Pesticide Programs recommends a NOAEL of 9.4 mg/kg bw with a Margin of Exposure of 100 for short-term exposures (1-30 days). This recommendation is used to derive a surrogate acute RfD of 0.094 mg/kg bw, which is applied to all acute exposure scenarios to characterize risks.

The EPA derived two chronic RfDs for endothall: 0.02 mg/kg bw/day from the Office of Research and Development and 0.007 mg/kg bw/day from the Office of Pesticide Programs. The higher RfD is based on a chronic feeding study in dogs; the lower RfD is based on a reproductive study in rats. Consistent with the conservative risk assessment assumptions used in all Forest Service risk assessments, the lower chronic RfD of 0.007 mg/kg bw/day is used in the current risk assessment to characterize risks associated with longer-term exposures to endothall.

Generally, Forest Service risk assessments use only the chronic RfD to assess the risks to workers associated with general exposure levels which might occur during the application of a pesticide. For endothall, the EPA Office of Pesticide Programs used both the acute and chronic RfD to assess risks to workers. This approach is adopted in the current Forest Service risk assessment simply to illustrate the differences in risk for workers involved in frequent versus infrequent applications of endothall. As with most Forest Service risk assessments, dose-severity relationships are considered in an attempt to more fully characterize the nature of risks for exposures that exceed the RfD. An overview of these relationships is presented in Table 8.

3.3.2. Acute RfD

Acute RfD values are used in this and other Forest Service risk assessments to assess the consequences of an exposure event that may occur on only a single day, such as the consumption of water at the peak concentration or after an accidental spill. This approach is identical to the application of acute RfDs in pesticide risk assessments conducted by the EPA.

The U.S. EPA/OPP (2005e) declined to derive an acute dietary RfD for endothall. The rationale for not deriving an acute RfD is as follows:

An appropriate endpoint attributable to a single dose was not available from any study, including the prenatal developmental toxicity study in rats. An acute RfD was not established.

U.S. EPA/OPP 2005c, p. 32

The *prenatal developmental toxicity study* referenced by the EPA in the above quotation is the study by Trutter (1993a) discussed in Section 3.1.9.1 of the current Forest Service risk assessment. As indicated in this discussion, there were no adverse effects on offspring. In a developmental study, U.S. EPA/OPP generally regards effects on offspring as being associated with exposure on a single day. The body weight loss in dams reported in the Trutter (1993a) study is not considered appropriate because the effect is most likely to be associated with the entire period of exposure—i.e., from day 6 to 15 of gestation.

U.S. EPA/OPP (2005c) recommends the NOAEL of 9.4 mg/kg bw/day for assessing short-term (1-30 day) incidental oral exposures. The NOAEL of 9.4 mg/kg bw/day is based on decreased pup weights from the multigeneration reproduction study by Trutter (1993b), discussed in Section 3.1.9.2 of the current Forest Service risk assessment. U.S. EPA/OPP (2005c) recommends a margin of exposure (MOE) of 100. The MOE is conceptually equivalent to an uncertainty factor of 100. This factor is a composite of a factor of 10 for intraspecies variation and a factor of 10 for interspecies variation. Thus, the equivalent short-term surrogate RfD is 0.094 mg/kg bw/day.

The U.S. EPA Office of Drinking Water (ODW) derives 1-day, 10-day, and lifetime health advisories for chemical concentrations in drinking water. In the ODW review of endothall, U.S. EPA/ODW (1987) adopts an approach similar to that use in U.S. EPA/OPP (2005c), in that no 1-day health advisory was proposed. Nonetheless, ODW does propose a 10-day health advisory based on the maternal NOAEL of 8 mg/kg bw/day from the developmental toxicity study in rats by Science Applications, Inc (1982), discussed in Section 3.1.9.1, and an uncertainty factor of 100. Thus, the 10-day health advisory would be equivalent to a short term RfD of 0.08 mg/kg bw.

The differences in the short-term toxicity values from U.S. EPA/OPP (2005c) and U.S. EPA/ODW (1987) are insubstantial. Nonetheless, there are issues with both of these values. The 9.4 mg/kg bw/day NOAEL for pup weight used in U.S. EPA/OPP (2005c) and the 8 mg/kg bw/day maternal NOAEL used in U.S. EPA/ODW (1987) are greater than the maternal LOAEL of 2 mg/kg bw/day in the study by Trutter (1993b). The current Forest Service risk assessment adopts the more recent EPA evaluation (U.S. EPA/OPP 2005c); furthermore, the surrogate RfD of 0.094 mg/kg bw is used to assess the consequences of short-term exposures to endothall.

3.3.3. Chronic RfD

The RED for endothall (U.S. EPA/OPP 2005a) adopts a chronic RfD of 0.007 mg/kg bw/day for general population exposure. Most RfDs are based on a NOAEL for a chronic toxicity study, which is not the case for endothall. As discussed in Section 3.1.9.2., the 2-generation reproduction study in rats yielded a LOAEL of 2 mg/kg bw/day based on lesions to the gastrointestinal tract (Trutter 1993b). This LOAEL is lower than the subchronic rat NOAEL of 39 mg/kg bw/day from the study by Trutter (1994a) and the chronic rat NOAEL of 8 mg/kg bw/day from the study by Plankenhorn (1990). All of these studies involved dietary exposures, and the most sensitive endpoint in all of these studies involved gastrointestinal effects—i.e., portal of entry effects. In the absence of a

compelling reason to do otherwise, the selection of the 2 mg/kg bw/day LOAEL from the reproduction study by Trutter (1993b) as the basis of the chronic RfD is judged to be appropriate.

Because the chronic RfD is based on a LOAEL, U.S. EPA/OPP (2005a) uses an uncertainty factor of 300. This uncertainty factor consists of three components: a factor of 10 for extrapolating from animals to humans, a factor of 10 for extrapolating to sensitive individuals within the human population, and a factor of 3 for extrapolating from a LOAEL to a NOAEL. Thus, the chronic RfD of 0.007 mg/kg bw/day is calculated by dividing the LOAEL of 2 mg/kg bw/day by 300 [$2 \text{ mg/kg bw/day} \div 300 = 0.00666\dots$] and rounding to one significant place.

A higher RfD of 0.02 mg/kg bw/day is posted on IRIS (Integrated Risk Information System), an EPA database of RfDs reviewed by the Office of Research and Development (U.S. EPA/ORD 1991). This RfD was also adopted by the EPA Office of Drinking Water (U.S. EPA/ODW 1992) and reviewed by Ghali (1986). As discussed in Section 3.1.5, this RfD is based on a 2-year dog feeding study (Eibert 1966) in which the NOAEL was 2 mg/kg bw/day with a LOAEL of 6 mg/kg bw/day, based on gastrointestinal effects. The RfD of 0.02 mg/kg bw/day is calculated using a standard uncertainty factor of 100.

Unlike the situation with the acute RfD, the differences between the chronic RfD of 0.007 mg/kg bw/day proposed by U.S. EPA/OPP (2005a) and the chronic RfD of 0.02 mg/kg bw/day proposed by U.S. EPA/ODW (1992) are substantial. The current Forest Service risk assessment adopts the lower and more recent chronic RfD of 0.007 mg/kg bw/day from U.S. EPA/OPP (2005a).

3.3.4. Surrogate RfD for Occupational Exposures

Typically, Forest Service and most EPA risk assessments use only the chronic RfD for assessing risks to workers. This approach is taken under the assumption that workers may travel from location to location and apply the pesticide repeatedly over a prolonged period of time. This assumption, however, is often questionable. In some circumstances, it may be more reasonable to assume that workers apply the pesticide only once or, at most, infrequently over the course of a year.

For endothall, the U.S. EPA/OPP (2005j, p. 24) uses both the short-term and intermediate-term toxicity values. For short-term (1- 30 days) occupational exposures, the EPA uses the NOAEL of 9.4 mg/kg bw/day with an MOE of 100. As discussed in Section 3.3.2, this is equivalent to using short-term surrogate RfD is 0.094 mg/kg bw/day. For intermediate-term (30-90 days) occupational exposures, the EPA uses LOAEL of 2 mg/kg bw/day with an MOE of 300. As discussed in Section 3.3.3, this is equivalent to using the chronic RfD of 0.007 mg/kg bw/day.

As discussed further in Section 3.4.2, the risk characterization worksheets (E02) of the EXCEL workbooks that accompany this risk assessment are based only on the chronic RfD. Nonetheless, risk quotients based on both the surrogate acute RfD and the chronic RfD are discussed in Section 3.4.2 (Risk Characterization for workers).

3.3.5. Dose-Severity Relationships

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

As discussed further in Section 3.4 (Risk Characterization), exposure scenarios for workers and members of the general public result in exposures that exceed the acute and chronic RfDs. Consequently, a consideration of dose-severity relationships for both acute and chronic exposures would be useful.

As with all dose-severity relationships derived in Forest Service risk assessments, the following caveat applies to the dose-severity relationships derived for endothall:

Dose-severity relationships should not be interpreted as suggesting that acute exposures above the acute RfD or longer-term exposures above the chronic RfD are acceptable.

For both acute and chronic exposures, the dose-severity relationships are limited according to the nature and detail of the available data on endothall. The proposed acute and chronic dose-severity relationships are summarized in Table 8. Table 8 is organized into four columns: dose, the corresponding hazard quotient, a verbal description of the effect, and the reference. All acute hazard quotients are based on the surrogate acute RfD of 0.094 mg/kg bw (Section 3.3.2), and all chronic hazard quotients are based on the chronic RfD of 0.007 mg/kg bw/day (Section 3.3.3). While these values are not human doses in the sense that they have or can be verified experimentally, these RfDs are interpreted as doses at or below which no adverse effects would be expected in the most sensitive humans.

For acute exposures, the dose-severity relationship is based primarily on lethality. As discussed in Section 3.1.4, the case report by Allender (1983) of a suicidal ingestion of endothall clearly indicates that a dose of about 92 mg/kg bw will be lethal. In the absence of any additional human data, especially on non-lethal exposures, the dose of 92 mg/kg bw should not be viewed as an *approximate lethal dose* or *minimal lethal dose*. The LD₅₀ data on experimental mammals clearly indicate that doses in the range of 28.5 mg/kg bw to about 50 mg/kg bw are clearly lethal to experimental mammals and would probably be lethal to humans. It seems likely that the minimal lethal dose or potentially lethal dose in humans would be less than 28.5 mg/kg bw and perhaps substantially less than this dose. Based on the available data, however, the minimum or potentially lethal dose in humans cannot be characterized further. At the lower end of the dose-severity scale, the only proposed dose greater than the RfD is 0.6 mg/kg bw/day. This dose is based on the LOAEL from the study used to derive the acute RfD (Trutter 1993b) in which decreased pup weight was noted at 60 mg/kg bw. Using an uncertainty factor of 100, the dose of 0.6 mg/kg bw is suggested as a dose unlikely to be associated with overt toxicity in humans. The gaps between 0.6 mg/kg bw and the clearly lethal dose of 28.5 mg/kg bw is substantial, and the nature of potential risks in this range is indeterminate.

For chronic exposures, the dose-severity relationships are less detailed. The chronic RfD of 0.02 mg/kg bw/day proposed by U.S. EPA/ORD (1991) and U.S. EPA/ODW (1992) can be used to suggest that HQ values of up to about 3 – i.e., $0.02 \text{ mg/kg bw/day} \div 0.007 \text{ mg/kg bw/day}$ – might not be associated with any adverse effects in humans. The only other proposed dose is 0.06 mg/kg bw, based on the chronic dog study used by U.S. EPA/ORD (1991) and U.S. EPA/ODW (1992) in which adverse effects on the gastrointestinal tract were noted at 6 mg/kg bw. The estimated human equivalent dose of 0.06 mg/kg bw/day is derived by dividing 6 mg/kg bw/day by the uncertainty factor of 100 used to derive the RfD. Thus, it seems reasonable to suggest that an HQ of $0.06 \text{ mg/kg bw/day} \div 0.007 \text{ mg/kg bw/day} \approx 6.57$ – could be associated with adverse effects in humans.

3.4. RISK CHARACTERIZATION

3.4.1. Overview

The risk characterization for workers and members of the general public are similar in that high target concentrations for endothall may result in exposure levels greater than those considered acceptable. The risk characterizations for workers and members of the general public, however, differ substantially in terms of the sources of uncertainty.

For workers, uncertainty in the risk characterization is dominated by the assumptions used in the exposure assessment for routine exposures associated with aquatic applications (Section 3.2.2.1). The key assumption, adopted from U.S. EPA/OPP, is that workers will handle endothall in a manner that will limit dermal exposures because endothall is a severe skin irritant. Unlike the U.S. EPA/OPP, the current Forest Service risk assessment does quantitatively consider dermal exposures. Nonetheless, the exposure assessment for workers result in much lower estimates of dose than those for other aquatic pesticides covered in Forest Service risk assessments. The hazard quotients for workers are given based on both the acute and chronic RfDs. Based on the chronic RfD, all HQ values are below a level of concern for treatments of up to 150 acre-feet at target concentrations of up to 0.1 mg/L. Higher application rates lead to upper bound HQ values in the range of 1.1 to 16 over treatment volumes of 25 acre-feet to 150 acre-feet. At 5 mg/L, the maximum target concentration for Hydrothol formulations, the treatment of 10 acre-feet leads to an upper bound HQ of 1. Based on the acute RfD, the HQ values are at or below the level of concern (HQ=1) for the target concentrations of up to 5 mg/L and treatment volumes of up to 125 acre-feet.

For liquid formulations, accidental dermal exposure scenarios are derived for endothall. For exposure periods of 1-hour, all of these accidental dermal exposures result in HQs that exceed the level of concern—i.e., upper bound HQs from 2 to 18. While these exposure scenarios are of concern, the assumption used for general worker exposures may also apply to accidental dermal exposures. In other words, the dermal irritancy of endothall may be such that workers would not tolerate—i.e., would take mitigating measures—prolonged dermal exposures to endothall.

The risk characterization for workers also considers accidental exposure of the eyes to endothall formulations. Endothall is a severe eye irritant, and it is likely that eye contact with endothall formulations would lead to severe eye irritation. In an ocular irritation study, four of six rabbits treated with technical grade endothall died. This result may raise concern that ocular exposure to endothall formulations could cause severe eye irritation and perhaps systemic toxicity, which could be life-threatening. For endothall, the use of protective eyewear by workers should be rigorously enforced and monitored; however, in the event of accidental exposure, the eyes should be irrigated as soon as possible to minimize eye irritation and reduce the potential for systemic toxic effects.

For the general public, the only exposure scenarios of concern involve the consumption of contaminated water. Under a set of standard exposure assumptions used in most Forest Service risk assessments, accidental spills of large amounts of liquid formulations

are of greatest concern and could lead to life-threatening exposure levels in young children. These scenarios are not constructed to assess the likelihood of this risk but are intended to serve as guidance to the Forest Service in the event of a large spill. Clearly, aggressive mitigation to reduce the possibility of human exposure after an accidental spill would be justified.

At a target concentration of 1 mg/L, non-accidental acute exposures associated with drinking contaminated water lead to an upper bound HQ of 1.2. For this scenario, the HQs are linearly related to the target concentration. Thus, a target concentration at or below about 0.8 mg/L would be associated with acute non-accidental HQ values below the level of concern (HQ=1). The maximum target concentration for Aquathol formulations, 3.5 mg/L, would be associated with an upper bound HQ of about 4. The maximum target concentration for Hydrothol formulations, 5 mg/L, would be associated with an upper bound HQ of about 6. All of these non-accidental acute HQs are undesirable; yet, they are substantially below doses that would be clearly associated with life-threatening toxicity.

For longer-term exposures associated with the consumption of contaminated water, the HQs are 0.2 (0.01– 2) at a target concentration of 1 mg/L. Only the upper bound HQ exceeds the level of concern. At the maximum target concentration of 5 mg/L, the upper bound HQ would be 10. The upper bound HQ for this scenario, however, is based on an endothall half-life of 30 days in surface water. Even as a *worst case* exposure scenario, it seems extremely unlikely that individuals would drink the contaminated water, which would be stagnant and polluted with putrid vegetation.

3.4.2. Workers

3.4.2.1. General Exposures

The amount of endothall to which a worker will be exposed depends on the amount of endothall applied, which, in turn, depends on the target concentration and the volume of water to be treated. The EXCEL workbooks that accompany this risk assessment are based on a target application rate of 1 mg/L applied to one-hundred million liters of water—i.e., about 81 acre-feet. As indicated in Worksheet E02 of these workbooks, the central estimate of the hazard is 1.2 with a range of 1.0 to 1.7. As discussed in Section 3.3.5 (Dose-Severity Relationships), the central and upper bound of these HQ values are above the level of concern but it is not clear that exposures associated with these HQ values would be associated with adverse effects. As detailed in Worksheet E01, the doses associated with these HQ values are approximately 0.009 (0.007 – 0.01) mg/kg bw/day, below the chronic RfD of 0.02 mg/kg bw/day proposed by U.S. EPA/ORD (1991) and U.S. EPA/ODW (1992).

As discussed in the exposure assessment for workers, worker exposures are dependant the amount of endothall that is handled and this value, in turn, is dependant on the target concentration and the volume of water that is treated. The HQs for a much broader range of applications are given in Table 9. This table is taken from Attachment 5, a custom EXCEL workbook that details the calculation of the HQ values. Table 9 covers target concentrations of 0.05 ppm to 5 ppm, the range of labeled application rates for Hydrothol

formulations. The range of application rates for Aquathol formulations—i.e., 0.35 ppm to 3.5 ppm a.e.—is indicated by a rectangular area within Table 9. HQs are given across this range of application rates for treatment volumes of 1 acre-foot to 300 acre-feet. The upper bound of 300 acre-feet is given only for illustration. Based on the discussion of application practices in U.S. EPA/OPP (2005j), the maximum amount of water that a worker might treat in 1 day probably would not exceed 150 acre-feet. Table 9 is divided into three sections giving the central estimates, lower bounds, and upper bounds of the HQ values.

All HQs in Table 9 are based on the chronic RfD of 0.007 mg/kg bw/day. As illustrated in Table 9, the upper bound of the HQ for workers treating up to 150 acre-feet would be below the level of concern at target concentrations of up to about 0.1 ppm. Higher application rates lead to upper bound HQ values in the range of 1.1 to 16 over treatment volumes of 25 acre-feet to 150 acre-feet. At 5 mg/L, the maximum target concentration for Hydrothol formulations, the treatment of 10 acre-feet leads to an HQ of 1. As indicated in Table 9, the maximum target concentration for Aquathol formulations (3.5 mg/L) leads to an upper bound HQ of 1.8 at a treatment volume of about 25 acre-feet. Because the volume of water is directly proportional to the amount handled, the treatment volume leading to an HQ of 1 for a target concentration of 3.5 mg/L would be about 14 acre-feet [$25 \text{ acre-feet} \div 1.8 \approx 13.88 \text{ acre-feet}$].

As noted in Section 3.3.4, U.S. EPA/OPP (2005a) also uses a short-term toxicity value that is functionally equivalent to the surrogate acute RfD of 0.094 mg/kg bw (Section 3.3.2). The use of an acute toxicity value for workers could be appropriate in instances where the workers would apply endothall only once in a given season. Although using acute toxicity values for general worker exposures is not customary in Forest Service risk assessments, this approach is illustrated in Table 10. As with Table 9, Table 10 is taken from Attachment 5, a custom EXCEL workbook that details the calculation of the HQ values. As indicated in Table 10, only one of the HQ values at treatment areas of up to 150 acre-feet exceeds the level of concern (HQ=1). This exceedance involves the maximum target concentration for Hydrothol formulations (5 ppm) at a treatment volume of 150 acre-feet.

The risk characterization for workers is dominated by uncertainties in the exposure assessment. As detailed in Section 3.2.2.1, the current Forest Service risk assessment for endothall defers to the U.S. EPA/OPP (2005e) in selecting the study from PHED on which the worker exposure is based. Unlike the U.S. EPA/OPP, however, the current Forest Service risk assessment considers both inhalation and dermal exposures. Nonetheless, the worker exposure rates for endothall are not based on the same study (Nigg and Stamper 1983) used in previous Forest Service risk assessments for other aquatic pesticides – i.e., 2,4-D, fluridone, and rotenone. The study by Nigg and Stamper (1983) is not considered appropriate for endothall because endothall can be a severe skin irritant. Thus, consistent with U.S. EPA/OPP (2005e), the current Forest Service risk assessments is based on the general assumption that workers will handle endothall or any severe skin irritant much more carefully than other pesticides that are not skin irritants. As a consequence of this assumption, signs of dermal irritation in any worker would be

an indication that proper worker protection measures are not being employed and that the worker may be at risk of systemic toxic effects.

3.4.2.2. *Accidental Dermal Exposures*

Table 11 provides an overview of the HQs for worker accidental exposure levels. As discussed in Section 3.2.2.2, four accidental exposure scenarios are used for handling liquid formulations of endothall: wearing contaminated gloves for 1 minute, wearing contaminated gloves for 1 hour, spilling the formulation onto the hands, and spilling the formulation onto the lower legs. The hazard quotients are calculated as the estimate of the absorbed dose divided by the surrogate acute RfD.

For each of these exposure scenarios, the absorbed dose is directly proportional to the concentration of endothall in the formulation. Thus, the HQs for Aquathol (3 lb a.e./gallon) are higher than those for Hydrothol (2 lb a.e./gallon) by a factor of 1.5. The 1.5 ratio is not reflected exactly for all exposure levels summarized in Table 11 because of rounding rules used to calculate HQs.

The exposure scenario associated with wearing contaminated gloves for 1 minute results in HQs below the level of concern. All other exposure scenarios result in HQs that exceed the level of concern at least at the upper bound. The highest HQs are associated with wearing contaminated gloves for 1 hour. The upper bound HQs for these scenarios are 18 for Aquathol and 12 for Hydrothol. As discussed in Section 3.3.5, the systemic effects which might be associated with these HQs cannot be characterized. As summarized in Worksheet E01 of the EXCEL workbooks for these formulations, the doses associated with these upper bound exposure levels are about 1.7 mg/kg bw for Aquathol and 1.1 mg/kg bw for Hydrothol. These dose levels are below the lowest reported LD₅₀ for endothall in mammals (i.e., 28.5 mg/kg bw) by a factor of more than 16 for Aquathol [$28.5 \text{ mg/kg bw} \div 1.7 \text{ mg/kg bw} \approx 16.76$] and a factor of almost 26 for Hydrothol [$28.5 \text{ mg/kg bw} \div 1.1 \text{ mg/kg bw} \approx 25.91$].

For endothall, the relevance of the 1-hour exposure period in accidental exposure scenarios may be questioned. As discussed in Section 3.2.2.1, U.S. EPA/OPP (2005j) reasons that dermal exposures to endothall will be *self-limiting*. While this assumption is not used in the current risk assessment, endothall may be a severe skin irritant and it is possible that workers would not tolerate an exposure period of one-hour. If this is the case, it is not likely that workers will absorb sufficient amounts of endothall to cause systemic toxic effects.

Accidental exposure scenarios for granular formulations of endothall are not quantified. As discussed in Section 3.2.2.2, the limited acute toxicity data suggest that the dermal toxicity of granular formulations of endothall is less than that of liquid formulations. While somewhat speculative, it is likely that the lesser toxicity of the granular formulations reflects the lesser bioavailability of granular formulations due to binding of endothall with the granular matrices of the granular formulations.

3.4.3.3. Accidental Ocular Exposures

Many pesticides cause eye irritation. Unlike systemic toxicity, the risks associated with accidental exposure of the eyes of workers are addressed qualitatively and HQs are not derived. Nonetheless, the introduction of any chemical in granular or liquid form into the eye should be avoided during the application of any pesticide.

Eye irritation is a particular concern for endothall. As discussed in Section 3.1.11.3 (Ocular Effects), the eye irritation study by Mallory (1991) using technical grade endothall applied to the eyes of rabbits reports both severe eye irritation as well as death in four of six rabbits tested. The dosing of each rabbit involved placing 100 mg of endothall into one eye. This exposure would be associated with doses of about 36 mg/kg bw to 45 mg/kg bw. Based on the summary of Dykstra (1978) another eye irritation study with technical grade endothall noted mortality in three of six rabbits at a dose of about 44 mg a.e./kg bw (Section 3.1.11.3). It is plausible that these doses could have been lethal.

Workers are the group with the greatest potential for ocular exposure to endothall. Workers, however, will not handle technical grade endothall; instead, they will handle endothall formulations. The bibliography for the RED on endothall (U.S. EPA/OPP 2005a) cites eye irritation studies with Aquathol K (MRIDs 78207, 36566, 42338903), Aquathol Super K (MRID 44320106), Hydrothol 191 liquid (MRIDs 36559 and 84474), and Hydrothol 191 Granular (MRIDs 36578 and 78218). While MRID studies are not cited in the internal U.S. EPA/OPP review by Dykstra (1978) it seems likely that at least some of these MRIDs are included in the Dykstra (1978) summary. As discussed in Section (3.1.11.3) and summarized in Appendix 1 (Table 7), one eye irritation study in rabbits at a dose of about 10 mg a.e./kg bw also resulted in mortality.

In the review of registrant submitted eye irritations studies, Dykstra (1978) offers the following commentary:

That the rabbit may be hypersensitive to endothall is a distinct possibility. The rat has been shown to be much more resistant. Thus the question remains open whether the rat or the rabbit reflects man's sensitivity to this product. The lack of toxicological accidents under field conditions suggests that the rabbit may very well be hypersensitive.

- Dykstra 1978, p. 1

The extent to which the above statement reduces concern for potential effects in humans is limited. Dykstra (1978) does not summarize any eye irritation studies in rats; moreover, summaries of such studies were located in the materials reviewed in the preparation of the current Forest Service risk assessment. In an inhalation toxicity study on an Aquathol granular formulation using rats, Dykstra (1978) does note that eye membrane irritation was observed in rats. It is not clear, however, if this irritation was attributable to endothall or simply the irritant effects that might be expected in air exposures to any nuisance dust.

Another pattern suggested in the summary by Dykstra (1978) may have a greater impact on the risk characterization. As summarized in Appendix 1 (Table 7), Dykstra (1978) notes that the rabbits that died in the study with technical grade endothall were those whose eyes were not washed. Typically, in eye irritation studies, the treated eyes in half of the animals are irrigated after a brief period of time. This practice is intended to mimic a situation in which a human might accidentally splash a compound into the eyes and then take rapid remedial action by flushing the eyes. In the study with Hydrothol 191 liquid, the summary by Dykstra (1978) does not note that eyes were washed. Nonetheless, death was observed in only three of six rabbits. While somewhat speculative, it seems likely that the eyes of the other rabbits were washed shortly after instillation. In any event, it is clearly reasonable to assert that washing eyes immediately after ocular instillation would reduce the likelihood of both serious eye damage and systemic toxicity.

All product labels for endothall indicate that workers should use protective eyewear. This is a common and sensible practice in the handling and application of any pesticide. For endothall, the use of protective eyewear should be rigorously enforced and monitored. In the event of an accidental exposure to the eyes, the eyes should be irrigated as soon as possible to minimize eye irritation and reduce the potential for systemic toxic effects; furthermore, the individual should receive prompt medical care. These practices are prudent with any chemical but may be particularly important in the use of endothall.

3.4.3. General Public

The risk characterization for members of the general public exposed to endothall is summarized quantitatively in Worksheet E04 of the EXCEL workbooks that accompany this risk assessment. As with workers, the quantitative risk characterizations are expressed as HQs. Acute HQs are based on the surrogate acute RfD of 0.094 mg/kg/day (Section 3.3.2), and longer-term HQs are based on the chronic RfD of 0.007 mg/kg/day (Section 3.3.3).

3.4.3.1. Accidental Exposures

For aquatic applications of pesticides, the only exposure scenarios considered involve an accidental spill of the pesticide into a body of water. Exposures are based on water consumption as well as the consumption of contaminated fish, as discussed in Sections 3.2.3.4.3 and 3.2.3.5. The HQs associated with these scenarios are summarized in Table 12.

The scenario of greatest concern involves a child who consumes water contaminated with endothall as the result of an accidental spill. As indicated in Table 12, the highest HQ is 336, the upper bound of the HQ associated with the accidental spill of Aquathol K. The upper bound HQ for Hydrothol 191 liquid is 218, which reflects the lower concentration of endothall in the Hydrothol 191 liquid formulation (≈ 2 lbs. a.e./gallon) compared with Aquathol K (≈ 3 lbs a.e./gallon). The upper bound HQ for the granular formulations is 44, which reflects differences in the nature of the spill scenario for granular formulations.

The accidental spill scenarios, are standard in all Forest Service risk assessments, are used to suggest the importance of mitigation measures in the event of an accidental spill. These scenarios are based on a spill into a small pond—i.e., a surface area of 1000 m² and a depth of 1 m. Nonetheless, spills into a larger body of water would result in local areas of high concentrations near the spill site prior to complete mixing, which is one of the reasons that a small pond is used for this exposure scenario.

For endothall, the spill scenario clearly suggests that aggressive mitigation measures are justified in the event of an accidental spill. The HQ of 336 is associated with an exposure that is above the lowest reported LD₅₀ value in mammals (Table 8) and the HQ of 218 is associated with an exposure equivalent to about 70% of the lowest reported LD₅₀ value in mammals. Thus, in the event of a severe spill, the consumption of contaminated water by a small child could be life threatening. The lower bounds of the HQs for this scenario range from 4 to 14. While there is no basis for asserting that these exposures would be life threatening, the exposures would clearly justify mitigation.

The other accidental exposure scenarios are associated with the consumption of contaminated fish. These exposure scenarios lead to much lower HQs because endothall is not likely to bioconcentrate (Section 3.2.3.5). Given the high HQs for the consumption of contaminated water, the lower HQs for the consumption of contaminated fish do not lessen concern for accidental spills.

3.4.2.2. Non-accidental Exposures

3.4.2.2.1. Peak Concentrations

The risk characterization for non-accidental exposure scenarios given in the EXCEL workbooks that accompany this risk assessment are based on a target concentration of 1 mg/L (1 ppm). Because of the manner in which these exposure scenarios are constructed, the HQs are directly proportional to the target concentration.

For acute non-accidental exposures, the only exposure scenario that approaches a level of concern is the exposure scenario for the consumption of treated water by a small child. At a target concentration of 1 mg/L, the HQ for this scenario is 0.8 (0.5–1.2). Thus, in terms of the upper bound, an HQ of 1 would result at an application rate of about 0.83 mg/L. In terms of the lower bound, an HQ of 1 would be reached at an application rate of 2 mg/L. At the maximum application rate for Aquathol formulations, 3.5 mg/L, the HQs would be 2.8 (1.75–4.2). Typically, these HQs would be rounded to 3 (1.8–4). At the maximum application rate for Hydrothol formulations, 5 mg/L, the HQs, after rounding, would be 4 (3–6).

As summarized in Table 8, the maximum HQ of 6 is associated with the LOAEL from the study on which the acute RfD is based. An HQ of 6 is a factor of about 50 below the lowest reported LD₅₀ in experimental mammals. While these relationships do not suggest that an HQ of 6 should be viewed as acceptable, the upper bound HQs are substantially below dose levels associated with life-threatening toxicity.

3.4.2.2.2. Longer-term Concentrations

As with acute non-accidental exposures, the water consumption scenario is the only chronic exposure scenario that exceeds the level of concern. At a target concentration of 1 mg/L, the HQs are 0.2 (0.01–2). The variability in the HQs for this longer-term scenario is much greater than that for the acute scenario, because the chronic scenario considers the variability in the likely degradation and dissipation of endothall in surface water. As discussed in Section 3.2.3.4.2, the central estimate of the half-life of endothall in surface water is taken as 3 days with a range from 0.3 to 30 days.

The range of half-lives in surface water represents very different conditions. The lower bound half-life of 0.3 days would likely apply to situations in which partial applications are made to surface water or in cases of high water turnover rates in which dissipation is the primary mechanism in decreasing the endothall concentration in water. Under these conditions, the HQ of 0.01 at a target concentration of 1 mg/L corresponds to an HQ of 0.05 at 5 mg/L. In other words, in situations in which endothall is likely to dissipate rapidly from surface water, there is no plausible basis for suggesting that adverse effects are likely from the longer-term consumption of treated water.

The central estimate of the HQ of 0.2 at a target concentration of 1 mg/L is based on a half-life of 3 days. As discussed in Section 3.2.3.4.2, this half-life would apply in situations in which microbial decomposition of endothall is the predominant mechanism in decreasing the endothall concentration in water. In this situation, the maximum target application rate for Hydrothol formulations, 5 mg/L, would lead to an HQ of 1—i.e., a dose that is approximately equal to the chronic RfD. While this exposure would approach the level of concern, there would be no basis for asserting that adverse effects are likely.

The upper bound estimate of the HQ of 2 at a target concentration of 1 mg/L is based on a half-life of 30 days. As also discussed in Section 3.2.3.4.2, it is not likely that first-order half-lives on the order of 30 days would be observed in field applications. Instead, the 30 day half-life is intended to account for field observations indicating that endothall concentrations may remain relatively constant for weeks after application and then begin to decline rapidly (Ameel et al. 1997; Holmberg and Lee 1976; Simsiman and Chesters 1975). This biphasic pattern would most likely occur in situations in which dense vegetation is killed by endothall and the decay of the vegetation results in anaerobic conditions which inhibit the degradation of endothall by microorganisms. Under these conditions, application rates in excess of 0.5 mg/L would be associated with HQs greater than 1. While this may be viewed as a *worst case* exposure, it seems reasonable to suggest that the likelihood of individuals actually drinking the contaminated water would be low. For these worst-case exposures, the surface water would be stagnant and would contain a substantial amount of putrid vegetation.

3.4.2.2.3. Partial vs. Whole Lake Treatments

An additional reservation with the longer-term HQs based on a half-life of 30 days involves the practice of partial applications. As noted in Section 2, Aquathol formulations may be applied to whole lakes at concentrations of up to 3.5 mg a.e./L. In

other cases, Aquathol formulations may be applied only to lake margins or discrete areas within the lake. More explicit limitations are placed on Hydrothol formulations which may not be used in whole lake applications at concentrations greater than 1 mg a.e./L. In applications of Hydrothol formulations at target concentrations greater than 1 mg a.e./L no more than 1/10th of the water surface area may be treated at one time.

In any partial lake or pond application, the use of the 30-day upper bound for the half-life of endothall in surface water will probably overestimate risk, and the overestimate could be substantial. As discussed in the previous subsection, the upper bound value of 30 days is based on a very conservative approach used by the EPA, which multiplies an experimental half-life by a factor of 3. While this may be a reasonable approximation for worst-case conditions in which the degradation of endothall is suppressed and dissipation minimal, partial lake or pond treatments will, by definition, allow for the dissipation of endothall to untreated areas of the lake. Consequently, the upper bound HQs may not be relevant for partial lake applications.

3.4.4. Sensitive Subgroups

Both the acute and chronic RfDs for endothall used in the current Forest Service risk assessment are based on reproductive effects (Section 3.3). By definition, pregnant women and, more generally, any women of child-bearing age could be classified as a potentially sensitive subgroup. This group could include workers as well as members of the general public. Because the current risk assessment applies RfDs based on a reproductive toxicity study to all exposure scenarios for workers and members of the general public, this subgroup is explicitly considered in the current risk assessment.

There is no information to suggest that other specific groups or individuals may be especially sensitive to the systemic effects of endothall. Endothall is an irritant to the portal entry—i.e., the gastrointestinal tract on oral exposures, the skin on dermal exposures, and the eyes on ocular exposures. Some subpopulations with diseases of the gastrointestinal tract, skin, or eyes, might be more sensitive to endothall than are members of the general population.

In addition, it is obvious that any individuals with a severe disease or individuals who are in generally poor health may be more sensitive than others to any form of stress, including stresses associated with pesticide exposure.

3.4.5. Connected Actions

Considerations of connected actions are required under NEPA (National Environmental Policy Act). The Council on Environmental Quality (CEQ), which provides the framework for implementing NEPA, defines connected actions (40 CFR 1508.25) as actions which occur in close association with the action of concern; in this case, the use of endothall as proposed in Section 2. Actions are considered to be connected if they: (i) automatically trigger other actions which may require environmental impact statements; (ii) cannot or will not proceed unless other actions are taken previously or simultaneously, and (iii) are interdependent parts of a larger action and depend on the

larger action for their justification. Within the context of this assessment of endothall, “connected actions” include actions or the use of other chemicals which are necessary and occur *in close association* with use of endothall.

The use of inerts and adjuvants as well as the occurrence of impurities and metabolites would be classified as connected actions under the CEQ definition. As discussed in detail in Section 3.1.14 (Inerts and Adjuvants), adjuvants are not used with endothall but there is little information concerning the identity or toxicity of the inerts in endothall formulations. The very limited acute inhalation data on endothall (Section 3.1.13) suggests that the formulations may be more toxic than technical grade endothall with respect to inhalation exposure. This suggestion is a concern in the risk assessment for workers because the exposure assessment is based on inhalation exposures (Section 3.2.2.1); whereas, the dose-response assessment is based on oral exposures (Section 3.3). In the absence of additional information on the inhalation toxicity of formulations relative to technical grade endothall, this concern cannot be addressed further.

3.4.6. Cumulative Effects

Cumulative effects may involve either repeated exposures to an individual agent or simultaneous exposures to the agent of concern (in this case endothall) and other agents that may cause the same effect or effects by the same or a similar mode of action. Under the Food Quality Protection Act (FQPA), the U.S. EPA is required to consider cumulative effects.

In the RED on endothall, the U.S. EPA makes the following assessment:

The Agency has found no information indicating endothall shares a common mechanism of toxicity with other substances. Endothall does not appear to produce a toxic metabolite produced by other substances. Therefore, for the purposes of tolerance reassessment and a decision on reregistration eligibility, EPA has not assumed that endothall shares a common mechanism of toxicity with other compounds. In the future, if additional information suggests endothall shares a common mechanism of toxicity with other compounds, additional testing may be required and a cumulative assessment may be necessary.

- U.S. EPA/OPP (2005a, pp. 1-2)

While not explicitly stated in the above quotation, the statement is focused on pesticide tolerances and the term *other substances* appears to refer to *other pesticides*—i.e., compounds regulated by U.S. EPA/OPP. As discussed in Section 3.1.2, the mechanism of action of endothall at the cellular level involves the inhibition of a protein phosphatase. This mechanism of action is also displayed by cantharidin, a natural toxin produced by some beetles, as well as a number of cantharidin analogues. These agents, however, are not pesticides and would not fall under the EPA’s area of concern for cumulative effects.

More generally, endothall is an irritant, as are many other pesticides and other chemical compounds encountered or used by individuals who may also be exposed to endothall. For example, aqueous solutions of sodium hypochlorite (commonly referred to as *bleach*) are also irritants to the skin, eyes, and respiratory tract (SERA 2009b). While the mechanism of action of bleach at the molecular level is not the same as endothall, both agents will cause gross irritant effects. Thus, individuals who use or are exposed to other chemicals that cause substantial irritation to the skin, eyes, or respiratory tract could be at greater risk of exposures to endothall, compared with other individuals.

4. ECOLOGICAL RISK ASSESSMENT

4.1. HAZARD IDENTIFICATION

4.1.1. Overview

Mammals and birds are likely to be exposed to endothall via the consumption of contaminated water. Based on acute LD₅₀ values in rats, endothall is classified as *highly toxic* to mammals. In addition, endothall appears to be more toxic to dogs than to rodents, probably because dogs are less able than rodents to excrete weak acids. Birds appear to be less sensitive to endothall than mammals. Gavage studies in birds are of limited use in quantifying toxicity because birds will regurgitate endothall shortly after dosing. Based on dietary studies, however, endothall is classified as *practically non-toxic* to birds. No significant exposures are anticipated in terrestrial invertebrates, terrestrial plants, and terrestrial microorganisms.

For most groups of aquatic organisms, Hydrothol formulations appear to be much more toxic than Aquathol formulations. Based on the most sensitive species, Hydrothol formulations are more toxic than Aquathol formulations by factors of about 400 in fish, 2500 in aquatic invertebrates, and 20,000 in algae. The reason(s) for the greater toxicity of Hydrothol formulations is not clear. Based on an early study in fish using the mono-amine and di-amine salts of endothall, it appears that the greater toxicity of the amine moiety in Hydrothol formulations accounts for the greater toxicity of Hydrothol formulations to fish. Aquatic macrophytes, however, do not appear to be substantially more sensitive to Hydrothol formulations than to Aquathol formulations. Based on bioassays of both Aquathol and Hydrothol formulations in a standard test species (*Lemna gibba*), Aquathol formulations appear to be more toxic than Hydrothol formulations in terms of the NOEC but equitoxic in terms of the EC₅₀s. There are numerous efficacy studies on Aquathol and Hydrothol formulations; however, these studies are not easily compared. Nonetheless, the efficacy studies conducted with macrophytes generally indicate that both formulations offer similar levels of control.

4.1.2. Toxicity to Terrestrial Organisms

4.1.2.1. Mammals

As summarized in Section 3.1, the hazard identification for human health effects is based almost completely on data from experimental mammals. Thus, the hazard identification for species of mammalian wildlife is essentially identical to that for humans. Endothall is a severe irritant; accordingly, excessive exposures to endothall are most likely to be associated with portal of entry effects—i.e., damage to the gastrointestinal tract after oral exposure, skin irritation, which may be severe, after dermal exposure, and irritation to the respiratory tract after inhalation exposure. Because endothall is used only as an aquatic herbicide in Forest Service applications, the only significant exposures are likely to involve the consumption of contaminated water, and the most plausible effects of exposure are likely to involve irritation of the gastrointestinal tract.

For many chemicals, systematic or allometric relationships are apparent between body weight and toxicity (e.g., Boxenbaum and D'Souza 1990). For some chemicals, larger mammals are more sensitive than smaller mammals; for other chemicals, the opposite relationship is true. For endothall, the available acute toxicity data are not sufficient to identify allometric relationships among mammals. As summarized in Appendix 1 (Table 7), the early intravenous studies by Strensek and Woodward (1951) suggest that dogs may be somewhat more sensitive than rabbits; however, the differences in toxicity are not well quantified—i.e., the studies did not involve statistical estimates of LD₅₀ values. On the other hand, as discussed in Section 3.1.5, longer-term dietary toxicity values suggest that dogs are more sensitive than rats and mice; moreover, there is a plausible biological basis for the greater degree of sensitivity observed in dogs, which is that dogs have a limited capacity to excrete weak acids. The sensitivity of dogs to endothall is discussed further in the dose-response assessment (Section 4.3.2.1).

As summarized in Section 3.1.4, the EPA classifies endothall as Category I in terms of acute oral hazard for humans, based on the LD₅₀ value in rats of 44.4 mg/kg bw from the study by Mallory (1991b). The U.S. EPA Ecological Fate and Effects Division (EFED) uses a conceptually similar classification system in ecological risk assessments (SERA 2007a, Table 4-1). Based on the EFED classification scheme, the LD₅₀ value of 44.4 mg/kg bw in rats is used to classify endothall as *Highly Toxic* to terrestrial mammals (U.S. EPA/OPP 2005c, Appendix F, p. vii).

4.1.2.2. Birds

A standard set of toxicity studies submitted to the EPA in support of the registration of endothall are summarized in the EFED ecological risk assessment (U.S. EPA/OPP 2005c). The toxicity studies include single-dose gavage studies (Appendix 2, Table 1), 5-day dietary toxicity studies (Appendix 2, Table 2), and reproductive toxicity studies (Appendix 2, Table 3).

All gavage toxicity studies are summarized very briefly in U.S. EPA/OPP (2005c), and additional information on some of these studies is provided in an EPA review (Turner 1978). Cleared reviews (i.e., DERs) are available on two studies, one on technical grade endothall (Pedersen and Helsten 1992a) and the other on an Aquathol formulation—i.e., the dipotassium salt of endothall (Pedersen and Helsten 1992a). The gavage studies are of limited use in quantitatively assessing the toxicity of endothall to birds, because gavage dosing may induce vomiting. In addition to the vomiting observed in the studies by Pedersen and Helsten (1992a), U.S. EPA/OPP (2005c) notes that vomiting was observed in another gavage study of the amine salt conducted with mallards (MRID 42359601). All of these studies report values between about 62 and 100 mg/kg bw; however, the LD₅₀ values should be regarded as nominal since they were estimated based on the administered dose and do not consider the amount of material regurgitated by the birds. As noted explicitly in the studies by Pedersen and Helsten (1992a,b), birds in all treatment groups vomited within 1-2 hours after dosing. Earlier studies summarized in U.S. EPA/OPP (2005c) and Turner (1978) tend to report higher LD₅₀ values—i.e., in the range of 172-500 mg a.e./kg bw—and vomiting is not noted in the available summaries

of these studies. Based on the gavage studies, the U.S. EPA/OPP (2005c) classifies endothall acid, dipotassium salt, and amine salt as *moderately toxic* to birds.

Acute dietary toxicity studies are available on technical grade endothall as well as formulations containing the dipotassium and amine salts. As summarized in Appendix 2 (Table 2), four cleared reviews are available for these studies (Pedersen 1994a,b; Pedersen and Solatycki 1994a,b), and the information on the remaining studies is taken from U.S. EPA/OPP (2005c) and Turner (1978). Vomiting is not noted in any of the dietary studies. The most consistent signs of toxicity include lethargy, decreased food consumption, and decreased body weight. All of the acute dietary studies yield LC₅₀ values of >5000 ppm formulation for the endothall salts and >5000 ppm for endothall acid. Based on these toxicity values, U.S. EPA/OPP (2005c) classifies endothall acid, dipotassium salt, and amine salt as *practically non-toxic* to birds.

Two reproduction studies are available on endothall acid, one study in mallards (Pedersen and Fletcher 1992) and the other study in quail (Pedersen et al. 1992). Cleared reviews are available on both of these studies. The study on quail indicated no dose-related adverse effects at dietary concentrations of up to 250 ppm. The study in mallards noted decreased hatching at 250 ppm as well as decreased body weights at 10 and 250 ppm but not at 50 ppm. Because of the lack of a dose-response relationship in decreased body weights, U.S. EPA/OPP (2005c) classifies the 50 ppm dose group as a NOAEC.

The open literature includes very little additional information regarding the potential effects of endothall exposure on birds. A brief comment in the early report by Srensek and Woodward (1951, p. 337) notes that: *Domestic fowl were insensitive to doses four times as large as in the dog and cat*. No additional details are provided. Pierce (1968) provides field observations for areas in and around a pond treated repeatedly with endothall (2 ppm) as well as 2,4-D and 2,4,5-T. A brief note in this study states: *A resident family of twelve mallard ducks, eating continually from the pondweeds, appeared to suffer no ill effects*. While these brief and informal comments have limited use in hazard identification, the comments are consistent with the information summarized in U.S. EPA/OPP (2005c), indicates that birds appear to be less sensitive than mammals to potential effects of endothall exposure.

4.1.2.3. Reptiles

A database of toxicity studies in amphibians and reptiles (Pauli et al. 2000) does not include the effects of endothall on reptiles. Furthermore, no other sources of such data were identified in the open literature on endothall. Generally, in the absence of toxicity data concerning reptile exposure to pesticides, the EPA recommends the use of birds as suitable surrogates (e.g., U.S. EPA/OPP 2005c, p. xxiii).

4.1.2.4. Terrestrial Invertebrates

Because only aquatic applications of endothall are considered in the current Forest Service risk assessment, terrestrial invertebrates are not likely to be exposed to significant amounts of endothall; hence, this group of organisms is not considered to be at risk. In the ecological risk assessment for endothall, U.S. EPA/OPP (2005c) cites a study by

Atkins (1981), MRID 44038201, indicating that endothall as well as the amine and dipotassium salts of endothall are *practically non-toxic* to bees. The Atkins study is not further identified in the EPA ecological risk assessment; furthermore, the designated MRID is not cited in the endothall RED (U.S. EPA/OPP 2005a). Endothall is not included in the compendia by Atkins et al. (1975) on the toxicity of pesticides to honeybees. There is no suggestion in other studies in the published literature that endothall is toxic to honeybees (Moffett et al. 1972; Moffett and Morton 1972; Vaughan 1981) or earthworms (Caseley and Eno 1966).

4.1.2.5. Terrestrial Plants (Macrophytes)

As noted in Section 2.2, endothall was initially developed and is still used as a terrestrial herbicide. In addition to the standard battery of toxicity tests on terrestrial plants required by the EPA (U.S. EPA/OPP 2005a,c), there is a substantial amount of open literature regarding the toxicity of endothall to terrestrial plants, which generally focuses on the mechanism of action (e.g., Ehness et al. 1997; MacKintosh et al. 1991, 1994; MacDonald et al. 1993) or efficacy (e.g., Rubin et al. 1980; Simsiman et al. 1976).

Like terrestrial invertebrates, terrestrial plants are not likely to be exposed to significant amounts of endothall during aquatic applications; accordingly, terrestrial plants are not considered to be a group at risk in the current Forest Service risk assessment. One exception may be the use of treated water for irrigation. All product labels for endothall address this issue and indicate that water treated with endothall should not be used for irrigation until 7-25 days after treatment.

4.1.2.6. Terrestrial Microorganisms

Very little information is available on the toxicity of endothall to terrestrial microorganisms. Koch et al. (1993) indicate that the EC₅₀ for growth inhibition of baker's yeast (*Saccharomyces cerevisiae*) is 14 mg/L. The extremely limited information on endothall effects on terrestrial microorganisms is not a substantial issue in the current Forest Service risk assessment which considers only aquatic applications of endothall.

4.1.3. Aquatic Organisms

4.1.3.1. Fish

Studies on the toxicity of endothall to fish are summarized in Appendix 3. The information presented in Appendix 3 is taken from both the open literature and the EFED ecological risk assessment (U.S. EPA/OPP 2005c). Different formats are used to clearly indicate the source of information. Information from the open literature is cited in the standard author/date format—e.g., Johnson and Finley 1980. This citation format is also used for studies with cleared reviews or studies with 1-page summaries in the internal EPA review by Turner (1978). Information taken directly from EPA/OPP (2005c) is cited as the MRID number followed by the author-date citations used in EPA/OPP (2005c).

There is an important distinction between studies for which detailed documentation is available and information that must be taken directly from U.S. EPA/OPP (2005c) with

respect to how well the data can be interpreted. For example, Appendix 3 contains information taken from U.S. EPA/OPP (2005c) indicating LC₅₀ values for Aquathol formulations ranging from 98.1 to 457.6 mg a.e./L for bluegills and from 9.152 to 128.7 mg a.e./L for trout. All of these studies are cited as Mayer (1986), which is further identified as MRID 40098001. The MRID number is not identified further in EPA/OPP (2005c) or listed in the endothall RED (U.S. EPA/OPP 2005a). Moreover, Mayer (1986) is not included in the EPA ECOTOX database (U.S. EPA/ORD 2009). Available citations for Mayer (1986) suggest that it is a review of several aquatic toxicity studies (Section 4.1.3.3). It is likely, albeit unsubstantiated, that the variability in the LC₅₀ values for trout (i.e., a factor of about 14) and bluegills (i.e., a factor of about 4.6) is due to different experimental conditions. Without additional documentation for the Mayer (1986) study, the sources of variability in the LC₅₀ studies for a given species cannot be characterized further.

Despite the variability in the toxicity data on the Aquathol and Hydrothol formulations to fish, the most striking feature is that Hydrothol formulations (i.e., the mono-amine salt) are much more toxic than Aquathol formulations (i.e., the dipotassium salt). As summarized in Appendix 3, Table 2, several acute bioassays in several species of fish were conducted on Aquathol formulations and the LC₅₀ values range from about 9.1 mg a.e./L for rainbow trout to 457.6 mg a.e./L for bluegills. Both of these LC₅₀ values are taken from EPA/OPP (2005c) and are referenced to MRID 40098001, Mayer (1986). The reported LC₅₀ values for Hydrothol formulations are substantially lower, ranging from 0.02336 mg a.e./L for the emerald shiner (Swabey and Schenk 1963) to 1.5 mg a.e./L for bluegills (MRID 43472801, Bettencourt 1994). Thus, in terms of the upper and lower bounds of the ranges of LC₅₀ values, Hydrothol formulations appear to be more toxic than Aquathol formulations by factors of about 300 [$457.6 \text{ mg a.e./L} \div 1.5 \text{ mg a.e./L} = 305.06$] based on upper bounds and nearly 400 [$9.1 \text{ mg a.e./L} \div 0.02336 \text{ mg a.e./L} = 389.55$] based on lower bounds.

It is not clear from the available toxicological information on fish why the Hydrothol formulations are more toxic than the Aquathol formulations. In general, the amine moiety in the Hydrothol formulations could contribute to the enhanced toxicity of the formulations by either increasing the bioavailability of endothall or by the direct toxicity of the amine moiety. None of the available studies assess the potential impact of the mono-amine moiety to the bioavailability of endothall, and there appear to be no studies regarding the toxicity of the amine moiety to fish. An early study by Hughes and Davis (1962a) does suggest, however, that the amine moiety may be directly toxic to fish. In this study, Hughes and Davis (1962a) report a 24-hour LC₅₀ value of 0.8 mg/L for the mono-amine salt endothall and a 0.3 mg/L 24-hour LC₅₀ for the di-amine salt of endothall. According to the investigators, the amines considered for use in endothall formulations ... *have created considerable interest as piscicides and algicides* (Hughes and Davis 1962a, p. 89). Regardless of why Hydrothol formulations are more toxic than Aquathol formulations to fish, the difference in their degree of toxicity is substantial. Accordingly, as discussed further in Section 4.3.3.1 (the dose-response assessment for fish), different toxicity values are used for the dipotassium and mono-amine salts of endothall.

There is relatively little information on the sublethal effects of endothall. As summarized in Appendix 3, Eller (1969) noted transient damage to gills, liver, and testes in Redear sunfish exposed to 0.3 mg Hydrothol 191/L (0.07 mg a.e./L) or 0.03 mg Hydrothol 191/L (0.007 mg a.e./L) in artificial ponds. Pathological changes in all organs were transient, and no pathology was noted by day 56. The treatment of the ponds involved only a single initial application, and Eller (1969) does not provide any monitoring data for the 112-day observation period.

There is some indication that endothall may have an impact on smolting in anadromous fish. Using an unspecified formulation of endothall, Bouck and Johnson (1979) noted 100% mortality in coho salmon smolts after exposure to 5 mg/L for 60 minutes in freshwater followed by transfer to seawater. In a nominally duplicate test, however, no mortality was observed. In a study conducted with Aquathol K, Liguori et al. (1983) observed increased mortality in juvenile chinook salmon after transfer to saltwater at concentrations of 3 mg formulation/L (≈ 0.858 mg a.e./L) but not at 1.5 mg formulation/L (0.429 mg a.e./L). Using technical grade endothall, however, Serdar and Johnson (1996) noted no effects on smolting at concentrations of up to 5 mg a.e./L. Serdar and Johnson (1996) suggest that the differences in the results obtained by these investigators relative to the results obtained by Liguori et al. (1983) could be explained by the action of inerts in Aquathol K formulations. Conversely, the available data on the acute toxicity of technical grade endothall and Aquathol formulations to aquatic invertebrates do not indicate substantial differences between technical grade endothall and Aquathol formulations (Section 4.1.3.3). While this finding does not exclude the possibility that inerts in Aquathol formulations may affect the ability of anadromous fish to adjust from fresh to salt water, this supposition could be assessed more fully by a matched study using both technical grade endothall and an Aquathol formulation.

Most other aspects of the toxicity of endothall to fish are not remarkable. As with most pesticides, the toxicity of endothall increases with water temperature (Keller et al. 1988b; Mayer and Eilersieck 1986 and 1988). Paul et al. (1994) noted that smaller or younger fish are more sensitive than larger fish to the dipotassium salt of endothall. This is not an uncommon finding and is probably related to the greater surface area per unit body weight of smaller fish, relative to larger fish. In bioassays on the golden shiner, Finlayson (1980) noted that LC_{50} values for Hydrothol 191 are lower (by about a factor of 5) in hard water compared with soft water. On the other hand, consistent or substantial effects of water hardness were apparent in bioassays conducted on goldfish or bluegill and Redear sunfish (Inglis and Davis 1972).

Since fish generally avoid many toxic agents, avoidance is a potential mitigating factor for the exposure of fish to endothall. Berry (1984) found that goldfish exhibit avoidance behavior at endothall concentrations of 17 mg/L of the dipotassium salt or about 12 mg a.e./L but not at a 10-fold lower concentration (about 1.2 mg a.e./L). Similarly, Folmar (1976a) noted a lack of avoidance response in rainbow trout fry exposed to 10 mg Aquathol K/L (about 2.9 mg a.e./L).

Oxygen depletion may be an additional risk factor for fish in water treated with endothall (e.g., Serns 1975; Steucke 1961; Teitt and Maughan 1987) or any other aquatic herbicide. If an herbicide is applied at effective concentrations to a pond or lake with a dense population of aquatic vegetation, the vegetation will die. The decomposition of the dead vegetation will lead to oxygen depletion. Some fish may in turn be killed as a result of oxygen insufficiency. As noted in Section 2, all product labels for Hydrothol and Aquathol formulations contain appropriate language concerning the dangers of oxygen depletion in whole lake or whole pond treatments.

4.1.3.2. Amphibians

There is relatively little information available on the toxicity of endothall or endothall formulations to aquatic-phase amphibians. U.S. EPA/OPP (2005c) cites an LC₅₀ of 1.2 mg formulation/L or about 0.28 mg a.e./L Hydrothol 191 for Fowlers toad (*Bufo woodhousii fowleri*). This LC₅₀ is referenced to Mayer (1986, MRID 40098001). As discussed in the previous subsection, this same MRID is used as a reference to many toxicity values in fish. For the LC₅₀ in Fowlers toad, however, U.S. EPA/OPP (2005c, Appendix F, p. xvi) indicates that the toxicity value is taken from Saunders (1970a), a study from the open literature. Saunders (1970a) reports 24-, 48-, and 96-hour LC₅₀ values of 3.2 (1.7 -5.5) mg formulation/L, 1.8 (0.93-3.2) mg formulation/L, and 1.2 (0.40-3.4) mg formulation/L, respectively. Although Sanders (1970a) does not identify the type of Hydrothol formulation used in the study, U.S. EPA/OPP (2005c) indicates that Sanders was contacted and confirmed that Hydrothol 191 liquid was used in this study.

Reeder et al. (1998) indicates that intersex gonads were not noted in three specimens of cricket frogs (*Acris crepitans*) collected from an endothall-treated pond; however, the study does not include details about the pond treatment. This very brief report on only three specimens is of limited use in hazard identification.

Since amphibians are not a standard test species for pesticide registration, the limited data on the effects of pesticides on amphibians is not uncommon. In the absence of substantial data on amphibian exposures to pesticides, the EPA assumes that fish may be useful surrogates for aquatic life-stages of amphibians (e.g., U.S. EPA/OPP 2005c, p. xxiii).

4.1.3.3. Aquatic Invertebrates

Studies on the toxicity of endothall to aquatic invertebrates are summarized in Appendix 4. As with the corresponding appendix on fish, Appendix 4 includes studies from the open literature as well as the EFED ecological risk assessment (U.S. EPA/OPP 2005c), and the methods used for designating citations are identical to that used in the appendix on fish. While there are only two studies available on the toxicity of endothall acid to fish (Appendix 3, Table 1), there are eight studies available on the toxicity of endothall acid to aquatic invertebrates. The more extensive database on aquatic invertebrates permits a better assessment of the differences in acute toxicity between endothall acid (Appendix 4, Table 1), Aquathol formulations (Appendix 4, Table 2), and Hydrothol formulations (Appendix 4, Table 3). These data clearly indicate that the

Hydrothol formulations—i.e., the mono-amine salt—are much more toxic to aquatic invertebrates than either endothall acid or the Aquathol formulations—i.e., the dipotassium salt.

For endothall acid, the reported 48- or 72-hour EC_{50} values range from 32.5 mg a.e./L in *Daphnia magna* (MRID 71137, Vilkas, 1979) to 151 mg a.e./L in midge larvae (Hansen and Kawatski 1976). These toxicity values span a range of about 5. The study by Hansen and Kawatski (1976) is somewhat unusual in that both EC_{50} values for immobility and LC_{50} values (lethality) are reported. Typically, bioassays on aquatic invertebrates, at least very small invertebrates, do not make a clear distinction between immobility (i.e., EC_{50} values) and lethality (i.e., LC_{50} values). The methodological distinction between EC_{50} and LC_{50} values in the Hansen and Kawatski (1976) study is that immobility was determined at the end of the designated exposure period. Mortality was determined 24-hours after transfer of the organisms from test water to uncontaminated water. In terms of the current Forest Service risk assessment as well as most other ecological risk assessments, immobility is treated as functional mortality because an immobile invertebrate does not have the capacity to survive in the environment.

The 48-hour EC_{50} values for Aquathol K formulations range from 31 mg a.e./L in *Ceriodaphnia dubia* (Nelson and Roline 1998) to 91.23 mg a.e./L in *Daphnia magna* (MRID 00084150, Vilkas, 1979). These values span a range of only about a factor of 3. As with the toxicity values for endothall acid, this range of reported toxicity values is much less than the range of toxicity values for Aquathol formulations in fish—i.e., about a factor of 50 [457.6 mg a.e./L for bluegills \div 9.1 mg a.e./L for rainbow trout]. The range of EC_{50} values for technical grade endothall (i.e., from about 33 to 150 mg a.e./L) is quite similar to the range for Aquathol formulations (from about 31 to 91 mg a.e./L), and this similarity suggests that inerts in Aquathol formulations do not contribute substantially to the toxicity of Aquathol formulations.

As with fish, however, there is no doubt that Hydrothol formulations are substantially more toxic than either technical grade endothall or Aquathol formulations. As indicated in Appendix 4 (Table 3), the EC_{50} values for Hydrothol formulations range from 0.012 mg a.e./L in grass shrimp (Johnson and Finley 1980) to 1.13 mg a.e./L in a freshwater mussel (Keller 1993). This range of reported toxicity values—i.e., about a factor of 94—is much greater than the ranges in toxicity values for fish or the invertebrate toxicity values for technical grade endothall or Aquathol formulations. To some extent, this greater variability is probably attributable to the availability of the Keller (1993) study on the mussel (*Anodonta imbecilis*). The LC_{50} for this species is much higher than the corresponding values for arthropods and this probably reflects the ability of mussels and other bivalves to limit exposure by closing the shells.

Based on the lower bounds of the toxicity values for Aquathol (31 mg a.e./L) and the lower bounds for Hydrothol formulations (0.012 mg a.e./L), Hydrothol formulations are more toxic than Aquathol formulations by a factor of over 2500 [31 mg a.e./L \div 0.012 mg a.e./L \approx 2583]. This range is much greater than the differences based on bioassays in

fish—i.e., from about 300 to 400. Based on the upper bounds of the toxicity values for Aquathol (91.23 mg a.e./L) and the upper bounds for Hydrothol formulations (1.13 mg a.e./L), the differences are much smaller—i.e., about a factor of 80 [$91.23 \text{ mg a.e./L} \div 1.13 \text{ mg a.e./L} \approx 80.7$].

The bioassay in *Ceriodaphnia dubia* by Keller (1988a) indicates that the toxicity of the mono-amine salt of endothall increases with increasing temperature. As discussed in Section 4.1.3.1, the toxicity of endothall also increases with increasing temperature in fish (Keller et al. 1988b; Mayer and Ellersieck 1986 and 1988). Increasing toxicity with increasing temperature is a common relationship and, as discussed further in Section 4.1.3.4.1, this relationship is also evident in aquatic macrophytes.

The species differences in sensitivity to Hydrothol formulations are not entirely intuitive. The most sensitive species are glass shrimp ($EC_{50} \approx 0.0012 \text{ mg a.e./L}$) and *Daphnia magna* ($EC_{50} \approx 0.084 \text{ mg a.e./L}$). The least sensitive organisms are benthic—e.g., mussels, scuds, and stoneflies—with EC_{50} values ranging from 0.5 to 1.13 mg a.e./L. Another free-swimming daphnid, *Ceriodaphnia dubia*, however, has EC_{50} values in the range of 0.12 to 0.33 mg a.e./L, which is close to the EC_{50} values for benthic organisms.

Chronic toxicity data on invertebrates are available for Hydrothol formulations and technical grade endothall. Most of these studies are taken from U.S. EPA/OPP (2005c), and one apparent and important error in the EPA summary requires explicit clarification. As summarized in Appendix 4 (Table 5), U.S. EPA/OPP (2005c) reports a reproductive NOEC in *Daphnia magna* of 0.0159 mg a.e./L. This study is cited as Putt 1993 and is further designated with a MRID number of 43437901. In a tabular summary (U.S. EPA/OPP 2005c, Table F13, p. Appendix F-xv), this study is designated as a formulation of endothall acid. The MRID number cited elsewhere in the document indicates that this study involved the amine salt. Similarly, another study designated as MRID 43007801 and cited as Putt 1993 is summarized as a study on the amine salt (U.S. EPA/OPP 2005c, Table F14, p. Appendix F-xv). A cleared review of MRID 43007801 is available and this study is cited as Putt (1993) in the current Forest Service risk assessment. Putt (1993) is clearly a bioassay on technical grade endothall. Thus, the cited tables from U.S. EPA/OPP (2005c) appear to have reversed the agents used in the two studies.

The chronic toxicity data on invertebrates are consistent with the acute data indicating that Hydrothol formulations are much more toxic than technical grade endothall. In the study on technical grade endothall, Putt (1993) identified 5 mg a.e./L as a NOEC based on mean total weight of offspring. Based on a reanalysis of the data, however, the DER for this study rejects this NOEC and considers 2.2 mg a.e./L as an LOEC. There are two chronic bioassays on Hydrothol 191, one in *Daphnia magna* (MRID 43437901 as discussed above) and the other in *Ceriodaphnia dubia* (Keller et al. 1988a). Both studies yield similar LOEC values: 0.033 mg a.e./L for reproduction in *Daphnia magna* and 0.059 mg a.e./L for the number of offspring in *Ceriodaphnia dubia*. The lower LOEC of 0.033 mg a.e./L for Hydrothol suggests that Hydrothol is more toxic than technical grade endothall by a factor of about 67 [$2.2 \text{ mg a.e./L} \div 0.033 \text{ mg a.e./L} \approx 66.66\dots$]. Although there are no available chronic studies on Aquathol, the similarities in the acute toxicity

data for technical grade endothall and Aquathol suggest that the chronic bioassay on technical grade endothall may be used to assess the longer-term risks of exposures associated with Aquathol formulations.

4.1.3.4. Aquatic Plants

4.1.3.4.1. Macrophytes

Generally, the EPA requires toxicity bioassays on duckweed species, either *Lemna gibba* or *Lemna minor*; accordingly, standard assay protocols were developed for these species (U.S. EPA/OPPTS 1996). For endothall, the standard bioassays were conducted using *Lemna gibba* on both Aquathol K and Hydrothol 191, and for Aquathol K, there is a detailed, cleared review of the bioassay (Hoberg 1992f). For Hydrothol 191, two studies (MRID 44127806 and MRID 44949402) are briefly summarized in the EPA ecological risk assessment for endothall (U.S. EPA/OPP 2005c).

As summarized in Appendix 5 (Table 1), the differences in the toxicity of the two endothall formulations to aquatic macrophytes are insubstantial. The study on Aquathol K reports an EC₅₀ of 610 µg a.e./L, a NOEC of 4.6µg a.e./L, and a LOEC of 9.2 µg a.e./L. For Hydrothol 191, the EC₅₀ values are 430 and 740 µg a.e./L. The average of these two values, 585 µg a.e./L, is quite close to the Aquathol EC₅₀ of 610 µg a.e./L. The NOEC values from the Hydrothol studies on Hydrothol 191 are 50 µg a.e./L (MRID 44127806) and 150 µg a.e./L (MRID 44949402), higher than the NOEC from the Aquathol K study by factors of about 11 [$50 \mu\text{g a.e./L} \div 4.6\mu\text{g a.e./L} = 10.87$] and 33 [$150 \mu\text{g a.e./L} \div 4.6\mu\text{g a.e./L} = 32.61$]. In other words, the relative potency of Aquathol K and Hydrothol 191 formulations, at least to *Lemna*, appear to be about the same in terms of the EC₅₀; yet, Aquathol K appears to be substantially more toxic in terms of the NOEC.

Several efficacy studies, focused primarily on effects in macrophytes, have been conducted on various formulations of endothall (Appendix 5, Table 2). These studies are difficult to compare directly to laboratory bioassays. Many of the studies, particularly those conducted in the 1960s and 1970s, do not specify the nature of the units for the target concentrations—i.e., a.e., a.i., or formulation. In addition, the conditions under which the different efficacy studies were conducted are variable. Consistent with the labeled target concentrations, the efficacy studies indicate that both Aquathol and Hydrothol formulations are effective against a number of macrophytes at application rates ranging from about 1 to over 5 ppm. Some efficacy studies do involve applications of both Aquathol and Hydrothol (i.e., Nelson et al. 2001; Slade et al. 2008). The study by Nelson et al. (2001) suggests that Aquathol K and Hydrothol 191 are effective against salvinia; however, relative potencies cannot be estimated. The more recent study by Slade et al. (2008) suggests that Hydrothol 191 may be somewhat more effective than Aquathol K in the control of sago pondweed. The study by Netherland et al. (2000) indicates that the phytotoxicity of endothall increases with increasing temperature.

4.1.3.4.2. Algae

While there is little indication that the amine salt of endothall is more toxic than the dipotassium salt of endothall to macrophytes, endothall acid and the disodium salt of endothall appear to be essentially nontoxic to algae, while the amine salt of endothall is clearly highly toxic to algae.

Information about the toxicity of endothall acid and the disodium salt of endothall to algae is limited to the study by Walsh (1972). This is the only study on the effects of endothall acid and the disodium salt of endothall cited in the EPA ecological risk assessment (U.S. EPA/OPP 2005c) and the only study identified in the open literature during the preparation of the current Forest Service risk assessment. Walsh (1970) reports EC₅₀ values of 15-50 mg a.e./L to four species of algae for endothall acid (Appendix 5, Table 3). In addition, the study reports EC₅₀ values of 500-1500 mg /L to the same four species of algae for the dipotassium salt of endothall (Appendix 5, Table 4). This corresponds to EC₅₀ values of 355-1065 mg a.e./L, using the a.e/a.i. factor of 0.71 (Table 2).

Numerous algal bioassays were conducted on the toxicity of the mono-amine salt of endothall (Appendix 5, Table 5). About half of the bioassays are from the open literature (Mudge et al. 1986; Ruzycki et al. 1998), while the results of the remaining bioassays are from registrant submitted studies summarized in U.S. EPA/OPP (2005c). As with the toxicity studies on aquatic invertebrates (Section 4.1.3.3) the range of EC₅₀ values in algae is substantial—i.e., from 1.9 µg a.e./L (MRID 44127804) to 1000 µg a.e./L (USDI Bureau of Reclamation, 1964) – spanning a factor of over 500 [$1000 \mu\text{g a.e./L} \div 1.9 \mu\text{g a.e./L} \approx 526.32$]. In terms of the upper and lower bounds of the EC₅₀ values, the mono-amine salt is more toxic than the dipotassium salt by factors of 355 [$355,000 \mu\text{g a.e./L} \div 1000 \mu\text{g a.e./L}$] to over 55,000 [$1065,000 \mu\text{g a.e./L} \div 1.9 \mu\text{g a.e./L} \approx 56,053$]. These differences in toxicity are consistent with the labeling of the two types of formulations—i.e., only Hydrothol formulations (the mono-amine salt) are labeled for the control of algae.

4.1.3.5. Aquatic Microorganisms

Only one study is available on the toxicity of endothall to aquatic microorganisms. Beckmann et al. (1984) treated a pond with the dipotassium salt of endothall at a concentration of 0.3 ppm. This concentration is presumably the a.i. and would correspond to a concentration of about 0.2 mg a.e./L. No substantial impact of exposure was observed on bacterial populations. In laboratory cultures, a concentration of 5 ppm (i.e., $\approx 3.5 \text{ mg a.e./L}$) was associated with transient increases in respiration rates of *Aeromonas hydrophila*, a species of *Pseudomonas*, and *Acinetobacter anitratus*; however, there was no observed adverse effect on a species of *Bacillus*.

4.2. EXPOSURE ASSESSMENT

4.2.1. Overview

The exposure assessments for the ecological risk assessment generally parallel those used for the general public in the human health risk assessment. In other words, the exposure scenarios are similar in the basic assumptions concerning the application of endothall, and the differences in the estimated doses from those in the human health risk assessment are attributable to differences in body size and consumption rates for food or water. Also as in the human health risk assessment, the exposure scenarios for terrestrial vertebrates are a subset of those used in most Forest Service risk assessments. Some exposure scenarios, such as the consumption of terrestrial vegetation, are not relevant to aquatic applications of endothall.

The exposure scenarios for terrestrial wildlife are summarized in Worksheet G01 of the EXCEL workbook that accompanies this risk assessment. The highest exposure scenarios involve the accidental spill of endothall into a small pond. As in the human health risk assessment, the estimated doses associated with the spill scenario vary according to the formulation (Table 6). All non-accidental exposure scenarios are based on the target concentration of 1 mg a.e./L.

Exposure of aquatic organisms to endothall is also taken as the nominal application rate or target concentration. In the EXCEL workbook that accompanies this risk assessment, the maximum application rate of 1 mg a.e./L is used. The consequences of using lower or higher application rates are considered in the risk characterization.

4.2.2. Mammals and Birds

All exposure scenarios for terrestrial animals are summarized in Worksheet G01 in the EXCEL workbooks that accompany this risk assessment (Attachments 1 to 4). As with the exposure assessments for members of the general public (Section 3.2.3), the exposure assessments for terrestrial animals are a subset of those typically included in Forest Service risk assessments. Endothall will be applied directly to surface water; consequently exposure scenarios concerning the consumption of contaminated vegetation or fruit, the direct spray of a small mammal, and the consumption of a sprayed small mammal by a predator are not included in the ecological risk assessment.

While not all standard exposure scenarios are relevant to endothall applications, the section designations for the excluded scenarios are given below as a matter of convenience for individuals who regularly use many different Forest Service risk assessments—i.e., the section designations in all Forest Service risk assessments are consistent.

4.2.2.1. Direct Spray

This scenario is not relevant to aquatic applications.

4.2.2.2. Dermal Contact with Contaminated Vegetation

This scenario is not relevant to aquatic applications.

4.2.2.3. Ingestion of Contaminated Vegetation or Prey

This scenario is not relevant to aquatic applications.

4.2.2.4. Ingestion of Contaminated Water

Since ingestion of contaminated water by terrestrial wildlife is likely to occur, five sets of exposure scenarios, each involving water consumption by a mammal or bird—i.e., a small mammal, a canid, a large mammal, a small bird, and a large bird—are included for an accidental spill (Worksheets F05a to F05e), the peak expected concentration in water (Worksheets F06a to F06e), and the longer-term consumption of contaminated water (Worksheets F07a to F07e).

The accidental spill scenario is identical to that considered in the exposure assessment for members of the general public (Section 3.2.3.4). Also like the exposure assessment for members of the general public, the peak concentration in surface water is taken as the target application rate. Longer-term exposures are considered based on a 90-day average using the target application rate and the estimated dissipation half-lives in surface water of 3 days with a range from 0.3 to 30 days, as discussed in Section 3.2.3.4.2. Although Worksheets F07a and F07b calculate the longer-term doses based on water consumption estimates for a small mammal and a small bird, respectively, both of these worksheets use the longer-term concentrations in water calculated in Worksheet B04b.

The exposure scenarios for contaminated water are based on metabolic water requirements, and the assumption is made that the mammal or bird gets all of its water from the contaminated water body. In most instances, both mammals and birds may obtain a significant fraction of their metabolic water requirements from natural food sources—e.g., vegetation or prey. As discussed further in Section 4.4 (Risk Characterization), these conservative assumptions have no impact on the interpretation of risks associated with non-accidental exposures, because the resulting hazard quotients (HQs) for terrestrial mammals and birds are far below the level of concern.

4.2.2.5. Oral Exposure from Contaminated Fish

The consumption of contaminated fish by a fish-eating bird is handled similarly to the corresponding exposure scenarios for human health (Section 3.2.3.5). As with the exposure scenarios in the human health risk assessment, three specific exposure scenarios are provided based on an accidental spill (Worksheet F08), expected peak concentrations (Worksheet F09a), and expected longer-term concentrations (F09b).

The only exception involves the bioconcentration factor (BCF). In the human health risk assessment, the BCF is taken as 0.08 based on bioconcentration in edible fish tissue (i.e., muscle) under the assumption that most members of the general public will not consume the entire fish. For wildlife, the assumption is made that the entire fish is consumed. Thus, a higher BCF of 0.35 is used based on bioconcentration factors in whole fish (U.S. EPA/OPP 2005c).

4.2.3. Terrestrial Invertebrates

Exposure scenarios for terrestrial plants are not relevant to aquatic applications.

4.2.4. Terrestrial Plants

Exposure scenarios for terrestrial plants are not relevant to aquatic applications.

4.2.5. Aquatic Organisms

Expected peak concentrations to which aquatic organisms will be exposed from the direct application of endothall to water are based on the target concentration; endothall water concentrations from accidental spills, and longer-term concentrations of endothall in water are based on the same values used in the exposure assessment for mammals (Section 4.2.2.4). As in the human health risk assessment, the EXCEL workbook that accompanies this risk assessment is based on the target concentration of 1 mg a.e./L. The consequences of using lower or higher application rates are discussed in the risk characterization (Section 4.4).

4.3. DOSE-RESPONSE ASSESSMENT

4.3.1. Overview

The specific toxicity values used in this risk assessment are summarized in Tables 13, 14, and 15. The derivation of each of the toxicity values is discussed in the various subsections of this dose-response assessment. Table 13 summarizes toxicity values for carnivorous mammals, other mammals, and birds. The same toxicity values are used for both Aquathol (disodium salt) and Hydrothol (mono-amine salt), because the available toxicity data do not suggest a substantial difference in the toxicity of these two salts to terrestrial mammals.

For aquatic organisms, the available toxicity data indicate different degrees of toxicity for the two salts. Accordingly, the dose-response assessments for aquatic organisms are summarized separately: Table 14 for Aquathol formulations and Table 15 for Hydrothol formulations. In general, Hydrothol formulations appear to be much more toxic than Aquathol formulations. The only exception involves aquatic macrophytes. For this group of organisms, Aquathol is more toxic than Hydrothol, at least in terms of NOEC values for sensitive species. For algae, the pattern of toxicity is reversed. Hydrothol formulations are very toxic to algae, while Aquathol formulations are virtually nontoxic.

Because of the nature of the available information on the effects of endothall to aquatic organisms, many of the acute NOEC values derived for both Aquathol and Hydrothol formulations are estimated from LC₅₀ or EC₅₀ values. Following an approach analogous to that adopted by U.S. EPA for the assessment of risks to threatened and endangered species, the general approach to estimating an NOEC is to divide the LC₅₀ or EC₅₀ value by 20. In some cases, however, this approach leads to estimated acute NOEC values that are below experimental chronic NOEC values. In these cases, the chronic NOEC is used as a conservative estimate of the acute NOEC.

4.3.2. Toxicity to Terrestrial Organisms

4.3.2.1. Mammals

4.3.2.1.1. Acute Toxicity Value

Most Forest Service risk assessments adopt the acute toxicity value for mammals from the NOAEL used for the acute RfD, and this approach is maintained in the current risk assessment. As discussed in Section 3.3.2 (Acute RfD), the acute RfD for endothall used in the current Forest Service risk assessment taken from the most recent RfD proposed by U.S. EPA for the reregistration of endothall (U.S. EPA/OPP 2005a). This acute RfD is based on the 9.4 mg/kg bw/day NOAEL for pup weight from the reproduction study in rats by Trutter (1993b). As discussed in Section 3.3.2, the reproduction study by Trutter (1993b) identifies 9.4 mg/kg bw/day as a NOAEL for pup weight. At the next lowest dose, a dietary concentration of 30 ppm, which is equivalent to about 2 mg/kg bw/day, male and female parental rats had gastrointestinal tract lesions. Implicit in the decision by U.S. EPA/OPP (2005a) to use the pup weight NOAEL of 9.4 mg/kg bw as the basis for the acute RfD is that the effect in pups occurred over a relatively brief period of

exposure—i.e., the gestation period of about 15 days. The parental LOAEL of 2 mg/kg bw/day, on the other hand, is associated with the much longer period of exposure of the parental generations during a multigeneration reproduction study—i.e., several months.

While the acute toxicity value of 9.4 mg/kg bw/day may be appropriate for most groups of mammalian wildlife, there is a concern that canids may be more sensitive to endothall than other mammals. As discussed in Section 3.1.3, endothall is a weak acid that appears to be excreted by the kidney. In mammals, this process involves active secretion by the proximal tubules of the kidney. Dogs, however, have a limited capacity to excrete weak acids and are often more sensitive to weak acids than are other mammals (e.g., Timchalk and Nolan 1997). The acute toxicity studies using dogs, however, are limited to early i.v. studies (Appendix 1, Table 8) which do not provide a good quantitative basis for assessing the sensitivity of dogs, relative to other mammals. Subchronic and chronic studies, however, consistently indicate that dogs are more sensitive than rats or mice to endothall (Section 3.1.5). As summarized in Appendix 1 (Table 10), the subchronic LOAEL for dogs is 27.5 mg/kg bw/day (Trutter 1994b) and the subchronic LOAEL in rats is 118 mg/kg/day (Trutter 1994a). Based on this comparison, dogs are more sensitive than rats by a factor of about 4 [$118 \text{ mg/kg/day} \div 27.5 \text{ mg/kg bw/day} \approx 4.2$]. As also summarized in Appendix 1 (Table 10), the subchronic NOAEL for dogs is 11.5 mg/kg bw/day (Trutter 1994b) and the subchronic NOAEL in rats is 39 mg/kg/day (Trutter 1994a). Based on this comparison, dogs are more sensitive than rats by a factor of about 3 [$39 \text{ mg/kg/day} \div 11.5 \text{ mg/kg bw/day} \approx 3.3$]. For the current Forest Service risk assessment, an adjustment factor of 4, based on a comparison of the subchronic LOAELs, is used to adjust the acute toxicity value of 9.4 mg/kg bw/day from rats to estimate an acute toxicity value for dogs of 2 mg/kg bw/day—i.e., $9.4 \text{ mg/kg bw/day} \div 4 \approx 2.35 \text{ mg/kg bw/day}$.

4.3.2.1.2. Longer-Term Toxicity Value

The longer-term toxicity values for mammalian wildlife parallel the approach taken with the acute toxicity values—i.e., the chronic toxicity value for most mammals is based on the same approach used in deriving the chronic RfD. The chronic RfD is based on the same study used to derive the acute RfD (Trutter 1993b) but uses the chronic LOAEL of 2 mg/kg bw/day, based on lesions to the gastrointestinal tract in parental rats rather than the NOAEL of 9.2 mg/kg bw/day, based on pup weight (Section 3.3.3). The derivation of both the acute and chronic RfD from the same study is somewhat unusual. As discussed in the previous subsection, however, this approach is justified because the response in pups involved a relatively short period of exposure (the gestation period), whereas the response in adult animals involved an exposure period of several months. Taking the same approach as that used by the EPA in deriving the chronic RfD, the LOAEL of 2 mg/kg bw/day is divided by a factor of 3 to approximate a NOAEL of 0.7 mg/kg bw/day [$2 \text{ mg/kg bw/day} \div 3 \approx 0.666... \text{ mg/kg bw/day}$].

As summarized in Section 3.1.5, the available chronic toxicity values indicate that dogs are more sensitive than rodents to endothall. The chronic LOAEL in dogs is 6.5 mg/kg bw/day (Shellenberger 1990a), which is substantially below the chronic NOAEL of 16 mg/kg/day in rats (Plankenhorn 1990) as well as the chronic NOAEL of 45 mg/kg/day in

mice (Shellenberger 1990b). For adjusting a LOAEL to approximate at NOAEL, factors of 3-10 are typically applied, depending on the severity of the LOAEL (SERA 2007, Table 3-5). When the maximum uncertainty factor of 10 is used, the adjusted LOAEL for dogs becomes 0.65 mg/kg bw/day. This value is essentially the same as that used for other mammals—i.e., 0.7 mg/kg bw/day. Accordingly, a separate chronic toxicity value for canids is not derived in the current Forest Service risk assessment.

4.3.2.2. Birds

As discussed in Section 4.1.2.2, there are two types of endothall bioassays conducted with birds: gavage (intubation) studies and acute 5-day dietary exposures. As summarized in Appendix 2 (Table 1), the reported gavage LD₅₀ values range from 61.6 mg a.e./kg bw for the dipotassium salt of endothall in mallards (Pedersen and Helsten 1992b) to 500 mg a.e./kg bw for technical grade endothall acid in quail (U.S. EPA/OPP 2005c, MRID 74220). The gavage studies may not yield reliable estimates of the acute LD₅₀ because gavage dosing of birds with endothall induces vomiting. Furthermore, vomiting shortly after dosing is noted explicitly in several of the studies summarized in Appendix 2 (Table 1). Consequently, the reported gavage LD₅₀ values may underestimate the toxicity of endothall to birds, and the acute dietary studies are a better basis for deriving acute toxicity values for birds.

In the 5-day dietary studies on endothall and endothall formulations, the differences in the lowest reported dietary NOEC values are relatively modest—i.e., 312 ppm for endothall acid (Pedersen and Solatycki 1994b), 737.5 ppm for the dipotassium salt of endothall (Pedersen 1994b), and 500 ppm for the mono-amine salt of endothall (Fink and Beavers 1977d). For the current Forest Service risk assessment, the lowest NOEC—i.e., 312 ppm for endothall acid—is used to derive the acute toxicity value. The cleared review of the study by Pedersen and Solatycki (1994b) does not provide information on food consumption or body weight. Based on recent acute dietary studies in birds on another herbicide, aminopyralid, acute food consumption factors—i.e., kg food/kg body weight per day—for mallard ducks and bobwhite quail are in the range of 0.3 for mallards and 0.42 for quail (SERA 2007b). Since the Pedersen and Solatycki (1994b) study involved mallards, the factor of 0.3 is used to estimate an acute toxicity value of 94 mg/kg bw [312 mg/kg diet x 0.3 kg food/kg body weight = 93.6 mg/kg bw].

The results of reproductive toxicity values are used to derive longer-term toxicity values for birds. As summarized in Appendix 2 (Table 3), only two reproduction studies are available, one in mallards, which yields a dietary NOEC of 50 ppm (Pedersen and Fletcher 1992), and the other in quail, which yields a dietary NOEC of 250 ppm (Pedersen et al. 1992). For the current Forest Service risk assessment, the lower NOEC of 50 ppm for mallards is used to derive the longer-term toxicity value. As with the acute dietary studies, the cleared reviews for the reproduction studies in birds do not provide information on food consumption or body weights. Again using food consumption data from recent reproduction studies on aminopyralid, food consumption factors for mallard ducks and bobwhite quail in longer-term dietary studies are generally in the range of 0.07 for mallards and 0.068 for quail (SERA 2007b). When the factor of 0.07 for mallards is applied to the dietary concentration of 50 ppm, the corresponding daily dose is 3.5 mg/kg

bw/day [50 mg/kg diet x 0.07 kg food/kg body weight]. The chronic food consumption factors are much lower than the acute food consumption factors discussed above. This is a common pattern in acute and chronic dietary studies in birds. On average, young birds used in acute dietary studies will consume more food per unit body weight than will birds followed over a longer period of time in chronic dietary studies.

4.3.2.3. Terrestrial Invertebrates

Because no significant exposures to terrestrial invertebrates are plausible in aquatic applications of endothall, no dose-response assessment for this group is developed.

4.3.2.4. Terrestrial Plants (Macrophytes)

Because no significant exposures to terrestrial plants are plausible in aquatic applications of endothall, no dose-response assessment for this group is developed.

4.3.2.5. Terrestrial Microorganisms

Because no significant exposures to terrestrial microorganisms are plausible in aquatic applications of endothall, no dose-response assessment for this group is developed.

4.3.3. Aquatic Organisms

4.3.3.1. Fish

As discussed in Section 4.1.3.1 (hazard identification for fish), there are substantial differences between the toxicity of Aquathol and Hydrothol formulations to fish. Consequently, separate dose-response assessments are made for each formulation.

4.3.3.1.1. Aquathol Formulations

U.S. EPA/OPP (2005c) uses LC₅₀ values for risk characterizations associated with short-term exposures. For fish, the lowest LC₅₀ value used in U.S. EPA/OP (2005c) is 9.152 mg a.e./L for rainbow trout (MRID 40098001 Mayer, 1986). For longer-term exposures, U.S. EPA/OPP (2005c) uses an NOEC from a longer-term toxicity study. The lowest NOEC used in U.S. EPA/OPP (2005c) is 1.3 mg a.e./L, the NOEC for fatheads from the study by Bettencourt (1994). As summarized in Appendix 3 (Tables 2 and 5), these are the lowest reported acute and chronic toxicity values for the dipotassium salt of endothall, and these values form the basis for the dose-response assessment for sensitive species of fish used in the current Forest Service risk assessment.

The acute LC₅₀ value is not adopted directly because the Forest Service prefers to use NOEC values rather than LC₅₀ values for risk characterization. This approach is taken because of differences in the ways that the EPA and Forest Service prefer to express hazard quotients (which are called *risk quotients* or *RQs* by EPA). As discussed in SERA (2007), the EPA uses variable levels of concern, including 0.5 for acute risk and 0.05 for threatened and endangered species. The Forest Service prefers to use a single level of concern of 1.0 which is applied uniformly to all HQs. In the absence of information on an NOEC, the Forest Service will divide an LC₅₀ value by 20 to approximate an NOEC. This approach is almost identical to the approach used by EPA for threatened and

endangered species—i.e., an RQ based on an LC₅₀ with a level of concern of 0.05 is equivalent to an HQ of 1 based on an LC₅₀ divided by 20.

As summarized in Appendix 3 (Table 2), the lowest reported NOEC value is 5.7 mg a.e./L for young (8-10 days old) walleye from the study by Paul et al. (1994). This NOEC, however, is associated with an LC₅₀ of 16 (11-22) mg a.e./L. Because the LC₅₀ value for young walleye is higher than the LC₅₀ of 9.152 mg a.e./L in trout (MRID 40098001 Mayer, 1986), it is not appropriate to use the NOEC from the walleye study because walleyes are not the most sensitive species. Similarly, it is not appropriate to divide the trout LC₅₀ of 9.152 mg a.e./L by 20 because the resulting concentration of about 0.46 mg a.e./L [$9.152 \text{ mg a.e./L} \div 20 = 0.4576 \text{ mg a.e./L}$] would be below the chronic NOEC of 1.3 mg a.e./L from the chronic study in fatheads (Bettencourt 1994). In other words, it is not sensible to use an acute toxicity value which is below the chronic toxicity value.

An alternate approach may be based on the general relationship of LC₅₀ to NOEC values for the dipotassium salt of endothall. As summarized in Appendix 3 (Table 2), several studies report both LC₅₀ and NOEC values for several different species of fish. These data are summarized in Table 16. For studies that report several sets of LC₅₀ and NOEC values for different periods of observation, only the sets leading to the highest ratio of LC₅₀ to NOEC are included in Table 16. Based on these data, the average ratio of the LC₅₀ to the NOEC is about 5.17 with a 95% confidence interval of 1.06-9.28. The upper bound value of 9.28 would not be appropriate for adjusting the lowest LC₅₀ of 9.152 mg a.e./L because the resulting value—i.e., $9.152 \text{ mg a.e./L} \div 9.28 \approx 0.98 \text{ mg a.e./L}$ —is below the lowest chronic value of 1.3 mg a.e./L. Thus, for the current Forest Service risk assessment, the LC₅₀ of 9.152 mg a.e./L in trout (MRID 40098001 Mayer, 1986) is divided by 5.17, the average ratio of the LC₅₀ to the NOEC values from Table 16. Consequently, for sensitive species of fish, the acute NOEC is approximated as 1.8 mg a.e./L [$9.152 \text{ mg a.e./L} \div 5.17 = 1.7702$]. This estimated acute NOEC is below the lowest reported acute NOEC of 5.7 mg a.e./L (Paul et al. 1994) and above the lowest chronic NOEC of 1.3 mg a.e./L (Bettencourt 1994).

The acute toxicity value for tolerant species of fish is based on the same approach used for sensitive species. The highest LC₅₀ value for fish is 457.6 mg a.e./L for bluegills (MRID 40098001 Mayer, 1986). This acute LC₅₀ value is divided by 5.17 to approximate an acute NOEC of 89 mg a.e./L [$457.6 \text{ mg a.e./L} \div 5.17 = 88.5106$] for tolerant species of fish.

As noted above, the lowest longer-term NOEC used by U.S. EPA/OPP (2005c) is 1.3 mg a.e./L for fathead minnows in the Bettencourt (1994), which is based on endothall acid rather than the dipotassium salt of endothall. As discussed in Section 4.1.3.1, there are no substantial differences in the toxicity of endothall acid and the dipotassium salt of endothall. The only longer-term NOEC available on the dipotassium salt of endothall is the NOEC of 1.79 mg/L for the development of trout eggs from the study by Folmar (1976b). This study, however, involved only a 4-hour period of exposure of trout eggs to endothall with a longer-term exposure period to assess the impact of the short-term

exposure on the development and hatching of the eggs. While this study is classified as chronic by U.S. EPA/OPP (2005c, p. lii), it does not have the same interpretation as a standard egg-to-fry study, which involves continuous exposure over the period of development, typically about 35 days.

The lack of additional chronic studies in fish is a limitation because Forest Service risk assessments preferentially derive separate and distinct longer-term toxicity values for both sensitive and tolerant species. In some instances, acute-to-chronic ratios may be used to make conservative estimates of longer-term NOEC values for presumably sensitive species of fish. For example, the acute toxicity values used in the current Forest Service risk assessment are 1.8 mg a.e./L for sensitive species and 89 mg a.e./L for tolerant species. Making the conservative assumption that the chronic NOEC of 1.3 mg a.e./L for fathead minnows is representative of a tolerant species, the acute-to-chronic ratio method could be used to estimate a chronic NOEC of 0.026 mg a.e./L [$1.3 \text{ mg a.e./L} \times (1.8 \text{ mg a.e./L} \div 89 \text{ mg a.e./L})$] for sensitive species. For the dipotassium salt of endothall, however, this approach is not sensible because the acute toxicity value is based on trout. While the longer-term study by Folmar (1976b) is not a chronic study in terms of the duration of exposure, this study does not support the assertion that trout eggs are substantially more sensitive than fathead minnow eggs are to endothall. Consequently, for the current Forest Service risk assessment, the available range of longer-term toxicity values—i.e., 1.3–79 mg/L—are used to characterize longer-term risks to sensitive and tolerant species. The limitations in this approach are discussed further in the risk characterization (Section 4.4.3.1).

4.3.3.1.2. Hydrothol Formulations

As with the dose response assessment for Aquathol formulations, the longer-term toxicity values serve as a lower bound for acute toxicity values. Thus, the chronic toxicity values are addressed first. U.S. EPA/OPP (2005c, Appendix F, Table F-11, p. F-xii) explicitly considers two early life stage toxicity studies, Keller et al. (1988b) and Bettencourt (1994). As summarized in Appendix 3 (Table 5) of the current Forest Service risk assessment, both studies involved the exposure of fathead minnow embryos to Hydrothol 191 liquid. The study by Bettencourt (1994) is a standard egg-to-fry study covering a 35-day exposure period; whereas, the Keller et al (1988b) study involved only a 7-day exposure period but used two temperatures, 15 and 25°C. Based on the bioassay conducted at 25°C, Keller et al (1988b) identified an NOEC of 0.05 mg a.e./L, which is very close to the NOEC of 0.056 mg a.e./L reported by Bettencourt (1994).

The other longer-term toxicity study included in Appendix 3 (Table 5) is the study by Eller (1969) in redear sunfish. This study used artificial ponds in which the fish were treated with Hydrothol 191 at target concentrations of 0.03 and 0.3 mg a.e./L with an exposure period of 112 days. At the lower concentration, transient changes were noted in the testes. These changes were characterized as *ova-like* cells. These effects were not evident by day 14 of the study. Although U.S. EPA/OPP (2005c, p. Appendix F-xix) discusses the study by Eller (1969), it is not used for risk characterization in the EPA ecological risk assessment (U.S. EPA/OPP (2005c)).

The current Forest Service risk assessment adopts a somewhat different and more conservative approach. The development of ova-like cells appears to be clearly related to endothall exposure. The presence of ova-like cells is not noted by Eller (1969) in any control fish. In addition, the presence of ova-like cells are more pronounced in the 0.3 mg a.e./L exposure group in that these cells persisted in this exposure group until day 28 of the study. While the toxicological significance of the ova-like cells in male fish is not clearly demonstrated in the study by Eller (1969), it seems reasonable to classify this effect as adverse. Thus, the 0.03 mg a.e./L from the study by Eller (1969) is considered a LOAEC. In the absence of additional data, the LOAEC of 0.03 mg a.e./L is divided by 10 to approximate an NOEC of 0.003 mg a.e./L. This value is used to characterize risks associated with longer-term exposures in sensitive species fish. The NOEC of 0.056 mg a.e./L is used to characterize risks associated with longer-term exposures in tolerant species of fish.

Unlike the case with Aquathol formulations, LC₅₀ values are the only type of acute toxicity values reported for Hydrothol formulations (Appendix 3, Table 3), and there are no NOEC values. As discussed in Section 4.1.3.1, the reported LC₅₀ values for Hydrothol formulations range from 0.02336 mg a.e./L for the emerald shiner (Swabey and Schenk 1963) to 1.5 mg a.e./L for bluegills (MRID 43472801, Bettencourt 1994). The standard adjustment factor of 20 for estimating a NOEC from an LD₅₀ leads to an estimated acute NOEC of about 0.0012 mg a.e./L, based on the lowest LC₅₀ [0.02336 mg a.e./L ÷ 20 = 0.001168 mg a.e./L]. This approach is not reasonable because this estimated acute NOEC for sensitive species would be below the corresponding longer-term NOEC for sensitive species of 0.003 mg a.e./L. Consequently, for sensitive species of fish, the acute NOEC is based on and is identical to the chronic NOEC of 0.003 mg a.e./L. For tolerant species of fish, the acute NOEC is estimated at 0.075 mg a.e./L—i.e., the acute LC₅₀ of 1.5 mg a.e./L divided by 20—which is above the longer-term NOEC of 0.056 mg a.e./L.

4.3.3.2. Amphibians

As discussed in Section 4.1.3.2, very little information is available on the toxicity of endothall to amphibians. Consequently, no dose-response assessment is proposed for this group. Following the approach taken in U.S. EPA/OPP (2005c), the risk characterization for aquatic phase amphibians is based on the risk characterization for fish.

4.3.3.3. Aquatic Invertebrates

4.3.3.3.1. Aquathol Formulations

As discussed in Section 4.1.3.3, the toxicity of Aquathol formulations to aquatic invertebrates is quite similar to that of technical grade endothall. The LC₅₀ values for Aquathol formulations range from 31 mg a.e./L in *Ceriodaphnia dubia* (Nelson and Roline 1998) to 91.23 mg a.e./L in *Daphnia magna* (MRID 00084150, Vilkas, 1979). Only one set of acute NOEC and LC₅₀ values is available for Aquathol formulations, the NOEC of 24 mg a.e./L with a corresponding LC₅₀ of 92 mg a.e./L using technical grade endothall in a bioassay with *Daphnia magna* (McNamara, 1992). For Aquathol K, however, the study by Sanders (1969, 1970b) reports an NOEC of about 71 mg a.e./L for

amphipods. This value, however, is higher than LC₅₀ values reported for amphipods in MRID 40098001 (Mayer 1986). Thus, the NOEC of 71 mg a.e./L is not used in the dose-response assessment, and all acute toxicity values are estimated from LC₅₀ values.

There are no chronic toxicity values for studies conducted with an Aquathol formulation, and there is only one chronic toxicity study available on technical grade endothall. In the chronic study, the NOEC for reproduction in *Daphnia magna* is 5 mg a.e./L (Putt 1993).

Given this simple data set, the dose-response assessment for Aquathol formulations is relatively simple. The only problematic area involves the adjustment of the acute LC₅₀ values to approximate NOEC values. Dividing by 20, which is the default approach, is not sensible because both of the estimated acute NOEC values would be below the chronic value of 5 mg a.e./L. For the one available study reporting both an NOEC and an LC₅₀ (McNamara, 1992), the ratio of the LC₅₀ to the NOEC is about 3.8 [92 mg a.e./L ÷ 24 mg a.e./L ≈ 3.8333...].

As discussed in Section 4.3.3.1.1 and summarized in Table 16, the average ratio of the LC₅₀ to the NOEC for Aquathol K formulations in fish is about 5, which is reasonably close to the single value of 3.8 in the study by McNamara (1992). In the absence of additional information, the LC₅₀ values for Aquathol formulations is divided by a factor of 5 to estimate the NOEC values for aquatic invertebrates—i.e., 6.2 mg a.e./L for sensitive species [31 mg a.e./L ÷ 5] and 18 mg a.e./L for tolerant species [91.23 mg a.e./L ÷ 5 ≈ 18.245 mg a.e./L]. Both of these values are above the chronic NOEC of 5 mg a.e./L.

The single chronic toxicity value of 5 mg a.e./L for *Daphnia magna* is used to characterize risks associated with longer-term exposures to tolerant species. This approach seems reasonable because *Daphnia magna* is the most tolerant species based on the acute LC₅₀ of 91.23 mg a.e./L in *Daphnia magna* (MRID 00084150, Vilkas, 1979). For sensitive species, the ratio of acute LC₅₀ values for the most sensitive to the most tolerant species are used to adjust the estimated chronic NOEC. As discussed above, the acute values for sensitive and tolerant species are 31 mg a.e./L and 91.23 mg a.e./L, respectively. Thus, the chronic NOEC for sensitive species is estimated at 1.7 mg a.e./L [5 mg a.e./L × (31 mg a.e./L ÷ 91.23 mg a.e./L) ≈ 1.699 mg a.e./L].

4.3.3.3.2. Hydrothol Formulations

Hydrothol formulations are much more toxic than Aquathol formulations to aquatic invertebrates (Section 4.1.3.3); however, the dose-response assessment for Hydrothol formulations parallels that for Aquathol formulations because of the similar types of information available for both formulations.

Both the published and unpublished acute toxicity studies on Hydrothol formulations report LC₅₀ values but not NOEC values. Consequently, the LC₅₀ values must be used to approximate acute NOEC values. As summarized in Section 4.1.3.3, the LC₅₀ values for Hydrothol formulations range from 0.012 mg a.e./L in grass shrimp (Johnson and Finley

1980) to 1.13 mg a.e./L in a freshwater mussel (Keller 1993). As with Aquathol formulations, the default approach for estimating the NOEC—i.e., dividing the LC₅₀ value by 20—must be evaluated relative to the longer-term NOEC values, because it is not sensible to have an acute NOEC that is below the longer-term NOEC.

There are two reproductive NOEC values for Hydrothol formulations: 0.0023 mg a.e./L for *Ceriodaphnia dubia* (Keller et al. 1988a) and 0.0159 mg a.e./L for *Daphnia magna* (MRID 43437901). Dividing the lowest LC₅₀ value of 0.012 mg a.e./L by 20 yields an estimated acute NOEC of 0.0006 mg a.e./L, which is below the longer-term NOEC for sensitive species by a factor of about 4 [$0.0023 \text{ mg a.e./L} \div 0.0006 \text{ mg a.e./L} \approx 3.8333\dots$].

Two alternative approaches could be used to reconcile the estimated acute NOEC and the observed longer-term NOEC: The estimated acute NOEC of 0.0006 mg a.e./L could be applied as the chronic NOEC or the observed chronic NOEC of 0.0023 mg a.e./L could be applied as the acute NOEC. The former approach is more *conservative* in that it leads to a lower toxicity value. This approach, however, is not used in the current Forest Service risk assessment because it seems more sensible to rely on an observed longer-term NOEC rather than an estimated acute NOEC. Thus, for sensitive species, the longer-term NOEC of 0.0023 mg a.e./L is used to characterize risks associated with both acute and longer-term exposures of aquatic invertebrates.

For tolerant species, the acute NOEC estimated from the LC₅₀ is about 0.057 mg a.e./L [$1.13 \text{ mg a.e./L} \div 20 = 0.0565$]. As noted above, the highest observed reproductive NOEC—i.e., the NOEC that would be applied to tolerant species for longer-term exposures—is 0.0159 mg a.e./L, lower than the estimated acute NOEC of 0.057 mg a.e./L by a factor about 4 [$0.057 \text{ mg a.e./L} \div 0.0159 \text{ mg a.e./L} \approx 3.585$]. Thus, the acute NOEC for tolerant species of aquatic invertebrates is estimated as 0.057 mg a.e./L. The highest observed longer-term NOEC of 0.0159 mg a.e./L is rounded to 0.016 mg a.e./L and used to assess the consequences of longer-term exposures to tolerant aquatic invertebrates.

4.3.3.4. Aquatic Plants

4.3.3.4.1. Macrophytes

As discussed in Section 4.1.3.4.1, both Aquathol and Hydrothol formulations are highly toxic to aquatic macrophytes. The numerous efficacy studies (Appendix 5, Table 2) are difficult to use quantitatively in the dose-response assessment because of limitations in how the studies are reported and because of the differences in the field conditions under which the studies were conducted. The dose-response assessment for aquatic macrophytes is further limited by the relatively few controlled bioassays that are available—i.e., three bioassays on duckweed, one using Aquathol K, and the other two using Hydrothol 191 (Appendix 5 Tables 1).

Based on EC₅₀ values from the laboratory bioassays, Aquathol K and Hydrothol 191 are essentially equitoxic. The EC₅₀ value and 95% confidence interval for Aquathol K is 610 (548-696) µg a.e./L (Hoberg 1992f). The two EC₅₀ values for Hydrothol 191 are 430 µg a.e./L (MRID 44127806, Hoberg 1994) and 740 µg a.e./L (MRID 44949402, Drott et al.

1999). The mean of these two EC_{50} values is 585 $\mu\text{g a.e./L}$, which is not substantially different from the EC_{50} of 610 $\mu\text{g a.e./L}$ for Aquathol K. The similarities in the EC_{50} values are reflected in the similarities of the efficacy studies on both Aquathol and Hydrothol formulations.

In terms of NOEC values, however, Aquathol K (NOEC = 4.6 $\mu\text{g a.e./L}$) is substantially more toxic than Hydrothol 191 (NOEC values of 50 and 150 $\mu\text{g a.e./L}$). For assessing risks to nontarget plant species, NOEC values are more relevant than EC_{50} values. Consequently, for sensitive species of aquatic macrophytes, the NOEC of 4.6 $\mu\text{g a.e./L}$ is used for Aquathol formulations and the NOEC of 50 $\mu\text{g a.e./L}$ is used for Hydrothol formulations.

NOEC values for tolerant species of aquatic macrophytes are problematic because of the limited number of standard toxicity studies. Efficacy studies are potentially useful in identifying tolerant species of aquatic macrophytes under the assumption that tolerant target species may be representative of some tolerant nontarget species. The efficacy studies on endothall, however, do not identify clear NOEC values for tolerant species.

Several efficacy studies were conducted with Aquathol K formulations and the disodium salt of endothall (Appendix 5, Table 2). An early study on the disodium salt suggests that 2 mg/L is ineffective in controlling *Cladophora* species (McLarty 1960). Similarly, a more recent efficacy study with Aquathol K suggests that treatments at 1.5 mg/L to control milfoil may be beneficial to some species such as elodea, muskgrass, and bladderwort (Parsons et al. 2004). This beneficial effect, however, may not indicate a tolerance in these species but rather an adverse effect on milfoil which resulted in decreased competition and a better growing environment for elodea and the other species.

In general, the field studies conducted with Hydrothol formulations do not indicate substantial limitations on efficacy. As with virtually any toxic agent, the duration of exposure interacts with dose or concentration. This principle is illustrated in the study by Price (1994) in which a 9-hour exposure to 1 ppm was ineffective in macrophyte control in a drainage canal, while higher concentrations were effective over shorter periods of exposure. These results do not suggest that the macrophytes are tolerant to a 1 ppm treatment; instead, it suggests that the combination of the pesticide concentration and the exposure duration was not effective. Although other efficacy studies examine the interactions of endothall concentrations and exposure duration (e.g., Slade et al. 2008), they are not directly useful in quantifying threshold doses in nontarget species.

In the absence of any other information, the maximum application rates—i.e., 3.5 mg a.e./L for Aquathol formulations and 5.0 mg a.e./L for Hydrothol formulations—are used as a basis for estimating possible threshold doses for tolerant species of aquatic macrophytes. In other words, the maximum application rates suggest that for some tolerant target species the maximum target concentration might be required for effective control. To estimate a possible NOEC, the maximum application rates are divided by 2—i.e., a functional NOEC of 1.75 mg a.e./L for Aquathol formulations and 2.5 mg a.e./L for Hydrothol formulations. The underlying assumption in this approach is that

some nontarget species may have sensitivities to endothall similar to those of relatively tolerant target species—i.e., target species that require the maximum application rate for effective control. At least for Aquathol formulations, there is some suggestion that 1.75 mg a.e./L may be a reasonable estimate of an NOEC for tolerant species of macrophytes—i.e., the study by McLarty (1960), which suggests an NOEC of 2 mg/L for *Cladophora* species.

4.3.3.4.2. Algae

As discussed in Section 4.1.3.4.2, endothall acid and the dipotassium salt of endothall used in Aquathol formulations are much less toxic to algae, compared with the monoamine salt of endothall used in Hydrothol formulations. Thus, separate toxicity values are developed for Aquathol and Hydrothol formulations.

The publication by Walsh (1972) provides the only available information on the toxicity of endothall acid and dipotassium salt to algae. The toxicity values for endothall acid are reported as 15-50 mg a.e./L. The dipotassium salt is much less toxic with EC₅₀ values for growth ranging from 355 to 2130 mg a.e./L. For the dose-response assessment of Aquathol formulations, the EC₅₀ values for the dipotassium salt are most relevant. These EC₅₀ values are divided by 20 and rounded to two significant digits to estimate NOEC values of 18 mg a.e./L [$355 \text{ mg a.e./L} \div 20 = 17.75 \text{ mg a.e./L}$] for sensitive species of algae and 110 mg a.e./L [$2,130 \text{ mg a.e./L} \div 20 = 106.6 \text{ mg a.e./L}$] for tolerant species of algae.

Several studies examine the toxicity of Hydrothol 191 to algae (Appendix 5, Table 5). The open literature studies as well as the summaries of the unpublished studies in U.S. EPA/OPP (2005c) are relatively simple to apply to the current Forest Service risk assessment because most studies report NOEC values. The most sensitive species is clearly *Kirchneria subcapitata*, a type of freshwater green algae. In terms of both the EC₅₀ and NOEC values, two registrant submitted studies indicate that *Kirchneria subcapitata* is the most sensitive species, MRID 44949203 (EC₅₀ = 2.2 µg a.e./L, NOEC = 0.54 µg a.e./L) and MRID 44127804 (EC₅₀ = 1.9 µg a.e./L, NOEC = 0.5 µg a.e./L). Thus, the lower NOEC of 0.5 µg a.e./L, equivalent to 0.0005 mg a.e./L is used to characterize risk for sensitive species of algae. This is also the NOEC for bluegreen algae, *Anabaena flos-aquae* (MRID 44127803). The most tolerant species of algae is a *Cladophora* species, a filamentous algae, with an EC₅₀ of 1000 µg a.e./L and an NOEC of 250 µg a.e./L. Thus, the NOEC of 250 µg a.e./L, equivalent to 0.250 mg a.e./L, is used to characterize risk for tolerant species of algae.

4.3.3.5. Aquatic Microorganisms

There is limited information on the toxicity of endothall to aquatic microorganisms (Section 4.1.3.5). The one available study reports an LOAEC of 3.5 mg a.e./L associated with transient increases in respiration rates in two species of aquatic microorganisms after exposure to the dipotassium salt of endothall. This finding suggests that some aquatic microorganisms may be more sensitive to endothall than are algae which have NOEC values of approximately 18 and 110 mg a.e./L for sensitive and tolerant species, respectively. As discussed in Section 3.2.3.4.2, however, the most substantial impact on

aquatic microorganisms may be associated with oxygen depletion due to decaying vegetation. Because the toxicity data on aquatic microorganisms is scant and the effects associated with oxygen depletion are relatively well documented, risks to microorganisms are characterized qualitatively (Section 4.4.3.5) and a formal dose-response assessment is not developed for this group of organisms.

4.4. RISK CHARACTERIZATION

4.4.1. Overview

In the EXCEL worksheets that accompany this risk assessment (Attachments 1 to 4), a unit target application rate of 1 mg a.e./L (1 ppm a.e.) is used. The HQs for terrestrial organisms are given in Worksheet G02 of these attachments and the HQs for aquatic organisms are given in Worksheet G03. For all non-accidental exposures, the HQs are linearly related to the target concentration. The consequences of using higher or lower target concentrations are addressed in this risk characterization. Acute exposures based on a target application rate of 1 mg a.e./L are associated with longer-term endothall concentrations in water of about 0.048 (0.0048-0.42) mg a.e./L. The variability in the longer-term concentrations reflects the variability in the estimates of the half-times of endothall in surface water. As discussed in Section 4.4.2.1, the longer-term concentrations of endothall are based on half-lives in surface water of 3 (0.3-30) days. The upper bound value of 30 days is a worst-case value that probably over-estimates the longer-term concentrations of endothall in many instances. Modifications to the upper bound value of 30 days should be considered in site-specific applications of endothall.

The risk characterization for terrestrial animals associated with the aquatic application of endothall formulations is relatively simple. The only significant exposures are likely to involve the consumption of treated water by mammals and birds. Based on both expected peak concentrations as well as longer-term concentrations, none of the HQs exceeds the level of concern (HQ=1). The highest HQ associated with non-accidental exposures is 0.45, the upper bound of the longer-term HQ for the consumption of contaminated water by a small mammal. This value is below the level of concern by a factor of about 2. Some accidental exposures exceed the level of concern; in which case, adverse effects in mammals, particularly canids, are possible in cases of a severe spill—i.e., a large amount of endothall spilled into a small pond.

The risk characterization for aquatic species is much more complicated; moreover, for most groups of organisms, the risk characterization is highly dependant on the type of formulation applied. The dipotassium salt of endothall used in Aquathol formulations is much less toxic to aquatic animals and algae, compared with the mono-amine salt used in Hydrothol formulations. No toxicity studies are available on the di-amine moiety. The most plausible, but tentative, reason for the greater toxicity of Hydrothol versus Aquathol formulations to most groups of aquatic organisms is that the agent of concern in Hydrothol formulations is the mono-amine moiety rather than endothall.

In applications of Aquathol, risks to aquatic animals and algae are marginal. In applications of Hydrothol formulations, risks to aquatic animals and algae are substantial. The risks to algae reflect the registered use of Hydrothol formulations as algicides. The risks to aquatic animals associated with Hydrothol formulations are equally clear. These risks, however, can be reduced by treating subsections of water bodies rather than treating the entire body of water at a single time. For macrophytes, both Aquathol and Hydrothol formulations are very toxic. Since both types of formulations are labeled for

the control of aquatic macrophytes, the risk characterization for aquatic macrophytes is, in a sense, a reflection of the intended use of these products.

4.4.2. Terrestrial Organisms

4.4.2.1. Mammals

The risk characterization for mammals is relatively simple. For anticipated exposures — i.e., those based on the peak target concentration and the consequent longer-term concentrations in water—the maximum HQ is 0.09 at an application rate of 1 mg a.e./L (1 ppm a.e.), which is the upper bound HQ in the exposure scenario associated with the longer-term consumption of contaminated water by a small mammal. At the maximum application rate of 5 mg a.e./L for Hydrothol formulations, the upper bound HQ for this scenario would be about 0.45, below the level of concern by a factor of about 2. The maximum application rate for Aquathol formulations is only 3.5 mg a.e./L, and the upper bound HQ value for this scenario would be about 0.3. Thus, at the maximum target concentrations for Aquathol or Hydrothol formulations, there is no basis for asserting that adverse effects in mammals are likely to occur.

The application of any effective aquatic herbicide, including endothall, will alter aquatic vegetation. This alteration is likely to lead to some secondary changes that could have an impact on mammals—e.g., changes in water quality or food availability. These secondary effects are likely to vary over time and among different species of mammals; furthermore, the secondary effects could be considered beneficial or detrimental.

While expected concentrations of endothall in surface water do not appear to pose a risk to terrestrial mammals, accidental spills lead to HQs that exceed the level of concern. As summarized in Table 6, the exposure scenarios for an accidental spill lead to different estimates of endothall concentrations in water because of differences in the amount of endothall in liquid formulations as well as differences in the way in which the accidental spill scenarios are structured for liquid and granular formulations. The highest HQs are those associated with the accidental spill of Aquathol K into a small pond. Of the different receptors considered, the highest HQs are those for canids. For canids, the central estimate of the HQ is 6 with a range of 1.2 to 12. These HQs are associated with doses of 11.8 (2.26 to 23.6) mg a.e./kg bw (Attachment 1, Worksheet F05c).

As summarized in Table 8 and discussed in Section 3.2.3.4. (Dose-Severity Relationships), the lowest reported oral LD₅₀ value for endothall in mammals is 28.5 mg a.e./kg bw. This LD₅₀, however, is for a rodent and not a canid, and it is likely that canids will be more sensitive than rodents. Given the maximum estimated exposure of 23.6 mg a.e./kg bw, it seems plausible that some canid species could be adversely affected and perhaps killed if they were to consume water from a small pond after the worst-case accidental spill of Aquathol K into a small pond.

This type of risk characterization for the accidental spill scenario used in Forest Service risk assessments is not atypical. The accidental spill scenario is intended to be extreme with the objective of informing those involved in pesticide applications of the possible

consequences of an extreme spill. For endothall, the worse-case scenario does suggest that some mammals could be adversely affected.

4.4.2.2. Birds

As discussed in Section 4.3.2.2 and summarized in Table 13, birds are less sensitive than mammals to endothall. The acute and chronic toxicity values for birds are factors of 10 and 5 higher, respectively, than the corresponding values in mammals. Consequently, the risk characterization for birds is simple and unambiguous. Neither expected nor accidental exposure scenarios lead to HQs that exceed the level of concern—i.e., an HQ of 1.

The highest HQ for birds is 0.1, the upper bound HQ for an accidental spill of Aquathol K into a small pond. For expected exposures—i.e., those based on the peak target concentration and the consequent longer-term water concentrations—the maximum hazard quotient is 0.01 at an application rate of 1 mg a.e./L (1 ppm a.e.), below the level of concern by a factor of 100. At the maximum application rate of 5 mg a.e./L for Hydrothol formulations, the upper bound HQ for this scenario would be about 0.05, below the level of concern by a factor of about 20. The maximum application rate for Aquathol formulations is only 3.5 mg a.e./L; accordingly, the upper bound HQ for this scenario would be about 0.04, below the level of concern by a factor of 25. Thus, at the maximum target concentrations for either Aquathol or Hydrothol formulations, there is no basis for asserting that adverse effects in birds are likely to occur.

As with mammals, secondary effects in bird populations cannot be ruled out. This is true for any effective herbicide that causes changes in aquatic vegetation with subsequent changes in the community structure of surface waters. Also, as with mammals, the nature of the secondary effects may be considered beneficial or detrimental, and the secondary effects are likely to vary over time and among different species of birds.

4.4.2.3. Other Terrestrial Organisms

As discussed in Section 4.2 (Exposure Assessment), significant exposures of other terrestrial organisms from the application of endothall to surface water are not anticipated. Consequently, significant or even detectable risks to terrestrial plants, insects, and microorganisms are also not anticipated. As with birds and mammals, the potential secondary effects on other terrestrial organisms following aquatic applications of endothall cannot be excluded.

4.4.3. Aquatic Organisms

4.4.3.1. Fish

4.4.3.1.1. Aquathol Formulations

At an application rate of 1 mg a.e./L, the acute HQ for fish is 0.6 for sensitive species and 0.01 for tolerant species. Unlike most HQs given in this risk assessment, the acute HQs are not presented as a range because they are based only on the target concentration.

Also at the target concentration of 1 mg a.e./L, the longer-term HQs are 0.03 (0.003-0.2) for sensitive species of fish and 0.0005 (0.00005-0.005) for tolerant species of fish (Worksheet G03). Thus, at an application rate of 1 mg a.e./L, none of the HQs for fish associated with expected acute or longer-term concentrations of endothall in water exceeds the level of concern (i.e., 1.0).

The HQs for fish and other aquatic organisms are directly related to the endothall concentration in water. Thus, at the maximum application rate for Aquathol formulations, 3.5 mg a.e./L, the upper bound of the acute HQ would be about 2.1, modestly above the level of concern. Based on the longer-term concentrations, the highest HQ at the maximum application rate would be 0.7 [0.2×3.5], below the level of concern by a factor of about 1.4. Because the HQ is linearly related to the application rate, the maximum application that could be used without exceeding the level of concern for sensitive species of fish is about 1.4 mg a.e./L—i.e., $1 \text{ mg a.e./L} \div 0.7$.

As discussed in Section 4.3.3.1.1, the NOEC for sensitive species of fish is 1.8 mg a.e./L, and this value is estimated from the lowest reported LC₅₀ of 9.152 mg a.e./L (MRID 40098001 Mayer, 1986). Thus, the HQ of 2.1, based on a concentration of 3.5 mg a.e./L, is a factor of about 2.6 [$9.152 \text{ mg a.e./L} \div 3.5 \text{ mg a.e./L}$] below the lowest LC₅₀ value for fish.

Accidental spills of Aquathol formulations do lead to HQs that substantially exceed the level of concern. For Aquathol K, the liquid formulation, the HQs for sensitive species of fish from the spill scenario are 78 (16-156). For Aquathol Super K, the granular formulation, the corresponding HQs are 10 (4-20). Because of the artificial nature of the spill scenarios, these HQs should not be overly interpreted. They simply indicate that large spills of the dipotassium salt of endothall into a small body of water would probably be toxic to fish and could result in fish kills.

In any effective application of an aquatic herbicide, aquatic vegetation will be killed. As with terrestrial organisms, changes in the structure of the plant community in a pond or stream could impact fish in terms of habitat and food supply. More importantly, however, the death of aquatic vegetation could lead to decreases in oxygen levels in water that could also cause fish kills. This risk is acknowledged on the product labels for Aquathol K and Aquathol Super K. The risk of hypoxia in fish is one of the reasons that product labels recommend sectional treatments rather than whole lake applications.

4.4.3.1.2. Hydrothol Formulations

As discussed in Section 4.3.3.1.2, the mono-amine salt of endothall used in Hydrothol formulations is much more toxic to fish, compared with the dipotassium salt of endothall used in Aquathol formulations. Consequently, the risk characterization for fish associated with the application of Hydrothol formulations is much more severe than that associated with Aquathol formulations.

As summarized in Worksheet G03 of the Attachment 3 (Hydrothol liquid) and Attachment 4 (Hydrothol granular), an application of Hydrothol at a target concentration

of 1 mg a.e./L leads to acute HQs of 333 for sensitive species of fish and 13 for tolerant species of fish. These HQs need little elaboration. The reported LC₅₀ values for Hydrothol formulations range from 0.02336 mg a.e./L for the emerald shiner (Swabey and Schenk 1963) to 1.5 mg a.e./L for bluegills (MRID 43472801, Bettencourt 1994). An application rate of 1 mg a.e./L is a factor of over 40 greater than the LC₅₀ for the most sensitive species of fish [$1 \text{ mg a.e./L} \div 0.02336 \text{ mg a.e./L} \approx 42.8$]. Thus, sensitive species of fish could be killed at the target application rate of 1 mg a.e./L. The lowest labeled target concentration for Hydrothol formulations is 0.05 mg a.e./L. This is a factor of about 2 above the lowest reported LC₅₀ [$0.05 \text{ mg a.e./L} \div 0.02336 \text{ mg a.e./L} \approx 2.14$]. At the maximum application rate of 5 mg a.e./L, the acute HQ for sensitive species of fish is 1667. Thus, across the range of labeled application rates for Hydrothol formulations, fish kills associated with the toxicity of endothall to sensitive species of fish may occur. It is less clear that tolerant species of fish might be killed. Nonetheless, the exposures would be associated with concentrations that might cause sublethal effects—i.e., exceed the estimated NOECs.

At an application rate of 1 mg a.e./L, the HQs associated with longer-term exposures to sensitive species of fish are 16 (1.6-140). At the minimum application rate of 0.05 mg a.e./L, the HQs are 0.8 (0.08-7). At the maximum application rate of 5 mg a.e./L, the HQs for sensitive species of fish are 80 (8-701). The application rate that would be associated with a central estimate of a longer-term HQ of 1 (i.e., at but not above the level of concern) is a target concentration of 0.0625 mg a.e./L. At this application rate, the HQs for sensitive fish species would be 1 (0.1-9).

The product labels for Hydrothol formulations contain the following statement: *Fish may be killed by dosages in excess of 0.3 ppm.* This statement is correct. However, fish kills could also be expected at much lower concentrations, if sensitive fish species are in the treated water. A more important statement on the product labels is: *Use dosages over 1.0 ppm on very narrow margins or in areas where some fish kill is not objectionable.* Here, the important cautionary note involves marginal or partial treatments. As discussed in Section 4.1.3.1, there is some indication that fish may avoid high concentrations of the dipotassium salt of endothall. Fish might also avoid areas of surface water after partial lake or pond treatments with the mono-amine salt of endothall. While somewhat speculative, an avoidance response could mitigate the expected effects of Hydrothol applications on fish.

The risk characterization for fish presented in the current Forest Service risk assessment is similar to the risk characterization provided in U.S. EPA/OPP (2005c). For acute exposures to fish associated with applications of the mono-amine salt of endothall at the maximum application rate of 5 mg a.e./L, U.S. EPA/OPP (2005c, Table 25, p. lxii) gives an RQ (i.e., risk quotient) of 119. This RQ is based on an LC₅₀ rather than an NOEC. Multiplying by 20—i.e., to adjust for the use of an LC₅₀ rather than an NOEC—the RQ of 199 corresponds to an HQ of 2380. As noted above, the HQ for sensitive species of fish in the current Forest Service risk assessment is 1667. The HQ in the current risk assessment is somewhat lower than that provided by the EPA because the current Forest Service uses of the chronic NOEC for acute exposures in sensitive species of fish rather

than the LC₅₀ divided by 20. The methodological difference between the Forest Service risk assessment and the EPA risk assessment is noted only for clarity. Both risk assessments come to essentially the same conclusion. Applications of Hydrothol are likely to pose risks to fish.

Given the risk characterization associated with expected concentrations, considerations of oxygen depletion as well as accidental exposures need little interpretation. For the liquid formulation of Hydrothol 191, the HQs for accidental exposures range from 2419 to 60,560 for sensitive species of fish and from 242 to 2422 for tolerant species of fish. For the granular formulations, the HQs are lower—i.e., ranging from 2419 to 12,096 for sensitive species and from 97 to 284 tolerant species. All of these HQs suggest that accidental spills of Hydrothol 191 formulations into a relatively small body of water could lead to substantial mortality in fish.

As with Aquathol formulations, secondary effects in fish associated with damage to and changes in the aquatic plant community would lead to changes in food availability, habitat, and water quality. While these changes might not be considered detrimental, the apparent risks to fish from the toxicity of Hydrothol formulations would likely prevail over any beneficial or negative secondary effects.

A reservation with the risk characterization for Hydrothol formulations involves the lack of reported fish kills following the application of Hydrothol formulations. U.S. EPA/OPP maintains an incident data base in which adverse effects associated with pesticide use are recorded. The EPA ecological risk assessment of endothall (U.S. EPA/OPP 2005c) summarizes only one incident of fish kills reported from the use of Hydrothol formulations. The incident is reported as follows:

Spillage of a 5-gallon can of Hydrothol 191 (endothall N,N-dimethylalkylamine salt) into a drain in California resulted in the deaths of over 1000 carp.

U.S. EPA/OPP (2005c, p. 1v)

This incident is consistent with the very high HQs for accidental spills of Hydrothol formulations, as discussed above.

Nonetheless, given the very high HQs for Hydrothol formulations developed in the current Forest Service risk assessment as well as the high RQ values derived by U.S. EPA/OPP (2005c), it would be reasonable to expect many reports of fish kills after the application of Hydrothol formulations. U.S. EPA/OPP addresses this concern as follows:

Currently, no systematic or reliable mechanism exists for the accurate monitoring and reporting of wildlife kill incidents to the Agency. Moreover, before a pesticide incident can be reported or investigated, the dead animals must be found. In the absence of monitoring following pesticide applications, kills are not likely to be noticed in agro-environments, which are generally away from

human activity. Even if onlookers are present, dead wildlife species, particularly small song birds and mammals, are easily overlooked, even by experienced and highly motivated observers.

U.S. EPA/OPP (2005c, p. 1v)

The lack of field studies indicating adverse effects on fish was noted also by Keckemet (1969, p. 51) and discussed by Sprecher et al. (2002, p. 2) as follows:

Keckemet notes that the amine salts are used with few detrimental effects on fish because: (a) part of the dimethylalkylamine is quickly adsorbed and decomposed by plants and soil; (b) fish detect the compound and will move into those portions of the waterbody left untreated as recommended in the label application directions; and (c) in flowing water systems such as canals, concentrations decrease rapidly.

Sprecher et al. (2002, p. 2)

The comment concerning the rapid absorption and decomposition of the amine moiety appears to be a supposition. While this supposition may be reasonable, no studies on the decomposition of the amine moiety were encountered in the endothall literature. The mesocosm study by Eller (1969), which is used in the dose-response assessment for fish (Section 4.3.3.1.2), indicates that Hydrothol 191 can cause changes in the structure of fish testes for up to 28 days after a single application of 0.3 mg a.e./L.

The implication that few detrimental effects in fish were observed may be misinterpreted. A more precise statement would be that few detrimental effects in fish were reported. As summarized in Appendix 3 (Table 6), relatively few field studies report observations (positive or negative) on the state of fish populations. In addition, most of the available reports on fish involve applications of the disodium or dipotassium salts. As discussed in the previous subsection, adverse effects in fish are not anticipated as a result of the application of the dipotassium salt of endothall.

The one field study, or more precisely a mesocosm study, in which Hydrothol formulations were applied and observations on fish health were made, noted substantial mortality in bluegills after the application of granular and liquid formulations of Hydrothol (Blackburn et al. 1971). Numerous efficacy studies were conducted with both Aquathol and Hydrothol formulations (Appendix 5, Table 2). With the exception of the studies noted in Appendix 3 (Table 6), these efficacy studies do not provide observations on fish populations.

Severe risk characterizations based primarily on HQs derived from laboratory bioassays should always be regarded with some degree of skepticism, especially when the risk characterization is not strongly supported by field observations. This limitation is acknowledged. A parallel situation will sometimes exist in human health risk assessments, when an adverse risk characterization is given without supporting epidemiology studies. While the lack of supporting field studies must be appreciated,

this lack of information does not imply safety and does not substantially reduce concern for the extremely high HQs for fish.

4.4.3.2. Amphibians

As discussed in Section 4.3.3.2, no dose-response assessment is developed for aquatic-phase amphibians because of the limited toxicity data available for this group of organisms. Following the approach taken in U.S. EPA/OPP (2005c), the risk characterization for aquatic phase amphibians is based on the risk characterization for fish. Thus, as with fish, risks to amphibians are likely to be marginal after applications of Aquathol formulations but may be substantial after applications of Hydrothol formulations.

4.4.3.3. Aquatic Invertebrates

4.4.3.3.1. Aquathol Formulations

The risk characterization for Aquathol formulations is unremarkable and unambiguous. At the unit application rate of 1 mg a.e./L, the acute HQ for sensitive species of invertebrates is 0.2 (Attachments 1 and 2, Worksheet G03). At the maximum application rate of 3.5 mg a.e./L, the HQ is 0.7, below the level of concern by a factor of about 1.4. For longer-term exposures, the upper bound of the HQ for sensitive species is 0.07 at an application rate of 1 mg a.e./L. At the maximum application rate of 3.5 mg a.e./L, the HQ is 0.2, below the level of concern by a factor of 5. Thus, there is no plausible basis for asserting that adverse effects on aquatic invertebrates are likely across the range of labeled target concentrations for Aquathol formulations.

As with the risk characterization for fish, secondary effects on aquatic invertebrates are plausible. Applications of Aquathol formulations will kill aquatic macrophytes, which would result in changes in habitat availability and possibly food supply for some aquatic invertebrates. These changes could be regarded as positive or negative for different species or groups of aquatic invertebrates. In applications to surface water with dense populations of sensitive aquatic macrophytes, Aquathol applications could lead to a decrease in oxygen levels in the treated water due to decaying vegetation. The drop in oxygen levels could adversely affect some species of aquatic invertebrates. Hypoxia would be a more likely effect in whole water body applications, as opposed to partial lake/pond treatments or marginal (shoreline) applications.

Accidental spill scenarios lead to HQs that substantially exceed the level of concern (HQ=1). Because of the manner in which the accidental spill scenarios are developed, the HQs are higher for the liquid formulation of Aquathol—i.e., 23 (5-45) for sensitive species—than for the granular formulation of Aquathol—i.e., 3 (1.2-6). These HQs suggest the possibility of adverse effects in aquatic invertebrates due to an accidental spill; however, it is not clear that the effects would include substantial mortality.

4.4.3.3.2. Hydrothol Formulations

As summarized in Table 15, the acute and longer-term NOEC values for aquatic invertebrates are similar to but somewhat less than the corresponding values for fish. Consequently, the risk characterization for aquatic invertebrates following the application of Hydrothol formulations is similar to the risk characterization for fish.

At the unit application rate of 1 mg a.e./L, the HQs for sensitive species of aquatic invertebrates are 435 for acute exposures and 21 (2-183) for longer-term exposures (Attachments 3 and 4, Worksheet G03). At the lowest labeled application rate of 0.05 mg a.e./L, the HQs are 22 for acute exposures and 1 (0.1-9) for longer-term exposures. At the maximum labeled application rate of 5 mg a.e./L, the HQs for sensitive species of aquatic invertebrates are 2174 for acute exposures and 105 (10-915) for longer-term exposures.

As discussed in Section 4.3.3.3.2, the LC₅₀ values for Hydrothol formulations range from 0.012 mg a.e./L in grass shrimp (Johnson and Finley 1980) to 1.13 mg a.e./L in freshwater mussels (Keller 1993). The minimum application for Hydrothol formulations exceeds the LC₅₀ for sensitive species of aquatic invertebrates by a factor of about 4 [$0.05 \text{ mg a.e./L} \div 0.012 \text{ mg a.e./L} \approx 4.16$]. Thus, mortality in sensitive species of aquatic invertebrates would be expected across the range of application rates for Hydrothol formulations. Substantial mortality in tolerant species of aquatic invertebrates would be expected at application rates in excess of about 1 mg a.e./L.

The risk characterization for aquatic invertebrates in the current Forest Service risk assessment is similar to that in the EPA ecological risk assessment (U.S. EPA/OPP 2005c). For acute exposures at the maximum application rate, the EPA gives risk quotients based on LC₅₀ values of 60-417 (U.S. EPA/OPP 2005c, Table 25, p. lxii). Adjusted for the use of LC₅₀ values, the RQs would correspond to HQs of 1200-8340. As noted above, the acute HQ for sensitive species at the maximum application rate in the current Forest Service risk assessment is 2174. As with fish, the somewhat lower HQ value in the current Forest Service risk assessment, relative to those developed by the EPA (U.S. EPA/OPP 2005c), is related to the use of the chronic NOEC for acute exposures rather than the adjusted value of the lowest EC₅₀ by a factor of 20 (Section 4.3.3.3.2).

Also as with fish, the risk characterization for accidental exposures is simple. For the liquid formulation of Hydrothol 191, the HQs for accidental exposures range from 7899 to 60,560 for sensitive species of aquatic invertebrates and from 319 to 3187 for tolerant species of fish. For the granular formulations, the HQs are lower—i.e., from 3155 to 15,777 for sensitive species and from 127 to 637 tolerant species. All of these HQs suggest that accidental spills of Hydrothol 191 formulations into a relatively small body of water could lead to substantial mortality in sensitive and tolerant aquatic invertebrates.

Finally, field studies that would permit an assessment of plausibility of the risk characterization for aquatic invertebrates are not available. As with fish, this limitation is

acknowledged but does not impact the concern for aquatic invertebrates in the application of Hydrothol 191 formulations.

4.4.3.4. Aquatic Plants

4.4.3.4.1. Macrophytes

The endothall formulations considered in this risk assessment are all registered for the control of aquatic macrophytes. As summarized in Appendix 5 (Table 2), these formulations are effective for the control of aquatic macrophytes. These efficacy studies are consistent with the risk characterization based on laboratory studies—i.e., across the range of labeled application rates, both Aquathol and Hydrothol formulations will damage aquatic macrophytes.

The above conclusion is reflected in the HQs for sensitive species. For Aquathol formulations, the HQs are 217 for acute exposures and 10 (1-91) for longer-term exposures. For Hydrothol formulations, the HQs are 20 for acute exposures and 1 (0.1-8) for longer-term exposures. The differences in the HQs for the two types of formulations reflect differences in the labeled application rates. As summarized in Table 3 and discussed in Section 2.4, the labeled target concentrations for Aquathol formulations are 0.35-3.5 mg a.e./L. For Hydrothol formulations, the labeled target concentrations for the control of macrophytes are 0.5-5 mg a.e./L.

Based on HQs, Aquathol formulations might be considered more effective than Hydrothol formulations. This conclusion is not reflected consistently in the field efficacy studies Appendix 5 (Table 2) and is probably incorrect. The most likely reason for this apparent contradiction is that the HQs are based on NOECs. As discussed in Section 4.3.3.4.1, the NOEC for Aquathol is substantially below the NOECs reported for Hydrothol. As also discussed in Section 4.3.3.4.1, the EC₅₀ values for both Aquathol and Hydrothol formulations are essentially identical. In terms of efficacy studies, EC₅₀ values are probably better indices of effectiveness than are NOECs.

4.4.3.4.2. Algae

The risk characterization for algae is relatively simple. Aquathol formulations are not labeled for the control of algae and do not appear to be effective algicides. Hydrothol formulations are labeled for the control of algae and appear to be very effective algicides.

As summarized in Worksheets G03 of the Aquathol workbooks that accompany this risk assessment for an application rate of 1 mg a.e./L (Attachments 1 and 2), the acute HQ for Aquathol formulations at an application rate of 1 mg a.e./L are 0.06 and 0.009 for sensitive and tolerant species, respectively. At the maximum labeled rate of 3.5 mg a.e./L, the HQs are 0.2 and 0.03 for sensitive and tolerant species, respectively, below the level of concern by factors ranging from 5 to over 30. Thus, there is no basis for suggesting that the application of Aquathol formulation will harm algae even at the maximum labeled rate. Accidental spills do lead to HQs above the level of concern—i.e., up to 16 for Aquathol K (liquid) and up to 2 for Aquathol Supper K (granular).

The labeled application rates for Hydrothol formulations for the control of algae range from 0.05 to 1.5 mg a.e./L, which are below those for the control of aquatic macrophytes—i.e., 0.5 to 5 mg a.e./L. These differences in labeled rates are clearly justified because algae are much more sensitive than are macrophytes to Hydrothol formulations. As summarized in Worksheets G03 of the Hydrothol workbooks that accompany this risk assessment for an application rate of 1 mg a.e./L (Attachments 3 and 4), the acute HQs for algae are 2000 for sensitive species and 4 for tolerant species. This substantial range of HQs reflects the documented differences in the sensitivity of different species of algae to Hydrothol formulations (Section 4.3.3.4.2). At the minimum application rate of 0.05, the acute HQs are 100 for sensitive species of algae but only 0.2 for tolerant species of algae. In other words, the minimum application rate for Hydrothol formulations could damage some species of algae but not others.

Application rates have a greater impact in terms of the duration of control or, for nontarget species, the duration of any adverse effect. At the lowest application rate of 0.05 mg a.e./L, the lower bound of the HQ—i.e., that associated with the rapid dissipation of the herbicide—is only 0.5. At the highest application rate of 1.5 mg a.e./L, the lower bound of the HQ for sensitive species is 14. Consequently, the use of the upper bound target concentrations for Hydrothol formulations may be required to achieve effective control of algae in areas or under conditions in which the formulations may disperse or degrade rapidly.

The above discussion is not intended to imply that effects on nontarget algal species are desirable. By definition, this is not the case. Nonetheless, the use of algicides to control algal populations is generally based on the assessment that the existing algal community—i.e., both target and nontarget species—is creating undesirable conditions in surface water and that the reduction in algal populations is the desired outcome. This is essentially the justification for using any algicide.

4.4.3.5. Aquatic Microorganisms

As discussed in Section 4.1.3.5, relatively little information is available on the toxicity of endothall formulations to aquatic microorganisms. The limited information that is available suggests that some aquatic microorganisms may be somewhat more sensitive than algae to dipotassium salt of endothall. No information, however, is available on the toxicity of the mono-amine salt of endothall to aquatic microorganisms.

As discussed in Section 3.2.3.4.2, treatment of surface water with endothall formulations may result in a substantial decrease in oxygen, if the treated water contains dense populations of sensitive aquatic plants. Simsiman and Chesters (1975) suggest that this severe oxygen depletion will result in a substantial decrease in microbial activity. This secondary effect would likely enhance any direct toxic action of endothall on aquatic microorganisms.

5. REFERENCES

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

E-Docket01	E-Docket No. EPA-HQ-OPP-2004-0370 at Regulations.gov. A total of 129 files.
E-Docket02	E-Docket No.EPA-HQ-OPP-2007-0097 at Regulations.gov. A total of 19 files, most of which are not specific to endothall.
EPA01	Studies summarized in various reports from the U.S. EPA/OPP as specified for each citations.
Internet	Various publications located on the Internet.
SET00	Papers from previous risk assessments and preliminary scoping [n=4].
SET01-TOXL	Preliminary TOXLINE literature search [n=75].
SET01-AGRI	Preliminary AGRICOLA literature search [n=9].
SET01-ECOT	Preliminary ECOTOX literature search [n=41].
SET02	Tree search of key reviews [n=24].
SET03	Supplemental tree search of primary literature [n=13].
SET04	Supplemental tree search of primary literature.
SET05	References from external peer review.
Std	Standard references used in most Forest Service risk assessments.
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Table 1: Physical and chemical properties of endothall(acid)

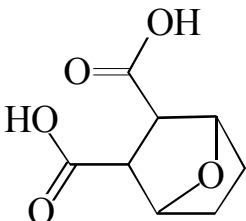
Property	Value	Reference
Nomenclature		
Common Name	Endothall (U.S.) or Endothal (British and French)	Tomlin 2004
IUPAC Name	7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acid	Tomlin 2004
CAS Name	7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acid	Tomlin 2004
Structure		U.S. EPA/OPP 2005c
Appearance/state, ambient	Colorless crystals (monohydrate).	Tomlin 2004
Bioconcentration	Dipotassium salt: 0.08x (edible) 0.35x (whole) (MRID 4264001) 10 (<i>Gambusia affinis</i>) 1.05 0.653 0.003 to 0.008 0.09 (whole body, 72 h) 0.023 (max edible at 12 h)	U.S. EPA/OPP 2005c, Table 1 Isensee 1976 Chiou et al. 1977 Neely and Mackay 1982 Serns 1977 Sikka et al. 1975
CAS number	145-73-3 [unstated stereochemistry]	Tomlin 2004
Density	1.431 at 20 °C	Tomlin 2004
Henry's law constant	$3.8 \times 10^{-13} \text{ Pa m}^3 \text{ mol}^{-1}$ (calculated)	Tomlin 2004
K_{a-ads}/K_{d-des}	0.15/0.0(loamy sand) 0.80/4.3 (sandy loam) 0.56/2.57 (clay loam) 7.94/37.25 (silt loam)	U.S. EPA/OPP 2005c, Table 1
Kd	0.958	Reinert and Rogers 1984
log K_{ow}	-2.09 (unspecified pH) -3.1 ($K_{ow} = 0.0008$) 1.91 (acid, unspecified pH) 0.132 (dipotassium salt)	Tomlin 2004 U.S. EPA/OPP 2005j Reinert and Rogers 1984 Reinert and Rogers 1985
Melting point	144 °C (monohydrate)	Tomlin 2004 USDA/ARS 1995
Molecular formula	$C_8H_{10}O_5$	Tomlin 2004
Molecular weight (g/mole)	186.2	Tomlin 2004
Sediment-Water half life	9 days (Dipotassium salt, silt loam soil, anaerobic)	U.S. EPA/OPP 2005c, Table 1
Sediment dissipation half life	8.9 days (MRID 44093403, dipotassium salt) 2.5-3.4 days (MRID 44093402, dipotassium salt)	U.S. EPA/OPP 2005c, Table 1

Table 1: Physical and chemical properties of endothall(acid)

Property	Value	Reference
SMILES Notation	<chem>OC(=O)[C@H]1[C@H]([C@@H]2CC[C@H]1O2)C(=O)O</chem> [with stereochemistry] <chem>OC(=O)C1C(C2CCC1O2)C(=O)O</chem> [without stereochemistry]	Tomlin 2004
Soil half life, field dissipation		
Soil metabolism half life (aerobic)	14.5 days (Dipotassium salt in sandy loam soil)	U.S. EPA/OPP 2005c, Table 1
Soil metabolism half life (anaerobic)		
Soil photolysis half life	48.7 days (irradiated), 100.4 days (dark)	U.S. EPA/OPP 2005c, Table 1
U.S. EPA Docket Number	EPA-HQ-OPP-2004-0370 EPA-HQ-OPP-2007-0097	
Vapor pressure	2.09×10^{-5} mPa (24.3 °C) <i>[This appears to apply to DMAA salt. See Table 0]</i>	Tomlin 2004
Vegetation half-life	7 days	Knissel and Davis 2000
Water hydrolysis half-life	DMAA and potassium salts stable at pH 5, 7, and 9	U.S. EPA/OPP 2005c, Table 1
Water, aquatic metabolism half life	10 days (dipotassium salt, aerobic, flooded silt loam) 4 days (experimental pools)	U.S. EPA/OPP 2005c, Table 1; Reynolds 1992 Reinert and Rogers 1985; Reinert et al. 1985b
	8.45 days	Reinert et al. 1986
	12 days (experimental pools)	Yeo 1970
Water photolysis half-life	does not absorb light at >290nm	U.S. EPA/OPP 2005c, Table 1
Water, dissipation half-life	0.1 to 0.23 days (lake)	Reinert and Rogers 1985; Reinert et al. 1988
	3.3 (1.9-4.9)	Maini 1992
Water solubility (mg/L)	100 g/kg (20 °C) 100,000 mg/L	Tomlin 2004 USDA/ARS 1995

Table 2: Comparison of endothall acid and salts

Property ¹	Acid	Dipotassium salt	Mono (N,N-dimethylalkyl-amine) salt ²
CAS No.	145-73-3	2164-07-0	66330-88-9
EPA PC Code	038901	038904	038905
Molecular weight	186.2	262.4	N/A
Molecular formula	C ₈ H ₁₀ O ₅	C ₈ H ₈ K ₂ O ₅	N/A
a.i. to a.e. conversion	N/A	0.71 [186.2/262.4]	0.44 ³
Aquatic dissipation half life (days)	No data	0.8 (lake water) (MRID 44093403) 0.4 (uncontained) 5.4-8.5 (contained) (MRID 44093402)	<24 h in sediment (MRID 44820103)
pKa ₁ , pKa ₂	4.32, 6.22	4.16, 6.14	4.24, 6.04
Soil field dissipation half life (days)	No data	CA: <7.0 (loam) PA: <9.0 (silty clay loam)	CA: 13 (loam) PA: 19 (silty clay loam)
Vapor pressure (mm Hg@24.3°C)	3.92 x 10 ⁻⁵	3.92 x 10 ⁻⁵	2.09 x 10 ⁻⁵
Water Solubility	100,000 mg/kg	>650,000 mg/L	>500,000 mg/L

¹ Adapted from U.S. EPA/OPP, 2005c, Table 1, unless otherwise specified.

² Alkyl is C8 to C18 derived from coconut oil.

³ The conversion factor for the amine salt is based on the a.i. and a.e. content from the product labels:

Hydrothol 191 liquid: 23.36% a.e. ÷ 53% a.i. = 0.441

Hydrothol 191 granular: 5% a.e. ÷ 11.2% a.i. = 0.446

Table 3: Commercial formulations of endothall

Trade Name, (Supplier), Date of most recent EPA label.	Type of Formulation, a.i., [CAS No.], EPA Reg. No.	a.i. and a.e. % by weight ^a (Bulk density ^b)	Lbs per Gallon	Application Rates and Recommended Uses
Aquathol K (United Phosphorus Limited), Aug. 16, 2006.	Liquid, dipotassium salt, [2164-07-0], 4581-204	40.3% a.i. 28.6% a.e. (10.7 lb/gal.)	4.23 lb a.i./gallon 3 lb a.e./gallon	Spray to surface or injection below surface. Apply with least amount of water compatible with equipment. Dose rates are given in ppm a.i. Entire water body: 0.5 to 5 ppm (salt) [Equivalent to 0.35 to 3.5 ppm a.e.] Spot or Lake Margin: 1.5 to 5 ppm (salt) [Equivalent to 1 to 3.5 ppm a.e.] Surface application only.
Aquathol Super K (United Phosphorus Limited), Aug. 18, 2006.	Granular, dipotassium salt, [2164-07-0], 4581-388	63% a.i. 44.7% a.e.	N/A	Dose rate units not specified on label. Based on composition and application directions, the rates are in a.i. Entire water body: 0.5 to 5 ppm (salt) [Equivalent to 0.35 to 3.5 ppm a.e.] Spot or Lake Margin: 1.5 to 5 ppm (salt) [Equivalent to 1 to 3.5 ppm a.e.]
Hydrothol 191 (United Phosphorus Limited) Aug. 22, 2006.	Liquid, mono(N,N,-dimethyl-alkylamine) salt, [66330-88-9], 4581-174	53% a.i. 23.36% a.e. (8.7 lb/gal.)	2 lb a.e./gallon	Spray to surface or injection below surface. A minimum contact time of two hours is recommended. Dose rates are given in ppm endothall acid. Do not treat more than 1/10 of lake or pond at doses greater than 1.0 ppm. Algae: 0.05 to 1.5 ppm Macrophytes in Lakes and Ponds: 0.5 to 3 ppm Drainage Canals ¹ : 3 to 5 ppm for heavy infestation 1 to 2 ppm for moderate infestation Apply evenly to water surface.
Hydrothol 191 Granular (United Phosphorus Limited), Aug. 22, 2006.	Granular, mono(N,N,-dimethyl-alkylamine) salt, [66330-88-9], 4581-172	11.2% a.i. 5% a.e.	N/A	Dose rates are given in ppm endothall acid. Do not treat more than 1/10 of lake or pond at doses greater than 1.0 ppm. Algae: 0.05 to 1.5 ppm Macrophytes in Lakes and Ponds: 0.5 to 3 ppm Drainage Canals ¹ : 3 to 5 ppm for heavy infestation 1 to 2 ppm for moderate infestation

U.S. EPA labels obtained from <http://oaspub.epa.gov/pestlabl/ppls.home>. U.S. EPA documents and labels reference Cerexagri Inc. as the registrant. Cerexagri Inc., however, has been purchased by United Phosphorus Limited in 2006. See Section 2.2 for details.

^a The % a.i. for Hydrothol formulations are approximations reported in the label for the granular and MSDS for the liquid formulation.

^b Bulk density is used by WorksheetMaker only for liquid formulations. For Aquathol K, the bulk density is based on specific gravity of 1.285 and water density of 8.3290 lb/gal. For Hydrothol 191 liquid, the bulk density is based on a specific gravity of 1.044.

Table 4: Known inert ingredients contained in commercial formulations of endothall

Formulation (% of formulation classified as inert)^a	Listed Inerts: Name, CAS No.	Inert % by Weight
Aquathol K (59.7%)	No listed inerts	
Aquathol Super K (37%)	2-propenamide, polymer with potassium, 31212-13-2	27.5%
Hydrothol 191 (47%)	No listed inerts	
Hydrothol 191 Granular (89%)	No listed inerts	

^a See Table 3 for additional information on formulations.

^b See Section 3.1.14 for a discussion of inerts

NOTE: No inerts for endothall formulations are listed at the NCAP web site:

<http://www.pesticide.org/FOIA/inertlinks.html>

Table 5: Worker exposure assessments for accidental skin contact

Scenario	mg/kg bw		
	Central	Lower	Upper
Aquathol Liquid (3 lbs a.e./gallon)			
Contaminated Gloves, 1 min.	0.016	0.009	0.029
Contaminated Gloves, 1 hour	0.932	0.533	1.732
Spill on Hands, 1 hour	0.117	0.043	0.311
Spill on lower legs, 1 hour	0.288	0.105	0.767
Hydrothol Liquid (2 lbs a.e./gallon)			
Contaminated Gloves, 1 min.	0.010	0.006	0.019
Contaminated Gloves, 1 hour	0.605	0.346	1.123
Spill on Hands, 1 hour	0.076	0.028	0.202
Spill on lower legs, 1 hour	0.187	0.068	0.497

Table 6: Concentrations in water after an accidental spill into a small pond

	Concentrations in Water (mg a.e. /L)		
	Central	Lower	Upper
Aquathol K	140.0	28.0	280.1
Hydrothol 191 (liquid)	90.8	18.2	181.7
Aquathol and Hydrothol Granular	18.1	7.3	36.3

Table 7: Summary of toxicity values used in human health risk assessment			
Duration	Derivation of RfD	Reference	Comment
Short-term Incidental Exposure (1 to 30 days)			
NOAEL Dose	9.4 mg/kg bw/day	Trutter 1993 MRID 43152101	See discussion of study in Section 3.1.9.2 and discussion of surrogate RfD in Section 3.3.2. U.S. EPA/OPP (2005a, p. 7) also notes that this NOAEL is designated for shorter-term (1-30 day) occupational exposures.
LOAEL Dose	60 mg/kg bw/day		
LOAEL Endpoint(s)	Decreased pup weight		
Species, sex	Rats, male and females		
Uncertainty Factor	100	U.S. EPA/OPP 2005a, 2005e	
Surrogate RfD	0.094 mg/kg bw/day		
Chronic – lifetime exposure			
NOAEL Dose	N/A	Trutter 1993 MRID 43152101	See discussion of study in Section 3.1.9.2 and discussion of RfD in Section 3.3.3. U.S. EPA/OPP (2005a, p. 7) also notes that this NOAEL is designated for longer-term (1-6 months) occupational exposures.
LOAEL Dose	2 mg/kg bw/day		
Species, sex	Rats, 2-generation reproduction stud		
LOAEL Endpoint(s)	Gastric lesions		
Uncertainty Factor	300	U.S. EPA/OPP 2005a	
RfD	0.007 mg/kg bw/day		
Occupational Exposure – (1 to 30 days)			
NOAEL Dose	9.4 mg/kg bw/day	Trutter 1993 MRID 43152101	Identical to surrogate acute RfD. See discussion in Section 3.3.4.
LOAEL Dose	60 mg/kg bw/day		
LOAEL Endpoint(s)	Decreased pup weight		
Species, sex	Rats, male and females		
Uncertainty Factor	100	U.S. EPA/OPP 2005a	
Surrogate RfD	0.094 mg/kg bw/day		
Occupational – 1 to 6 month exposure periods			
NOAEL Dose	N/A	Trutter 1993 MRID 43152101	Identical to chronic RfD. See discussion in Section 3.3.4.
LOAEL Dose	2 mg/kg bw/day		
LOAEL Endpoint	Rats, 2-generation reproduction stud		
Species, sex	Gastric lesions		
Uncertainty Factor/MOE	300	U.S. EPA/OPP 2005a	
Equivalent RfD	0.007 mg/kg bw/day		

Table 8: Estimates of dose-severity relationships in humans

NOTE: The dose-severity relationships detailed in this table and discussed in Section 3.3.5 should not be interpreted as suggesting that acute exposures above the surrogate acute RfD of 0.094 mg/kg bw or longer-term exposures above the chronic RfD of 0.007 mg/kg bw/day are acceptable.

Dose (mg/kg bw)	Corresponding Hazard Quotient	Endpoint	Reference
Acute Toxicity			
0.094	1	Surrogate acute RfD based on NOAEL of 9.4 mg/kg bw \div 100.	Section 3.3.2
0.6	6	Acute LOAEL of 60 mg/kg bw \div 100. Associated with decreased pup weight.	Section 3.3.2
N/A	N/A	Potentially lethal dose in human.	Section 3.3.5
28.5	303	Lowest oral LD ₅₀ in experimental mammals	Section 3.1.4
92	979	Lethal dose in humans. The minimum lethal dose in humans cannot be characterized.	Allender 1983
Chronic Toxicity			
0.007	1	Chronic RfD from U.S. EPA/OPP	Section 3.3.3.
0.02	3	Chronic RfD from U.S. EPA/ORD	Section 3.3.3.
0.06	8	LOAEL of 6 mg/kg bw from ORD chronic RfD \div 100	Section 3.3.3.

Table 9: Elaborated HQ for workers based on the chronic RfD

Central Estimates of HQ

Treatment Volume (acre-feet)	Target Concentration in mg/L (ppm)							
	0.05	0.1	0.35	0.5	1	1.5	3.5	5
1	8E-04	2E-03	5E-03	8E-03	2E-02	2E-02	5E-02	8E-02
5	4E-03	8E-03	3E-02	4E-02	8E-02	0.1	0.3	0.4
10	8E-03	2E-02	5E-02	8E-02	0.2	0.2	0.5	0.8
25	2E-02	4E-02	0.1	0.2	0.4	0.6	1.3	1.9
50	4E-02	8E-02	0.3	0.4	0.8	1.1	3	4
100	8E-02	0.2	0.5	0.8	1.5	2	5	8
150	0.1	0.2	0.8	1.1	2	3	8	11
300	0.2	0.5	1.6	2	5	7	16	23

Lower Bounds of HQ

Treatment Volume (acre-feet)	Target Concentration in mg/L (ppm)							
	0.05	0.1	0.35	0.5	1	1.5	3.5	5
1	6E-04	1E-03	4E-03	6E-03	1E-02	2E-02	4E-02	6E-02
5	3E-03	6E-03	2E-02	3E-02	6E-02	1E-01	0.2	0.3
10	6E-03	1E-02	4E-02	6E-02	0.1	0.2	0.4	0.6
25	2E-02	3E-02	0.1	0.2	0.3	0.5	1.1	1.6
50	3E-02	6E-02	0.2	0.3	0.6	1.0	2	3
100	6E-02	0.1	0.4	0.6	1.3	1.9	4	6
150	1E-01	0.2	0.7	1.0	1.9	3	7	10
300	0.2	0.4	1.3	1.9	4	6	13	19

Upper Bounds of HQ

Treatment Volume (acre-feet)	Target Concentration in mg/L (ppm)							
	0.05	0.1	0.35	0.5	1	1.5	3.5	5
1	1E-03	2E-03	7E-03	1E-02	2E-02	3E-02	7E-02	0.1
5	5E-03	1E-02	4E-02	5E-02	0.1	0.2	0.4	0.5
10	1E-02	2E-02	7E-02	0.1	0.2	0.3	0.7	1.0
25	3E-02	5E-02	0.2	0.3	0.5	0.8	1.8	3
50	5E-02	0.1	0.4	0.5	1.0	1.6	4	5
100	0.1	0.2	0.7	1.0	2	3	7	10
150	0.2	0.3	1.1	1.6	3	5	11	16
300	0.3	0.6	2	3	6	9	22	31

All HQ values are based on the chronic RfD of 0.007 mg/kg bw/day (Section 3.3.3). The box enclosing target concentrations of 0.35 to 3.5 mg/L spans the range of target concentrations for Aquathol formulations. The full table with the target concentrations of 0.05 to 5 mg/L spans the range of target concentrations for Hydrothol formulations.

Table 10: Elaborated HQ for workers based on the acute RfD

Central Estimates of HQ

Treatment Volume (acre-feet)	Target Concentration in mg/L (ppm)							
	0.05	0.1	0.35	0.5	1	1.5	3.5	5
1	6E-05	1E-04	4E-04	6E-04	1E-03	2E-03	4E-03	6E-03
5	3E-04	6E-04	2E-03	3E-03	6E-03	8E-03	2E-02	3E-02
10	6E-04	1E-03	4E-03	6E-03	1E-02	2E-02	4E-02	6E-02
25	1E-03	3E-03	1E-02	1E-02	3E-02	4E-02	1E-01	0.1
50	3E-03	6E-03	2E-02	3E-02	6E-02	8E-02	0.2	0.3
100	6E-03	1E-02	4E-02	6E-02	0.1	0.2	0.4	0.6
150	8E-03	2E-02	6E-02	8E-02	0.2	0.3	0.6	0.8
300	2E-02	3E-02	0.1	0.2	0.3	0.5	1.2	1.7

Lower Bounds of HQ

Treatment Volume (acre-feet)	Target Concentration in mg/L (ppm)							
	0.05	0.1	0.35	0.5	1	1.5	3.5	5
1	5E-05	1E-04	3E-04	5E-04	1E-03	1E-03	3E-03	5E-03
5	2E-04	5E-04	2E-03	2E-03	5E-03	7E-03	2E-02	2E-02
10	5E-04	1E-03	3E-03	5E-03	1E-02	1E-02	3E-02	5E-02
25	1E-03	2E-03	8E-03	1E-02	2E-02	4E-02	8E-02	0.1
50	2E-03	5E-03	2E-02	2E-02	5E-02	7E-02	0.2	0.2
100	5E-03	1E-02	3E-02	5E-02	1E-01	0.1	0.3	0.5
150	7E-03	1E-02	5E-02	7E-02	0.1	0.2	0.5	0.7
300	1E-02	3E-02	0.1	0.1	0.3	0.4	1.0	1.4

Upper Bounds of HQ

Treatment Volume (acre-feet)	Target Concentration in mg/L (ppm)							
	0.05	0.1	0.35	0.5	1	1.5	3.5	5
1	8E-05	2E-04	5E-04	8E-04	2E-03	2E-03	5E-03	8E-03
5	4E-04	8E-04	3E-03	4E-03	8E-03	1E-02	3E-02	4E-02
10	8E-04	2E-03	5E-03	8E-03	2E-02	2E-02	5E-02	8E-02
25	2E-03	4E-03	1E-02	2E-02	4E-02	6E-02	0.1	0.2
50	4E-03	8E-03	3E-02	4E-02	8E-02	0.1	0.3	0.4
100	8E-03	2E-02	5E-02	8E-02	0.2	0.2	0.5	0.8
150	1E-02	2E-02	8E-02	0.1	0.2	0.4	0.8	1.2
300	2E-02	5E-02	0.2	0.2	0.5	0.7	1.6	2

All HQ values are based on the surrogate acute RfD of 0.094 mg/kg bw/day (Section 3.3.2).

Table 11: Risk characterization for accidental exposures in workers

Scenario	Hazard Quotients		
	Central	Lower	Upper
Aquathol Liquid (3 lbs a.e./gallon)			
Contaminated Gloves, 1 min.	0.2	9E-02	0.3
Contaminated Gloves, 1 hour	10	6	18
Spill on Hands, 1 hour	1.2	0.5	3
Spill on lower legs, 1 hour	3	1.1	8
Hydrothol Liquid (2 lbs a.e./gallon)			
Contaminated Gloves, 1 min.	0.1	6E-02	0.2
Contaminated Gloves, 1 hour	6	4	12
Spill on Hands, 1 hour	0.8	0.3	2
Spill on lower legs, 1 hour	2.0	0.7	5

All HQ values are based on the surrogate acute RfD of 0.094 mg/kg bw/day (Section 3.3.2).

Table 12: Risk characterization for the general public after accidental spills

Scenario	Receptor	Hazard Quotients		
		Central	Lower	Upper
Aquathol K				
Water consumption (spill)	Child	112	14	336
Fish consumption (spill)	Adult Male	0.3	5E-02	0.5
Fish consumption (spill)	Subsistence Populations	1.3	0.3	3
Hydrothol 191 (Liquid)				
Water consumption (spill)	Child	73	9	218
Fish consumption (spill)	Adult Male	0.2	3E-02	0.3
Fish consumption (spill)	Subsistence Populations	0.9	0.2	1.7
Aquathol and Hydrothol Granular Formulations				
Water consumption (spill)	Child	15	4	44
Fish consumption (spill)	Adult Male	3E-02	1E-02	7E-02
Fish consumption (spill)	Subsistence Populations	0.2	7E-02	0.3

All HQ values are based on the surrogate acute RfD of 0.094 mg/kg bw/day (Section 3.3.2).

Table 13: Summary of toxicity values for terrestrial organisms

Group/Duration	Organism	Endpoint, Note	Toxicity Value (a.e.)	Reference
Acute				
	Non-canine Mammals	NOAEL, Gastric lesions	9.4 mg/kg bw	Section 4.3.2.1.1.
	Canine Mammals	Estimated NOAEL from rats	2.0 mg/kg bw	Section 4.3.2.1.1
	Birds	NOAEL, acute dietary	94.0 mg/kg bw	Section 4.3.2.2
	Honey Bee	N/A	Practically non-toxic	Section 4.3.2.3.1
Longer-term				
	Non-canine Mammal	LOAEL of 2 mg/kg bw ÷ 3	0.7 mg/kg bw/day	Section 4.3.2.1.2
	Canine Mammal	Same as other mammals	0.7 mg/kg bw/day	Section 4.3.2.1.2
	Bird	Reproduction NOEC	3.5 mg/kg bw/day	Section 4.3.2.2.
The toxicity values in this table are used for all forms of endothall.				

Table 14: Aquathol toxicity values for aquatic organisms

Group/Duration	Organism	Endpoint, Note	Toxicity Value (mg a.e./L)	Reference
Aquatic Animals				
Acute				
Fish	Sensitive	NOEC estimated from LC ₅₀	1.8	Section 4.3.3.1.1.
	Tolerant	NOEC estimated from LC ₅₀	89	Section 4.3.3.1.1.
Invertebrates	Sensitive	NOEC estimated from LC ₅₀	6.2	Section 4.3.3.3.1.
	Tolerant	NOEC estimated from LC ₅₀	18	Section 4.3.3.3.1.
Longer-term				
Fish	Sensitive	NOEC, egg-to-fry	1.3	Section 4.3.3.1.1
	Tolerant	NOEC, egg development	1.79	Section 4.3.3.1.1
Invertebrates	Sensitive	Estimated reproductive NOEC	1.7	Section 4.3.3.3.1
	Tolerant	Reproductive NOEC	5	Section 4.3.3.3.1
Aquatic Plants				
Algae	Sensitive	NOEC estimated from EC ₅₀ .	18	Section 4.3.3.4.2
	Tolerant	NOEC estimated from EC ₅₀ .	110	Section 4.3.3.4.2
Macrophytes	Sensitive	14-day NOEC	0.0046	Section 4.3.3.4.1
	Tolerant	½ maximum application rate	1.75	Section 4.3.3.4.1

Table 15: Hydrothol toxicity values for aquatic organisms

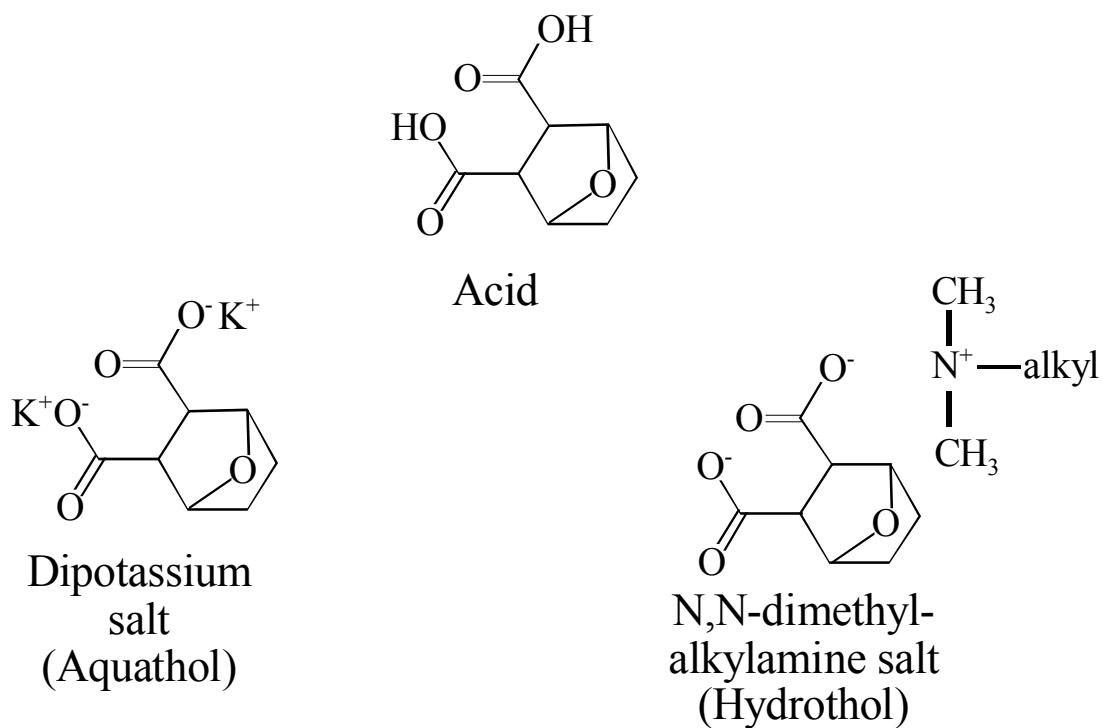
Group/Duration	Organism	Endpoint, Note	Toxicity Value (mg a.e./L)	Reference
Aquatic Animals				
Acute				
Fish	Sensitive	Identical to chronic value	0.003	Section 4.3.3.1.1.
	Tolerant	Estimated NOEC from LC ₅₀	0.075	Section 4.3.3.1.1.
Invertebrates	Sensitive	Identical to chronic value	0.0023	Section 4.3.3.3.2.
	Tolerant	Estimated NOEC from LC ₅₀	0.057	Section 4.3.3.3.2.
Longer-term				
Fish	Sensitive	Estimated NOEC from LOEC	0.003	Section 4.3.3.1.2
	Tolerant	NOEC	0.056	Section 4.3.3.1.2
Invertebrates	Sensitive	Reproductive NOEC, <i>Daphnia</i>	0.0023	Section 4.3.3.3.2
	Tolerant	Reproductive NOEC, <i>Ceriodaphnia</i>	0.016	Section 4.3.3.3.2
Aquatic Plants				
Algae	Sensitive	NOEC, green algae	0.0005	Section 4.3.3.4.2
	Tolerant	NOEC, filamentous algae	0.250	Section 4.3.3.4.2
Macrophytes	Sensitive	14-day NOEC	0.050	Section 4.3.3.4.1
	Tolerant	½ maximum application rate	2.5	Section 4.3.3.4.1

Table 16: Relationship of LC₅₀ and NOEC values in fish for dipotassium salt

Species	LC₅₀	NOEC	Ratio	Reference
Bluegills	316	170	1.9	Bettencourt, 1993c
Goldfish	268	23	11.7	Berry 1984
Chinook Salmon	62.5	25.54	2.4	Liguori et al. 1983
Walleye, young	66	5.7	11.6	Paul et al. 1994
Walleye, older	73	23	3.2	Paul et al. 1994
Smallmouth Bass	60	23	2.6	Paul et al. 1994
Largemouth Bass	280	100	2.8	Paul et al. 1994

Statistical analysis for 95% Confidence Interval

Item Number	Value	Square of Error
1	1.9	10.702248
2	11.7	42.622239
3	2.4	7.680819
4	11.6	41.326525
5	3.2	3.886532
6	2.6	6.612247
7	2.8	5.623676
Average	5.17	
SSE	118.45	
Sample Standard Deviation	4.44	
Critical Value of t at 0.025	2.447	
Value of 2.5% Lower Bound	1.06	
Value of 97.5% Upper Bound	9.28	



Modified from U.S. EPA/OPP 2005c, Table 1

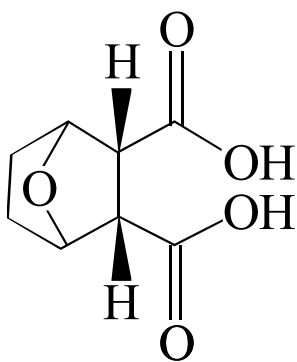
Figure 1: Endothall Acid and Salts

(Modified from Figure 1 in Sprecher et al. 2002)

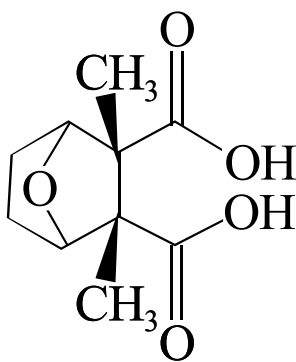


Figure 2: Aquatic Uses of Endothall in FS Regions

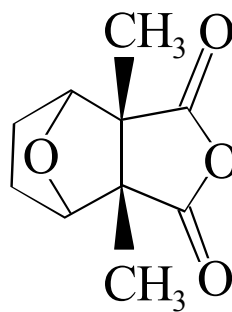
States with aquatic uses designated with an X.
 Modified from U.S. EPA/OPP (2005c), Figure 1, p. xix.



Endothall



Cantharidic
Acid



Cantharidin

Figure 3: Endothall, Cantharidic acid, and Cantharidin

Modified from Keckemet (1969) and Graziano and Casida (1987)

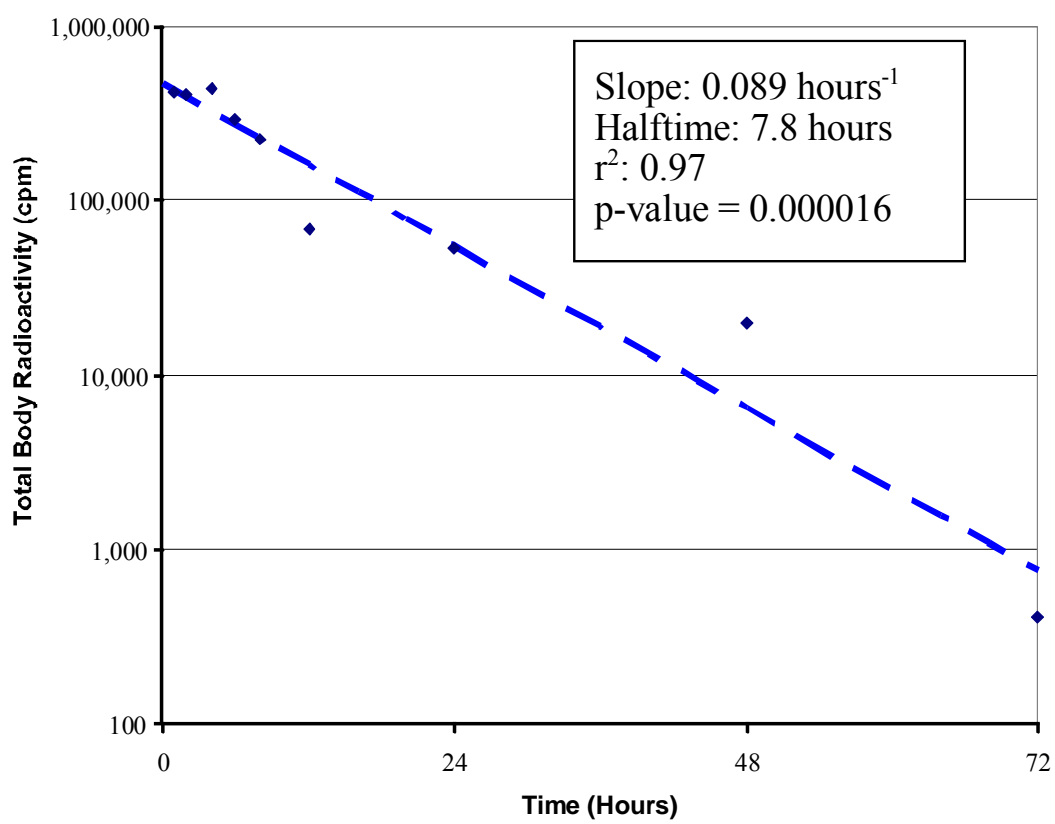


Figure 4: Whole-body elimination of endothall in rats

Data from Soo et al. 1967, p. 1020, Table III
See Section 3.1.3.1 for discussion.

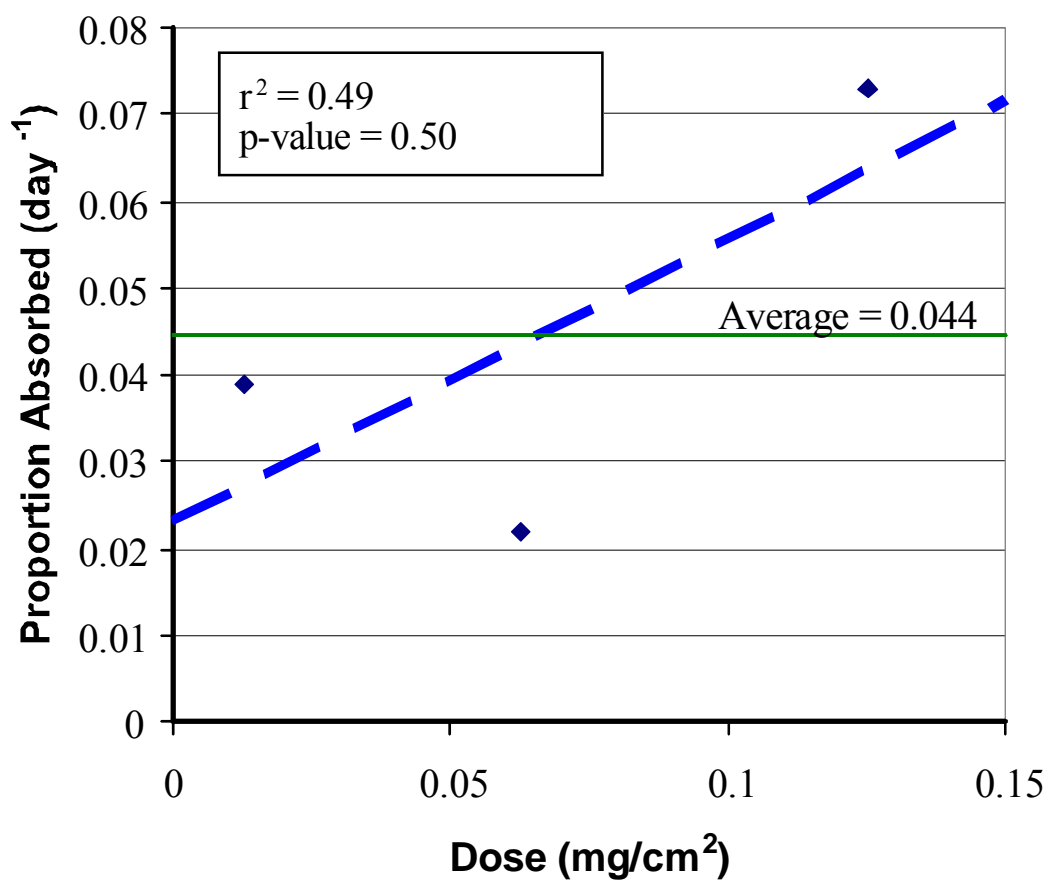


Figure 5: Relationship of dose to dermal absorption of endothall

Data from U.S. EPA/OPP 2005e, p.24
See Section 3.1.3.2 for discussion.

Appendix 1: Toxicity to mammals.

Note on Appendix 1: This appendix consists of a series of tables, listed below covering information on the toxicity of endosulfan, primarily from the open literature. Additional information on registrant submitted studies taken from various EPA documents is discussed in Section 3.

A1 Table 1: Oral LD ₅₀ data from Material Safety Data Sheets	143
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A1 Table 1: Oral LD₅₀ data from Material Safety Data Sheets

Formulation	a.i	a.e	LD ₅₀ (mg/kg bw)		
			MSDS	a.i.	a.e.
Aquathol K	40.3%	28.6%	99.5	40.1	28.5
Aquathol Super K	63.0%	44.7%	98	61.7	43.8
Hydrothol 191	53.0%	23.36%	233.4	123.7	54.5
Hydrothol 191 Granular	11.2%	5.0%	1540	172.5	77.0
See Section 3.1.4 for discussion.					

A1 Table 2: Dermal LD₅₀ data from Material Safety Data Sheets

Formulation	a.i	a.e	LD ₅₀ (mg/kg bw)		
			MSDS	a.i.	a.e.
Aquathol K	40.3%	28.6%	2,000	806	572
Aquathol Super K	63.0%	44.7%	>2,000	>1,260	>894
Hydrothol 191	53.0%	23.36%	480.9	255	112
Hydrothol 191 Granular	11.2%	5.0%	>10,000	>1,120	>500
See Section 3.1.12 for discussion.					

Appendix 1: Toxicity to mammals (*continued*)

A1 Table 3: Inhalation 4-hour LC₅₀ data from Material Safety Data Sheets

Formulation	a.i	a.e	LD ₅₀ (mg/L)		
			MSDS	a.i.	a.e.
Aquathol K	40.3%	28.6%	0.83	0.33	0.24
Aquathol Super K	63.0%	44.7%	N/A	N/A	N/A
Hydrothol 191	53.0%	23.36%	0.7	0.37	0.16
Hydrothol 191 Granular	11.2%	5.0%	5.32	0.60	0.27
See Section 3.1.13 for discussion. The inhalation LC ₅₀ for Hydrothol 191 Granular is noted in Dykstra (1978, p. 30). No other inhalation studies on other formulations are summarized.					

A1 Table 4: Acute Oral Toxicity

Species	Exposure	Response	Reference
Rats	Endothall (NOS)	LD ₅₀ Males: 57 (52-64) mg/kg bw Females: 46 (40-56) mg/kg bw	Gaines and Linder 1986
Rats, 0.25 to 0.26 kg males and 0.172 to 0.206 kg females	1 mg/rat oral dose	No signs of toxicity. NOAEL for overt signs of acute toxicity: 3.8 to 5.8 mg/kg bw.	Soo et al. 1967
Rats, 10/dose, 0.2 to 0.3 kg bw	Hydrothol 191 Liquid: 50, 150, 250, 250, 450, and 500 mg/kg bw.	LD ₅₀ : 221 mg/kg bw. Working Note: Cannot determine if the doses are in mg formulation or mg a.e. The LD ₅₀ reported is very close to the LD ₅₀ of 233.4 mg formulation/kg bw reported on MSDS.	Dykstra 1978, pp. 16-17
Rats	Aquathol NOS : 150, 250, 350, 450, 5000 mg/kg bw.	LD ₅₀ : 329 mg/kg bw Working Note: Cannot determine formulation.	Dykstra 1978, pp. 22
Rats, groups of 10/dose, 0.2 to 0.3 kg bw	Aquathol Granular: 100, 500, 1000, 2500, and 5000 mg/kg bw.	LD ₅₀ : 1340 mg/kg bw. Working Note: This is far above the LD ₅₀ given on the MSDS.	Dykstra 1978, pp. 24
Rats, groups of 10/dose, 0.2 to 0.3 kg bw	Hydrothol Granular: 1000, 2000, 3000, 4000, and 5000 mg/kg bw.	LD ₅₀ : 1540 mg/kg bw. Working Note: This corresponds to LD ₅₀ given on the MSDS.	Dykstra 1978, pp. 25

A1 Table 5: Acute Dermal Toxicity

Species	Exposure	Response	Reference
Rats	Endothall (NOS)	LD ₅₀ > 1000 mg/kg bw in males and females.	Gaines and Linder 1986
Rabbits	10 – 20% powder (NOS)	Mortality in rabbits with the most severe skin irritation	Goldstein 1952
Rabbits (6)	200 mg/kg bw, technical grade endothall	All six rabbits died overnight	Dykstra 1978, p. 2
Rabbits (n=6)	200 mg/kg bw Aquathol K (≈57.2 mg a.e./kg bw)	5/6 animals died overnight. Surviving rabbit recovered within 7 days.	Dykstra 1978, pp. 2-3

Appendix 1: Toxicity to mammals (*continued*)

A1 Table 5: Acute Dermal Toxicity			
Species	Exposure	Response	Reference
Rabbits, 4/dose, 2.3-3 kg bw	Aquathol liquid: 2, 5, and 10 g/kg bw	LD ₅₀ : 5,000 mg/kg bw Working Note: The LD ₅₀ reported on MSDS is 2000 mg/kg bw.	Dykstra 1978, pp. 22
Rabbits (n=8), 4 abraded and 4 unabraded	Animals dosed at 23.41 mg/kg bw and 52.67 mg/kg bw. Doses appear to be as a.e.	2/4 mortality at lower dose and 4/4 mortality at higher dose.	Dykstra 1978, pp. 12-13
Rabbits (4 per dose), 2.3-3 kg bw	Aquathol K liquid: 2, 5, and 10 g/kg bw	One death at 10 g/kg bw. Working Note: Cannot determine if the doses are in mg formulation or mg a.e. The LD ₅₀ reported on MSDS is 2000 mg/kg bw.	Dykstra 1978, pp. 20
Rabbits (4 per dose, 2 clipped and 2 abraded)	Aquathol Granular (NOS): 2, 5, and 10 g/kg	No mortality. LD ₅₀ : > 10,000 mg/kg bw Working Note: This is identical to LD ₅₀ reported on MSDS.	Dykstra 1978, pp. 23

A1 Table 6: Skin Irritation Studies

Species	Exposure	Response	Reference
Rabbits	1% powder (NOS)	Mild lesions in abraded skin. No lesions in unbraided skin.	Goldstein 1952
Rabbits	10 to 20% powder (NOS)	Severe skin lesions with necrosis.	Goldstein 1952
Rabbits, n=6, abraded and non-abraded skin	Aquathol K liquid, 0.5 ml	Slight erythema and edema in one animal at 24 hours. No irritation at 72 hours.	Dykstra 1978, pp. 20
Rabbits, abraded and non-abraded skin	Aquathol K liquid, 0.5 ml	No irritation at 24 or 72 hours.	Dykstra 1978, pp. 21
Rabbits, abraded and non-abraded skin	Aquathol Granular, 0.5 ml	No irritation at 24 or 72 hours.	Dykstra 1978, pp. 22-23

Appendix 1: Toxicity to mammals (*continued*)

A1 Table 7: Eye Irritation Studies

Species	Exposure	Response	Reference
Rabbits (n=6), 3 washed and unwashed, bw no specified	0.1 g technical grade endothall. Using the bw of 2.25 kg, the dose would be 44 mg a.e./kg bw.	Unwashed eyes: Severe eye damage with corneal involvement within 2 hours. All 3 rabbits died overnight. Washed eyes: Conjunctival irritation and congestion of the iris with full recovery by Day 5 in 2 rabbits. Corneal opacity in one rabbit which did not recover by Day 7.	Dykstra 1978, pp. 1-2
Rabbits (n=6), 3 washed and unwashed	0.1 g Aquathol K (~28.6 mg a.e.) Using the bw of 2.25 kg, the dose would be 12.7 mg a.e./kg bw.	Unwashed eyes: Conjunctival irritation and congestion of the iris, corneal opacity. No recovery by Day 7. Washed eyes: Conjunctival irritation and congestion of the iris. Full recovery in 5 days. No mortality noted in any animals	Dykstra 1978, pp. 2-3
Rabbits (n=6), no indication of washing	0.1 ml Aquathol K liquid.	Corneal opacity at 7 Days.	Dykstra 1978, pp. 19
Rabbits (n=6), 2-2.5 kg bw, no indication of washing	0.1 ml Aquathol K liquid.	Corneal opacity in all rats by Day 4. Complete recovery in 5/6 rabbits by Day 7	Dykstra 1978, pp. 21
Rabbits (n=6), 3 washed and unwashed	0.1 g Aquathol Granular (~44.7 mg a.e. under the assumption that the material was Aquathol Super K). Dose ≈ 20 mg a.e./kg bw.	Unwashed eyes: Conjunctival irritation and congestion of the iris, corneal opacity. No recovery by Day 7. Washed eyes: Conjunctival irritation only. Full recovery in 5 days. No mortality noted in any animals.	Dykstra 1978, pp. 4-5
Rabbits (n=6), no indication of washing, 2-2.5 kg bw	Aquathol Granular: 0.1 g (~44.7 mg a.e. under the assumption that the material was Aquathol Super K).	Conjunctival irritation and congestion of the iris, corneal opacity. No recovery by Day 7. Approximate dose: 20 mg a.e./kg bw.	Dykstra 1978, pp. 23
Rabbits (n=6), no indication of washing	0.1 ml of Hydrothol 191 liquid. Working Note: Based on a specific gravity of 1.044 and 23.36 % a.e. w/w, 0.1 mg would correspond to about 23 mg a.e.	3/6 animals died within 72 hours. Corrosion with complete corneal opacity by Day 7. No mortality noted in any animals. Approximate dose: 10 mg a.e./kg bw.	Dykstra 1978, pp. 16
Rabbits (n=6), no indication of washing	0.1 g of Hydrothol 191 granular. Working Note: Based on 5 % a.e. w/w, 0.1 g would correspond to about 5 mg a.e.	Conjunctival irritation and congestion of the iris, corneal opacity. No recovery by Day 7. No mortality noted in any animals. Approximate dose: 2.2 mg a.e./kg bw	Dykstra 1978, pp. 24

Appendix 1: Toxicity to mammals (*continued*)

A1 Table 8: Acute Toxicity on Intravenous Administration

Species	Exposure	Response	Reference
Rabbits and Dogs	5 to 10 mg/kg bw	5 mg/kg: Potentially lethal 10 mg/kg invariably lethal Cause of death may be cardiac arrest rather than respiratory failure.	Goldstein 1952
Dogs	5-10 mg/kg bw	Vomiting. Some dogs died due to respiratory failure.	Strensek and Woodward 1951
Rabbits	25-50 mg/kg bw	All died due to respiratory failure within 130 minutes	Strensek and Woodward 1951

A1 Table 9: Acute Toxicity on Intraperitoneal Administration

Species	Exposure	Response	Reference
Mice	10 mg/kg bw endothallmonohydrate	Extreme liver enlargement in 45 minutes. Increase in hepatic glycogenolysis. Lethargy and decreased respiration. Death within 60 to 90 minutes.	Graziano and Casida 1987
Mice	Endothall (NOS)	LD ₅₀ : 14 mg/kg bw	Kawamura et al. 1990

Appendix 1: Toxicity to mammals (*continued*)

A1 Table 10: Subchronic and Chronic Toxicity Studies

Species	Exposure	Response	Reference
Rats	Amine Salt , dietary 0, 150, 600, 1800 ppm in the diet for 90 days M: 0, 10, 39, 118 mg/kg/d F: 0, 12, 51, 153mg/kg/d	NOAEL = 39 mg/kg/day LOAEL = 118 mg/kg/day based on treatment related deficits in body weight.	Trutter 1994a MRID 43480801
Dogs	Amine Salt , dietary 0, 100, 400, 1000 ppm in the diet for 90 days. M: 0, 3.2, 11.7, 27.5 mg/kg/d F: 0, 3.2, 13.0, 28.9 mg/kg/d	NOAEL = 11.7 mg/kg/day LOAEL = 27.5 mg/kg/day based on decreases in body weight gain.	Trutter 1994b MRID 43480802
Dogs	Salt not specified in available information. Chronic NOS. M: 0, 5.7, 17 or 40 mg/kg/d F: 0, 6.5, 18, 33 mg/kg/d	NOAEL = not determined LOAEL (LDT) = 6.5 mg/kg/d based on gastric epithelial hyperplasia.	Shellenberger 1990a MRID 40745202
Mice, Crl:CD®1(ICR)BR mice (64/sex/group)	Disodium salt Dietary, 21 months 0, 50, 100, 300 ppm in the diet. Doses: 0, 7.5, 15, 45 mg/kg/d	NOAEL = 15 mg/kg/day LOAEL = 45 mg/kg/day based on decreased body weight gain (17% less than controls). Minimal to mild multifocal mineralization in the kidneys of male rats: 3/60, 9/60, 8/60, or 23/60 for 0, 50, 100, or 300 ppm groups, respectively. No evidence of carcinogenicity.	Shellenberger 1990b MRID 40685301 ^a
Mice, Crl:CD-1®(ICR)BR albino (60/sex/group)	Disodium salt Dietary, 79 weeks 0, 750, 1500 ppm M: 0, 124, 258 mg/kg/d F: 0, 152, 319 mg/kg/d	NOAEL = not determined LOAEL = 124 mg/kg/day based on decreased body weight gain in males.	Shellenberger 1990b MRID 43608301 ^a
Shellenberger 1990b (<i>continued</i>): No evidence of carcinogenicity. Gross pathology revealed abnormalities indicative of a direct (irritant) toxic effect on the digestive tract. In the sacrificed animals treatment-related observations were dose-related thickened wall of the glandular stomach and prolapsed rectum. In the unscheduled death animals common findings included enlarged spleens, liver and kidneys, pale kidneys and dark areas of the stomach.			
Rats, Crl:CD®(SD) BR albino	Disodium salt Dietary: 0, 300, 900, 1800ppm for 2 years. M: 0, 12, 37, 80 mg/kg/d F: 0, 16, 49, 110 mg/kg/d	NOAEL = 8 mg/kg/day LOAEL = 16 mg/kg/day based on decreased body weight and body weight gain in females (76% of controls) by the end of the study. Increase in the incidence of thickened walls of the stomach. no evidence of carcinogenicity	Plankenhorn 1990 MRID 41040301 ^a
Summaries of the above studies are taken from U.S. EPA/OPP 2005e unless otherwise specified. See Section 3.1.5 for discussion. ^a Supplemental information taken from U.S. EPA/OPP 2005f			

Appendix 2: Toxicity to birds

Information in this Appendix is based on the data summary in U.S. EPA/OPP (2005c) and Turner (1978) as well as supplemented information from available cleared reviews. For clarity, studies on which cleared reviews are available are references by author and year. Studies for which cleared reviews are not available and no additional details are available from Turner (1978) are referenced to U.S. EPA/OPP (2005c). Each reference is followed by the MRID number.

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A2 Table 1: Acute Oral/Gavage Toxicity to Birds			
Species	Exposure	Response	Reference
Endothall Acid			
Mallard duck (<i>Anas platyrhynchos</i>)	Gavage, 83% a.e. 30, 48, 78, 120, and 200 mg/kg bw. Groups of 5M/5F at each dose. 21 day observation period.	Reported LD ₅₀ < 30 mg a.e./kg bw in U.S. EPA/OPP 2005c. Birds regurgitated and the LD ₅₀ could not be estimated. Working Note: See Pedersen and Helsten 1992b below on impact of vomiting. Study author reports LD ₅₀ of 111 mg/kg bw based on mortalities of 10%, 20%, 50%, and 100% at four highest doses with a NOAEL of 30 mg/kg bw for mortality. Vomiting in all treatment groups within 2 hours of dosing. Reduced food consumption at all doses. Transient over Days 1-7.	Pedersen and Helsten 1992a, MRID 42359701
Mallard duck (<i>Anas platyrhynchos</i>)	Gavage, 83.6 % a.e.	LD ₅₀ : 229 mg a.e./kg bw	U.S. EPA/OPP 2005c, MRID 160000
Northern bobwhite quail (<i>Colinus virginianus</i>)	Gavage, 75% a.e.	LD ₅₀ : 500 mg a.e./kg bw	U.S. EPA/OPP 2005c, MRID 74220
Ring-Necked Pheasant (<i>Phasianus colchicus</i>)	Gavage, 83.6% a.e.	LD ₅₀ : <198 mg a.e./kg bw. Birds regurgitated and the LD ₅₀ could not be estimated.	U.S. EPA/OPP 2005c, MRID 160000

Appendix 2: Toxicity to Birds (continued)

A2 Table 1: Acute Oral/Gavage Toxicity to Birds			
Species	Exposure	Response	Reference
Endothall Dipotassium Salt			
Mallard duck (<i>Anas platyrhynchos</i>), 5M/5F per dose	Gavage, 18.8 % a.e., Aquathol 47. Formulation doses of 255, 355, 510, 695, and 985 mg/kg. a.e. doses of ≈48, 67, 94, 131, and 185 mg/kg.	LD ₅₀ : 61.6 mg a.e./kg bw Mortalities by dose: 3, 4, 10, 10, 10. Vomiting in all birds within 5 minutes of dosing. All mortalities within 24 hours of dosing. Lethargy and incoordination. Adverse effects at all doses. LOAEL: ≈50 mg/kg bw.	Pedersen and Helsten 1992b, MRID 42359501
Endothall Amine Salt			
Mallard duck (<i>Anas platyrhynchos</i>)	Gavage, 23.4% a.e.	LD ₅₀ : 91 mg a.e./kg bw. Vomiting in birds at lowest dose tested – i.e., 14 mg a.e./kg bw.	U.S. EPA/OPP 2005c, MRID 42359601 [study not listed in U.S. EPA/OPP 2005a]
Northern bobwhite quail (<i>Colinus virginianus</i>)	Gavage, 23.4%. Formulation doses: 215, 464, 1000, 2150, and 4640 mg/kg.	LD ₅₀ : 172 (135-219) mg a.e./kg bw. NOEC (mortality): 50 mg a.e./kg bw Signs of toxicity: depression, reduced reaction to external stimuli, wing droop, shallow and rapid respiration, prostrate posture, and loss of righting reflex.	Fink and Beavers 1977a. MRID 35237
Adapted from U.S. EPA/OPP (2005c), Table F-2, p. F-v with elaboration based on available cleared reviews.			

Appendix 2: Toxicity to Birds (continued)

A2 Table 2: Acute Dietary Toxicity to Birds			
Species	Exposure	Response	Reference
Endothall Acid			
Mallard duck (<i>Anas platyrhynchos</i>), 10 per dose	83.16% a.e. Dietary concentrations of 312, 625, 1250, 2500, and 5000 ppm for 5 days.	LC ₅₀ : >5,000 ppm No mortality of signs of toxicity. Small reductions in body weight gain at 625 and 1250 ppm. Substantial reductions in weight gain at 1250 and 5000 ppm. Apparent NOEC: 312 ppm. NOEC could have been higher but the DER does not report bw data.	Pedersen and Solatycki 1994b, MRID 43167702
Mallard duck (<i>Anas platyrhynchos</i>)	Up to 10,000 ppm, 84% a.e.	LC ₅₀ : >10,000 ppm One mortality at highest dose on eighth day.	Fink 1975, MRID 116271
Northern bobwhite quail (<i>Colinus virginianus</i>)	Up to 10,000 ppm, 84% a.e.	LC ₅₀ : >10,000 ppm Test organisms observed an additional three days while on untreated feed. No mortalities were observed.	U.S. EPA/OPP 2005c, MRID 116270
Northern bobwhite quail (<i>Colinus virginianus</i>)	83.16% a.e. Dietary concentrations of 312, 625, 1250, 2500, and 5000 ppm for 5 days.	LC ₅₀ : >5,000 ppm Signs of intestinal irritation in 5 birds at concentrations from 1250 to 5000 ppm. Apparent NOEC: 625 ppm.	Pedersen and Solatycki 1994a, MRID 43167701
Endothall Dipotassium Salt (all concentrations as a.e. unless otherwise specified)			
Mallard duck (<i>Anas platyrhynchos</i>)	Up to 2860 ppm, 26.6% a.e. (Aquathol K)	LC ₅₀ : >2,860 ppm No mortalities.	Fink and Beavers 1977b, MRID 35239
Mallard duck (<i>Anas platyrhynchos</i>)	Up to 1,475 ppm, 29.5% a.e., Aquathol K. Formulation doses: 312, 6.25, 1250, 2500, and 5000 ppm.	LC ₅₀ : >1,475 ppm No mortalities. Decrease body weight and food consumption at 1475 ppm a.e. (5000 ppm formulation). No other signs of toxicity. Apparent NOEC: 737.5 ppm a.e. (2500 ppm formulation)	Pedersen 1994b, MRID 43167802
Northern bobwhite quail (<i>Colinus virginianus</i>)	Up to 1,475 ppm, 29.5% a.e.	LC ₅₀ : >1,475 ppm Two mortalities at 347 ppm and one mortality at 1343 ppm	Pedersen 1994a, MRID 43167801
Northern bobwhite quail (<i>Colinus virginianus</i>)	Up to 2860 ppm, 28.6% a.e.	LC ₅₀ : >2,860 ppm No mortalities.	U.S. EPA/OPP 2005c, MRID 35238
Endothall Amine Salt (all concentrations as a.e.)			
Mallard duck (<i>Anas platyrhynchos</i>)	Up to 2336 ppm, 23.4% a.e. Hydrothol 191 (NOS)	LC ₅₀ : >2336 ppm No mortality at any dose. At 2336 ppm, lethargy, reduced food consumption, and reduced weight gain. At 1086 ppm, transient lethargy was observed. NOEL: 500 ppm.	Fink and Beavers 1977d, MRID 35241

Appendix 2: Toxicity to Birds *(continued)*

A2 Table 2: Acute Dietary Toxicity to Birds			
Species	Exposure	Response	Reference
Mallard duck (<i>Anas platyrhynchos</i>)	Up to 1170 ppm, 23.4% a.e.	LC ₅₀ : >1170 ppm	U.S. EPA/OPP 2005c, MRID 43167902
Northern bobwhite quail (<i>Colinus virginianus</i>)	Up to 2336 ppm, 23.4% a.e.	LC ₅₀ : > 2336 pm	Fink and Beavers 1977c, MRID 35240
Northern bobwhite quail (<i>Colinus virginianus</i>)	Up to 1170 ppm, 23.7% a.e.	LC ₅₀ : >1170 ppm	U.S. EPA/OPP 2005c, MRID 43167901
Adapted from U.S. EPA/OPP (2005c), Table F-2, p. F-vi with elaboration based on available cleared reviews.			

Appendix 2: Toxicity to Birds *(continued)*

A2 Table 3: Reproductive Toxicity to Birds			
Species	Exposure	Response	Reference
Endothall Acid			
Mallard duck (<i>Anas platyrhynchos</i>)	Dietary concentrations of 0, 10, 50, and 250 ppm	<p>No dose-related mortality in adults and no signs of toxicity.</p> <p>Embryo mortality was significantly higher in 250 ppm group relative to controls.</p> <p>Decreased body weights in chicks from 10 ppm and 250 ppm groups but not from the 50 ppm group.</p> <p>No other treatment related effects.</p> <p>EPA NOAEL: 50 ppm</p> <p>EPA LOAEL: 250 ppm based on early embryonic mortality</p>	Pedersen and Fletcher 1992, MRID 42507301
Northern bobwhite quail (<i>Colinus virginianus</i>)	Dietary concentrations of 0, 10, 50, and 250 ppm	<p>Mortality of 22% in control and low dose groups. Mortalities of 11% and 5% in 50 ppm and 250 ppm groups.</p> <p>No treatment relative pathology and no effects on body weight and food consumption.</p> <p>NOAEL: > 250 ppm</p> <p>LOAEL: not determined.</p>	Pedersen et al. 1992, MRID 42507302
Adapted from U.S. EPA/OPP (2005c), Table F-2, p. F-vii with elaboration based on available cleared reviews.			

Appendix 3: Toxicity to fish.

Information from the open literature is cited in the standard author/date format – e.g., Johnson and Finley 1980. This citation format is also used for studies with cleared reviews or studies with one-page summaries in the internal EPA review by Turner (1978). Information that is taken solely from EPA/OPP (2005c) is cited as the MRID number followed by the author-date citations used in EPA/OPP (2005c).

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A3 Table 1: Acute Toxicity, Endothall Acid			
Species	Exposure	Response	Reference
Bluegills (<i>Lepomis macrochirus</i>)	24 and 48 hours to endothall acid	24-h LC ₅₀ : 450 mg a.e./L 48-h LC ₅₀ : 280 mg a.e./L	Hughes and Davis (1962a)
Bluegill sunfish (<i>Lepomis macrochirus</i>)	96-h exposures to measured concentrations of 0, 8.4, 15, 18, 23, 74, and 130 mg a.e./L, flow-through	96-h LC ₅₀ : 77 mg a.e./L NOEC (sublethal effects) : 18 mg a.e./L	Bettencourt 1992a, MRID 42327701
Rainbow trout, (<i>Oncorhynchus mykiss</i>)	96-h exposures to measured concentrations of 0, 13, 30, 35, 57, 65, and 120 mg a.e./L, flow-through	96-h LC ₅₀ : 49 mg a.e./L NOEC (sublethal effects) : 13 mg a.e./L	Bettencourt 1992a, MRID 42327702

A3 Table 2: Acute Toxicity, Dipotassium Salt			
Species	Exposure	Response	Reference
Rainbow trout (<i>Oncorhynchus mykiss</i>)	Aquathol K, 28.6% a.e.	EC ₅₀ : 65.78 mg a.e./L	MRID 40098001 Mayer, 1986
Rainbow trout (<i>Oncorhynchus mykiss</i>)	Aquathol K, 28.6% a.e.	EC ₅₀ : 128.7 mg a.e./L	MRID 40098001 Mayer, 1986
Rainbow trout (<i>Oncorhynchus mykiss</i>)	Aquathol K, 28.6% a.e.	EC ₅₀ : 9.152 mg a.e./L	MRID 40098001 Mayer, 1986
Rainbow trout (<i>Oncorhynchus mykiss</i>)	Aquathol K, 28.6% a.e.	EC ₅₀ : 151.29 mg a.e./L	MRID 83025 Vilkas, 1979
Rainbow trout (<i>Oncorhynchus mykiss</i>)	Aquathol K, 28.6% a.e.	EC ₅₀ : 107.09 mg a.e./L	MRID 42695402 Bettencourt 1991

Appendix 3: Toxicity to fish (*continued*)

A3 Table 2: Acute Toxicity, Dipotassium Salt			
Species	Exposure	Response	Reference
Channel catfish (<i>Ictalurus punctatus</i>)	Aquathol K, 28.6% a.e. , static	EC ₅₀ : >42.9 mg a.e./L	MRID 40098001 Mayer, 1986
Channel catfish (<i>Ictalurus punctatus</i>)	Aquathol K, 28.6% a.e. , static	EC ₅₀ : >28.6 mg a.e./L	MRID 40098001 Mayer, 1986
Bluegills (<i>Lepomis macrochirus</i>)	Aquathol K, 28.6% a.e. , static	EC ₅₀ : 98.1 mg a.e./L	MRID 40098001 Mayer, 1986
Bluegills (<i>Lepomis macrochirus</i>)	Aquathol K, 28.6% a.e. , static	EC ₅₀ : 277.42 mg a.e./L	MRID 40098001 Mayer, 1986
Bluegills (<i>Lepomis macrochirus</i>)	Aquathol K, 28.6% a.e. , static	EC ₅₀ : 306.02 mg a.e./L	MRID 40098001 Mayer, 1986
Bluegills (<i>Lepomis macrochirus</i>)	Aquathol K, 28.6% a.e. , static	EC ₅₀ : 457.6 mg a.e./L	MRID 40098001 Mayer, 1986
Bluegills (<i>Lepomis macrochirus</i>)	Aquathol K, 28.6% a.e. , static	EC ₅₀ : 300.3 mg a.e./L	MRID 40098001 Mayer, 1986
Bluegills (<i>Lepomis macrochirus</i>)	Aquathol K, 28.6% a.e. , static	EC ₅₀ : 278.85 mg a.e./L	MRID 40098001 Mayer, 1986
Bluegills (<i>Lepomis macrochirus</i>)	Aquathol K, 28.6% a.e. , static	EC ₅₀ : 294.58 mg a.e./L	MRID 40098001 Mayer, 1986
Bluegills (<i>Lepomis macrochirus</i>)	Aquathol K, 28.6% a.e., static	EC ₅₀ : 125.84 mg a.e./L	MRID 40098001 Mayer, 1986
Bluegills (<i>Lepomis macrochirus</i>)	Aquathol K, 28.6% a.e., static	EC ₅₀ : 125.84 mg a.e./L	MRID 71134 NOS
Bluegills (<i>Lepomis macrochirus</i>)	Aquathol K, 28.6% a.e., flow-through	EC ₅₀ : 316 mg a.e./L	MRID 42695401 Bettencourt, 1991
Bluegills (<i>Lepomis macrochirus</i>)	Aquathol K, 28.6% a.e., flow-through. Mean measured concentrations of 0, 110, 170, 260, 430, 710, and 1200 mg a.e. /L.	EC ₅₀ : 316 (246-424) mg a.e./L No mortality at two lowest concentrations. NOEC for mortality: 170 mg a.e./L.	Bettencourt, 1993c
Goldfish (<i>Carassius auratus</i>)	96-hour static	LC ₅₀ : 372 mg a.i./L (264 mg a.e./L) NOEC for pathology and lethality: 32 mg/L (23 mg a.e./L)	Berry 1984
Bluegill sunfish (<i>Lepomis macrochirus</i>)	Acute static	24-h LC ₅₀ : 428 mg a.e./L 48-h LC ₅₀ : 268 mg a.e./L	Davis and Hughes 1963
Rainbow trout	Aquathol K (3 lb a.e./gal)	96-h LC ₅₀ : 150 mg a.e./L	Folmar 1976a
Coho salmon	Aquathol K (40.3% a.i., 28.6% a.e)	96-h LC ₅₀ : >100 mg form/L [>28.6 mg a.e./L]	Johnson and Finley 1980

Appendix 3: Toxicity to fish (*continued*)

A3 Table 2: Acute Toxicity, Dipotassium Salt			
Species	Exposure	Response	Reference
Rainbow trout	Aquathol K (40.3%, 28.6% a.e))	96-h LC ₅₀ : 230 (187-283) mg form/L [66 (53-81 mg a.e./L]	Johnson and Finley 1980
Channel catfish	Aquathol K (40.3%, 28.6% a.e))	96-h LC ₅₀ : >150 mg/ form L [>42 mg a.e./L]	Johnson and Finley 1980
Bluegill sunfish	Aquathol K (40.3%, 28.6% a.e))	96-h LC ₅₀ : 343 (308-383) mg form/L [98 (88-110 mg a.e./L]	Johnson and Finley 1980
Rainbow trout	Potassium salt (40.3%, 28.6% a.e))	96-h LC ₅₀ : 450 mg form/L [129 mg a.e./L]	Johnson and Finley 1980
Bluegill sunfish	Potassium salt (40.3%)	96-h LC ₅₀ : 440 mg form/L [126 mg a.e./L]	Johnson and Finley 1980
Chinook Salmon (<i>Oncorhynchus tshawytscha</i>)	Aquathol-K, 14 days (28.6% a.e.)	14-day LC ₅₀ : 62.5 (53.4-73.1) mg a.e./L NOEC: 25.54 ppm a.e.	Liguori et al. 1983
Walleye (<i>Stizostedion vitreum</i>) (8-10 days old)	Static non-renewal. Aquathol-K. Concentrations expressed as a.i. (a.i. to a.e. conversion 0.71)	24-h LC ₅₀ : 66 (42-140) mg/L NOAEC: 5.7 mg/L LOAEL: 11 mg/L 48-h LC ₅₀ : 30 (24-37) mg/L NOAEC: 5.7 mg/L LOAEL: 11 mg/L 72-h LC ₅₀ : 27 (22-33) mg/L 96-h LC ₅₀ : 16 (11-22) mg/L NOAEC: 5.7 mg/L [4 mg a.e./L] LOAEL: 11 mg/L [7.8 mg a.e./L]	Paul et al. 1994
Walleye (<i>Stizostedion vitreum</i>) (41-43 days old)	Static non-renewal. Aquathol-K. Concentrations expressed as a.i. (a.i. to a.e. conversion 0.71)	24-h LC ₅₀ : 140 (100-1000) mg/L NOAEC: 45 mg/L LOAEL: 91 mg/L 48-h LC ₅₀ : 73 (58-100) mg/L NOAEC: 23 mg/L LOAEL: 45 mg/L 72-h LC ₅₀ : 62 (49-80) mg/L 96-h LC ₅₀ : 54 (42-68) mg/L NOAEC: 23 mg/L LOAEL: 45 mg/L	Paul et al. 1994

Appendix 3: Toxicity to fish (*continued*)

A3 Table 2: Acute Toxicity, Dipotassium Salt			
Species	Exposure	Response	Reference
Smallmouth Bass (<i>Micropterus dolomieu</i>), < 1 day old	Static non-renewal. Aquathol-K. Concentrations expressed as a.i. (a.i. to a.e. conversion 0.71)	24-h LC ₅₀ : > 91 mg/L NOAEC: 45 mg/L LOAEL: 91 mg/L 48-h LC ₅₀ : 60 (54-69) mg/L NOAEC: 23 mg/L LOAEL: 45 mg/L 72-h LC ₅₀ : 59 (55-64) mg/L 96-h LC ₅₀ : 47 (42-54) mg/L NOAEC: 23 mg/L LOAEL: 45 mg/L	Paul et al. 1994
Largemouth Bass (<i>Micropterus salmoides</i>), 10-14 days old	Static non-renewal. Aquathol-K. Concentrations expressed as a.i. (a.i. to a.e. conversion 0.71)	24-h LC ₅₀ : > 400 mg/L NOAEC: 200 mg/L LOAEL: 400 mg/L 48-h LC ₅₀ : 280 mg/L NOAEC: 100 mg/L LOAEL: 200 mg/L 72-h LC ₅₀ : 170 (150-190) mg/L 96-h LC ₅₀ : 130 (120-150) mg/L NOAEC: 50 mg/L LOAEL: 100 mg/L	Paul et al. 1994
Red shiner (<i>Notropis lutrensis</i>)	Static non-renewal. Aquathol-K, 1 or 30 mg a.e./L for 48-hours followed by thermal stress.	No effect on ability to tolerate thermal stress (critical thermal maximum). Concentrations of endothall in water dropped by about 33% at 1 mg/L and 66% at 30 mg/L.	Takle et al. 1983

All studies starting with the MRID number are taken from U.S. EPA/OPP 2005c.

Appendix 3: Toxicity to fish (*continued*)

A3 Table 3: Acute Toxicity, Amine Salt			
Species	Exposure	Response	Reference
Bluegills (<i>Lepomis macrochirus</i>)	Hydrothol liquid, 23.4% a.e., flow-through	EC ₅₀ : 1.5 mg a.e./L	MRID 43472801, Bettencourt 1994
Bluegills (<i>Lepomis macrochirus</i>)	Hydrothol liquid, 23.4% a.e., static	EC ₅₀ : 0.22 mg a.e./L	MRID 40094602, Johnson et al. 1980
Bluegills (<i>Lepomis macrochirus</i>)	Hydrothol liquid, 23.4% a.e., static	EC ₅₀ : 0.2808 mg a.e./L	MRID 84148 Vilkas, 1979
Bluegills (<i>Lepomis macrochirus</i>)	Hydrothol liquid, 23.4% a.e., static	EC ₅₀ : 0.1872 mg a.e./L	MRID 68507 Hughes et.al., 1962
Rainbow trout (<i>Oncorhynchus mykiss</i>)	Hydrothol liquid, 23.4% a.e., static	EC ₅₀ : 0.3042 mg a.e./L	MRID 84147 Vilkas, 1979
Rainbow trout (<i>Oncorhynchus mykiss</i>)	Hydrothol liquid, 23.4% a.e., static	EC ₅₀ : 0.2201 mg a.e./L	MRID 43196901 Bettencourt, 1994
Rainbow trout (<i>Oncorhynchus mykiss</i>)	Hydrothol liquid, 23.4% a.e., static	EC ₅₀ : 0.1301 mg a.e./L	MRID 40098001 Mayer, 1986
Cutthroat trout (<i>Oncorhynchus clarki</i>)	Hydrothol liquid, 23.4% a.e., static	EC ₅₀ : 0.0421 mg a.e./L	MRID 40094602 Johnson et. al. 1980
Channel catfish (<i>Ictalurus punctatus</i>)	Hydrothol liquid, 23.4% a.e., static	EC ₅₀ : 0.1147 mg a.e./L	MRID 40098001 Mayer, 1986
Fathead minnow (<i>Pimephales promelas</i>)	Hydrothol liquid, 23.4% a.e.	EC ₅₀ : 0.1755 mg a.e./L	MRID 40098001 Mayer, 1986
Golden shiner	Hydrothol-191 (23.26% a.e.). Concentrations measured at 24 and 96 h but are not reported.	<i>Reported values:</i> Hard water: 120 h-LC ₅₀ 0.32 (0.19-0.46) mg/L Soft water: 120 h-LC ₅₀ : 1.6 (1.2-2.0) mg/L <i>a.e. equivalent values:</i> Hard water: 120 h-LC ₅₀ 0.074 (0.044-0.11) mg/L Soft water: 120 h-LC ₅₀ : 0.37 (0.28-0.47) mg/L	Finlayson 1980
Bluegills (<i>Lepomis macrochirus</i>)	mono (N,N-dimethylalkylamine) salt (TD191). Aerated water. Static.	48-h LC ₅₀ s: 0.8 mg a.i./L 0.1872 mg a.e./L	Hughes and Davis 1962a,c; MRID 68507

Appendix 3: Toxicity to fish (*continued*)

A3 Table 3: Acute Toxicity, Amine Salt			
Species	Exposure	Response	Reference
Goldfish (<i>Carassius auratus</i>)	mono (N,N-dimethylalkylamine) salt	Reported value for amine salt: 24-h LC ₅₀ s: 0.81 to 1.39 mg/L 48-h LC ₅₀ s: 0.78 to 1.50 mg/L a.e. equivalents: 24-h LC ₅₀ s: 0.57 to 0.98 mg/L 48-h LC ₅₀ s: 0.55 to 1.06 mg/L No consistent differences in waters of different hardness.	Inglis and Davis 1972
Bluegills (<i>Lepomis macrochirus</i>)	mono (N,N-dimethylalkylamine) salt	24-h LC ₅₀ s: 0.90 to 1.49 mg/L 48-h LC ₅₀ s: 0.90 to 1.34 mg/L No consistent differences in waters of different hardness.	Inglis and Davis 1972
Redear sunfish (<i>Lepomis microlophus</i>)	mono (N,N-dimethylalkylamine) salt	24-h LC ₅₀ s: 0.68 to 0.81 mg/L No consistent differences in waters of different hardness.	Inglis and Davis 1972
Cutthroat trout	Hydrothol 191 (53%)	96-h LC ₅₀ : 0.18 (0.12-0.27) mg/L	Johnson and Finley 1980
Rainbow trout	Hydrothol 191 (53%)	96-h LC ₅₀ : 0.56 mg/L	Johnson and Finley 1980
Fathead minnow	Hydrothol 191 (53%)	96-h LC ₅₀ : 0.75 mg/L	Johnson and Finley 1980
Channel catfish	Hydrothol 191 (53%)	96-h LC ₅₀ : 0.49 mg/L	Johnson and Finley 1980
Bluegill sunfish	Hydrothol 191 (53%)	96-h LC ₅₀ : 0.94 mg/L	Johnson and Finley 1980
Rainbow trout	Hydrothol 191 (23.4%), static	96-h LC ₅₀ : 1.7 mg/L 0.4 mg a.e./L	Mudge et al. 1986
Emerald shiner (<i>Notropis atherinoides</i>)	Hydrothol 191, 23.36% a.e.	96-h LC ₅₀ : 0.1 mg/L 0.02336 mg a.e./L	Swabey and Schenk 1963

All studies starting with the MRID number are taken from U.S. EPA/OPP 2005c.

Appendix 3: Toxicity to fish (*continued*)

A3 Table 4: Acute Toxicity, other salts			
Species	Exposure	Response	Reference
Bluegills (<i>Lepomis macrochirus</i>)	disodium salt Note: Compare to data in this study for amine salt.	24-h LC ₅₀ S: 249 to 280 mg/L 48-h LC ₅₀ S: 181 to 219 mg/L 96-h LC ₅₀ S: 102 to 104 mg/L Somewhat less toxic in soft water.	Inglis and Davis 1972
Bluegills (<i>Lepomis macrochirus</i>)	24 and 48 hours to disodium salt of endothall acid	24-h LC ₅₀ : 450 mg a.e./L 48-h LC ₅₀ : 280 mg a.e./L	Hughes and Davis (1962a)
Black bass fry	Aquathol (disodium liquid), 5 and 10 mg/L	96-h NOEC (mortality): 10 mg/L	Jones 1962
Black bass fry	Disodium granular formulation (NOS), 2, 5, and 10 mg/L	96-h NOEC (mortality): 2 mg/L 96-h 50% mortality: 10 mg/L	Jones 1962
Channel catfish fry	Aquathol (disodium liquid), 2.5 to 100 mg/L	96-h NOEC (mortality): 100 mg/L	Jones 1962
Channel catfish fry	Disodium granular formulation (NOS), 2 to 100 mg/L	96-h NOEC (mortality): 50 mg/L 96-h 50% mortality: 100 mg/L	Jones 1962
Bluegill sunfish fry	Aquathol (disodium liquid), 2.5 to 100 mg/L	96-h NOEC (mortality): 50 mg/L 96-h 40% mortality: 100 mg/L	Jones 1962
Bluegill sunfish fry	Disodium granular formulation (NOS), 1 to 100 mg/L	96-h NOEC (mortality): 2 mg/L 4 mg/L: All fry dead in 16 hours	Jones 1962
Bluegill sunfish	Disodium salt (liquid formulation)	24-h LC ₅₀ S: 390 to 450 mg/L 48-h LC ₅₀ S: 240 to 320 mg/L 96-h LC ₅₀ S: 160 to 180 mg/L	Surber and Pickering 1962
Largemouth bass	Disodium salt (liquid formulation)	24-h LC ₅₀ S: >560 mg/L 48-h LC ₅₀ S: 320 mg/L 96-h LC ₅₀ S: 200 mg/L	Surber and Pickering 1962
Fathead minnows	Disodium salt (liquid formulation)	24-h LC ₅₀ S: >560 to 680 mg/L 48-h LC ₅₀ S: 480 to 660 mg/L 96-h LC ₅₀ S: 320 to 610 mg/L	Surber and Pickering 1962
Various species of minnows, catfish, and sunfish	Disodium salt (NOS)	LC ₅₀ : 95 to 210 mg/L Minimum lethal concentration: 60 to 150 mg/L	Walker 1963
Striped bass	Disodium salt (Aquathol formulation, 1.8 lbs a.i./gal.	24-h LC ₅₀ S: 2,000 mg/L 48-h LC ₅₀ S: 1,700 mg/L 96-h LC ₅₀ S: 710 mg/L	Wellborn 1971

Appendix 3: Toxicity to fish (*continued*)

A3 Table 5: Chronic toxicity			
Species	Exposure	Response	Reference
Fathead minnow (<i>Pimephales promelas</i>), embryos 2 to 24 hours old	Endothall acid Measured concentrations of 0.88, 1.3, 2.6, 6.1, 13, and 27 mg/L using intermittent flow proportional diluters. Exposure period: 35 days, standard egg-to-fry study.	Length and wet weight: NOAEC: 1.3 mg a.e./L LOAEL: 2.6 mg a.e./L	Bettencourt 1994, MRID 43295401
Redear Sunfish	Single treatments with Hydrothol 191 (53% a.i., 23.36% a.e.) at 0 (control), 0.03 ppm and 0.3 ppm for up to 112 days in artificial ponds. Concentrations reported as a.e. ... <i>using the 23.36% acid content.</i> No monitoring of concentrations over the exposure period.	No substantial mortality at either concentration. 0.03 mg a.e./L Abnormal (<i>ova-like</i>) cells in testes that reversed by Day 14. No other effects noted over course of study. 0.3 mg a.e./L Damage to gill, liver, testes, and blood. Ova-like cells in testes reversed by Day 28. Liver damage was transient and not apparent by Day 112	Eller 1969
Rainbow trout (<i>Oncorhynchus mykiss</i>)	Dipotassium salt , 4 hour exposures with observation period through hatching. Concentrations of 0.125, 1.25, 2.5, 6.25 and 12.5 mg/L.	Percent eggs hatch and sac fry survival NOAEC: 1.79 mg a.e./L LOAEL: 6.25 mg a.e./L	Folmar 1976b. MRID 00095812
Fathead minnow (<i>Pimephales promelas</i>), embryos	Hydrothol-191 (liquid formulation). 7-day static renewal. Endpoints: growth and survival at 15°C and 25°C. Authors define endothall, not the amine salt as the a.i. <i>Hydrothol concentrations were calculated based on per cent endothall, the active ingredient.</i>	15°C Growth NOEC: 0.265 mg a.e./L LOEC: not determined Survival: NOEC: 0.132 mg a.e./L LOEC: 0.265 mg a.e./L 25°C Growth NOEC: 0.05 mg a.e./L LOEC: 0.132 mg a.e./L Survival: NOEC: 0.200 mg a.e./L LOEC: 0.265 mg a.e./L	Keller 1988b
Fathead minnow (<i>Pimephales promelas</i>)	Hydrothol 191 (23.4% a.e.) 35 days	Survival at 35 days: NOAEC: 0.056 mg a.e./L LOAEL: 0.12 mg a.e./L % hatched, length, and wet weight: NOAEC: 0.12 mg a.e./L LOAEL: 0.240 mg a.e./L	MRID 43276501, Bettencourt 1994

All studies starting with the MRID number are taken from U.S. EPA/OPP 2005c.

Appendix 3: Toxicity to fish (*continued*)

A3 Table 6: Field Studies			
Species	Exposure	Response	Reference
Bluegills () and Redear () Sunfish	Field treatment at 4 mg/L of dipotassium salt as Aquathol-K. Equivalent to 2.84 ppm a.e.	No effect on nest abandonment.	Bettoli and Clark 1992
Bluegills	Experimental ponds treated with 2 ppm Hydrothol (granular, liquid, and pellet) for the control of hydrilla.	All fish in artificial ponds were killed after treatments with granular and liquid formulations. No clear if mortality was due to toxicity or oxygen depletion. No fish mortality with pellet formulations.	Blackburn et al. 1971
Bluegills	Pond application at 5 mg/L as Aquathol K.	No noticeable mortality in bluegills.	Holmberg and Lee (1976)
Bluegills in 0.31 ha (0.77 ac) pond	5 mg a.i./L dipotassium salt	No change in survival or reproductive statistics for bluegills. Bluegills did grow more slowly than in control pond. No detectable uptake of endothall. Modest decrease in survival of bluegill young relative to control pond.	Serns 1977
Mixed fish populations in 0.05 acre pond	5 mg a.i./L dipotassium salt, partial treatment, 20% of pond area	No fish kills or signs of distress. Not clear that observations in fish were thorough. This is primarily an efficacy study.	Simes 1961
Mixed fish populations including bluegills and largemouth bass	Disodium endothall in pond at 2 ppm (liquid or granular)	No adverse effects on fish. This is an abstract only.	Steuchke 1961
Sunfish (<i>Lepomis</i> sp.) in small pond	Initial treatment at 0.579 mg/L using potassium salt of endothall. Dropped to 0.21 mg/L by Day 8.	Transient decrease in oxygen levels in water associated with changes in fish diet. No adverse effects on fish.	Teitt and Maughan 1987
Bass, sunfish, and mosquitofish	Initial concentrations of 0.3 to 2 mg/L of dipotassium or disodium salts.	Effective weed control but no signs of mortality or distress in bass or sunfish. Mortality observed in mosquito fish but not associated with treatment.	Yeo 1970

Appendix 4: Toxicity to aquatic invertebrates.

Information from the open literature is cited in the standard author/date format – e.g., Johnson and Finley 1980. This citation format is also used for studies with cleared reviews or studies with one-page summaries in the internal EPA review by Turner (1978). Information that is taken solely from EPA/OPP (2005c) is cited as the MRID number followed by the author-date citations used in EPA/OPP (2005c).

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A4 Table 1: Acute toxicity of endothall acid			
Species	Exposure	Response	Reference
<i>Daphnia magna</i>	89.5% a.e.	48-h EC ₅₀ : 32.5 mg a.e./L	MRID 71137 Vilkas, 1979
<i>Daphnia magna</i>	75-86% a.e.	26-h EC ₅₀ : 46 mg a.e./L	MRIDs 115863, 17800. Crosby et. al. 1966
Mussel (<i>Mytilus edulis</i>) (embryo)	89.5% a.e.	48-h EC ₅₀ : 49.2 mg a.e./L	MRID 74227 Bailey, 1980
Grass shrimp (<i>Palaemonetes pugio</i>)	89.5% a.e.	48-h EC ₅₀ : 85.1 mg a.e./L	MRID 84151 Vilkas, 1980
<i>Daphnia magna</i>	NOS	26h-EC ₅₀ : 46 (36-57) mg a.e./L Working Note: These authors report >30 day post-exposure survival times for some organisms surviving 26h exposures and then transferred to fresh water. A survival time of 30 days for <i>Daphnia</i> is unusual.	Crosby and Tucker
Midge larvae (<i>Chironomus tentans</i>)	Endothall monohydrate. Mortality assessed as immobile organisms at 24 hours post-exposure.	24 h-EC ₅₀ (immobilization): 354 (161-780) mg a.e./L 24 h-LC ₅₀ (lethality): 205 (151-278) mg a.e./L 72 h-EC ₅₀ (immobilization): 151 (112-203) mg a.e./L 72 h-LC ₅₀ (lethality): 120 (81.6-176) mg a.e./L	Hansen and Kawatski 1976
Ostrocod (<i>Cypretta kawatai</i>)	Endothall monohydrate. Mortality assessed as immobile organisms at 24 hours post-exposure.	24 h-EC ₅₀ (immobilization): 180 (141-230) mg a.e./L 24 h-LC ₅₀ (lethality): 249 (191-324) a.e. mg/L 72 h-EC ₅₀ (immobilization): 123 (89.9-168) mg a.e./L 72 h-LC ₅₀ (lethality): 173 (102-278) mg a.e./L	Hansen and Kawatski 1976
<i>Daphnia magna</i>	Endothall technical, 77.9% a.e. Flow-through. Mean measured concentrations of 0, 24, 35, 62, 92, and 180 mg a.e./L.	48-h EC ₅₀ : 92 (62-180) mg a.e./L NOEC: 24 mg a.e./L	McNamara, 1992, MIRD 42359702

Appendix 4: Toxicity to aquatic invertebrates (continued)

A4 Table 2: Acute toxicity of dipotassium salt			
Species	Exposure	Response	Reference
Scud (<i>Gammarus lacustris</i>)	Aquathol K, static	48-h: EC ₅₀ : 89.52 mg a.e./L	MRID 40098001 Mayer, 1986
Scud (<i>Gammarus lacustris</i>)	Aquathol K, static	48-h: EC ₅₀ : 63.8 mg a.e./L	MRID 42695403 ^a Putt, 1991
<i>Daphnia magna</i>	Aquathol K, static	48-h: EC ₅₀ : 91.23 mg a.e./L	MRID 00084150 Vilkas, 1979
Asian hydrilla leaf-mining fly (<i>Hydrellia pakistanae</i>), larvae	2, 4, or 8 ppm a.i.	Significant increase in mortality at 8 ppm (≈5.7 ppm a.e.). This could have been due to habitat loss rather than toxicity.	Haag and Buckingham 1991
Hydrilla tuber weevil (<i>Bagous affinis</i>), adults	2, 4, or 8 ppm a.i.	No significant mortality.	Haag and Buckingham 1991
Rotifer (<i>Brachionus calyciflorus</i>)	Technical grade	24-hour: EC ₅₀ : >270 mg/L (>192 mg a.e./L)	Nelson and Roline 1998
<i>Ceriodaphnia dubia</i>	Technical grade	Reported values: 24-h: LC ₅₀ : 66.73 (55.8-80.0) mg/L 48-h: LC ₅₀ : 48.28 (40.2-57.9) mg/L Acid equivalents: 24-h: LC ₅₀ : 47 (40-57) mg a.e./L 48-h: LC ₅₀ : 31 (29-41) mg a.e./L	Nelson and Roline 1998
<i>Daphnia magna</i>	Aquathol K (29.5% a.e.), static. Mean measured concentrations of 0, 140, 170, 330, 620, and 1100 mg formulation/L.	48-h: LC ₅₀ : 72 (58-85) mg a.e./L NOEC: 41.3 mg a.e./L.	Putt, 1991, MRID 42695403
Amphipod (<i>Gammarus lacustris</i>)	Technical grade (NOS). The material may have been Aquathol K but this is not clear.	NOEC (mortality): 100 mg/L (≈71 mg a.e./L).	Sanders 1969; Sanders 1970b
Amphipod (<i>Hyaella azteca</i>)	Aquathol-K (23.4% a.e.) : 0, 1, 3, and 10 mg a.i./L, flow-through for 120 hours	No significant increase in mortality. NOEC: ≈2.34 mg a.e./L	Williams et al. 1984
Isopod (<i>Asellus communis</i>)	Aquathol-K : 0, 1, 3, and 10 mg a.i./L, flow-through for 120 hours	No significant increase in mortality. NOEC: ≈2.34 mg a.e./L	Williams et al. 1984

^a The DER for MRID of 42695403 indicates that the test was conducted on *Daphnia magna*. The Putt (1991) study cited in U.S. EPA/OPP (2005c) does not appear to be the same study summarized below for *Daphnia magna*.

Appendix 4: Toxicity to aquatic invertebrates (continued)

A4 Table 3: Acute toxicity of mono-amine salt			
Species	Exposure	Response	Reference
<i>Daphnia magna</i>	Hydrothol 191, 23.4% a.e., static	48-h LC ₅₀ : 0.084 mg a.e./L	MRID 35242 Union Carbide, 1977
<i>Daphnia magna</i>	Hydrothol 191, 23.4% a.e., flow-through	48-h LC ₅₀ : >0.075 mg a.e./L	MRID 43196902 Putt 1994
Scud (<i>Gammarus lacustris</i>)	Hydrothol 191, 23.4% a.e., static	24-h LC ₅₀ : 0.234 mg a.e./L 96-h LC ₅₀ : 0.117 mg a.e./L	MRID 5009242 Sanders, 1969
Grass shrimp (<i>Palaemonetes pugio</i>)	Hydrothol 191, 23.4% a.e., static	48-h LC ₅₀ : 0.012 mg a.e./L This value is identical to the assay by Johnson and Finley 1980. See below.	MRID 40098001 Mayer, 1986
Scud (<i>Gammarus lacustris</i>)	Hydrothol 191, 23.4% a.e., static	48-h LC ₅₀ : 0.468 mg a.e./L 96-h LC ₅₀ : 0.117 mg a.e./L Data identical to Sanders 1970b	MRID 40098001 Mayer, 1986
Giant salmonfly (<i>Pteronarcys californica</i>)	Hydrothol 191, 23.4% a.e., static	48-h LC ₅₀ : 0.751 mg a.e./L	40098001 Mayer, 1986
Scud (<i>Gammarus lacustris</i>)	Hydrothol 191 (53% a.i., 23.36% a.e)	96-h LC ₅₀ : 0.50 (0.37-0.67) mg/L or 0.12 (0.09-0.15) mg a.e./L	Johnson and Finley 1980
Shrimp (<i>Palaemonetes</i> sp.)	Hydrothol 191 (53% a.i., 23.36% a.e)	96-h LC ₅₀ : 0.05 (0.02-0.12) mg/L or 0.012 (0.0048-0.028) mg a.e./L	Johnson and Finley 1980
Stonefly (<i>Pteronarcys</i> sp.)	Hydrothol 191 (53% a.i., 23.36% a.e)	48-h EC ₅₀ : 3.52 mg/L or 0.74 mg a.e./L	Johnson and Finley 1980
Daphnid (<i>Ceriodaphnia dubia</i>)	Hydrothol -191 (liquid formulation, 53% a.i., 23.36% a.e)	48-h LC ₅₀ s 15 °C: 1.43 (1.09-2.00) mg/L or 0.33 (0.25-0.46) mg a.e./L 25 °C: 0.495 (0.363-0.765) mg/L or 0.12 (0.085-0.018) mg a.e./L	Keller et al. 1988a
Mussel (<i>Anodonta imbecilis</i>)	Hydrothol -191 (liquid formulation, 53% a.i., 23.36% a.e)	48-h LC ₅₀ : 4.85 mg/L or 1.13 mg a.e./L	Keller 1993
Scud (<i>Gammarus fasciatus</i>)	Hydrothol-191 (NOS, presumably 53% a.i., 23.36% a.e)	Reported values in mg form/L: 24-hour: LC ₅₀ : 3.1 (1.8-15) 48-hour: LC ₅₀ : 2.1 (1.4-9.5) 96-hour: LC ₅₀ : 0.48 (0.20-1.1) Acid equivalents in mg a.e./L: 24-hour: LC ₅₀ : 0.7 (0.42-3.5) 48-hour: LC ₅₀ : 0.5 (0.33-2.2) 96-hour: LC ₅₀ : 0.11 (0.048-0.26)	Sanders 1970b

Appendix 4: Toxicity to aquatic invertebrates (continued)

A4 Table 4: Acute toxicity of other endothall species or salt not specified			
Species	Exposure	Response	Reference
Scud (<i>Gammarus lacustris</i>)	Aquathol (disodium salt)	96-hour LC50: >320 mg/L	Nebeker and Gaufin 1964
American oysters (<i>Crassostrea virginica</i>)	Endothall (NOS)	EC ₅₀ (egg hatching): 28.22 mg/L	Davis and Hidu 1969
American oysters (<i>Crassostrea virginica</i>)	Endothall (NOS)	EC ₅₀ (larval survival): 48.08 mg/L	Davis and Hidu 1969
Clams (<i>Mercenaria mercenaria</i>)	Endothall (NOS)	EC ₅₀ (egg hatching): 51.02 mg/L	Davis and Hidu 1969
Clams (<i>Mercenaria mercenaria</i>)	Endothall (NOS)	EC ₅₀ (larval survival): 12.50 mg/L	Davis and Hidu 1969

A4 Table 5: Chronic toxicity			
Species	Exposure	Response	Reference
<i>Daphnia magna</i>	Hydrothol 191 Working Note: This MRID number is summarized as an assay on endothall acid in U.S. EPA/OPP 2005c but this appears to be an error. See discussion in Section 4.1.3.3.	Reproductive NOEC: 0.0159 mg a.e/L LOEC: 0.033 mg a.e/L for reproduction. Survival and growth NOEC: 0.033 mg a.e/L LOEC: 0.066 mg a.e/L for survival and growth of young.	MRID 43437901, Putt 1993
<i>Daphnia magna</i>	Technical grade endothall, flow-through. Measured concentrations of 0, 2.2, 5.0, 8.9, 17, and 35 mg/L.	Study authors NOEC: 5 mg a.e/L LOEC: 8.9 mg a.e/L for EFED reanalysis rejected all concentrations as an NOEC. LOEC: 2.2 ppm	Putt 1993, MRID 43007801
<i>Ceriodaphnia dubia</i>	Hydrothol-191 (53% liquid formulation, 23.4% a.e.): 7-days. Concentrations of 0.025 mg/L to 3.2 mg a.i./L at 25°C. A separate chronic study was also conducted with controls and 0.01 mg a.i./L.	Reproduction values are reported for formulation. NOEC: 0.01 mg/L LOEC: 0.025 mg/L Acid equivalents : NOEC: 0.0023 mg a.e./L LOEC: 0.059 mg a.e./L	Keller et al. 1988a
<i>Ceriodaphnia dubia</i>	Hydrothol-191 (53% liquid formulation, 23.4% a.e.) as above but assay conducted at 15°C.	No reproduction in any groups including the control group. This effects was associated with temperature and decreased metabolic rate rather than exposure to endothall.	Keller et al. 1988a

Appendix 5: Toxicity to aquatic plants

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A5 Table 1: Toxicity of Endothall Formulations to Macrophytes			
Species	Exposure	Response	Reference
Duckweed (<i>Lemna gibba</i>)	Dipotassium salt, 40.3% a.i., 28.6% a.e. This is consistent with Aquathol K but is not explicitly identified as such in the DER. 14-day period of exposure to nominal concentrations of 0.0065, 0.013, 0.25, 0.5, and 1.0 mg a.i./L.	<i>Reported values:</i> EC ₅₀ : 0.86 (0.77-0.98) mg a.i./L NOEC: 0.0065 mg a.i./L LOEC: 0.013 mg a.i./L <i>a.e. equivalents</i> EC ₅₀ : 610 (548-696) µg a.e./L NOEC: 4.6 µg a.e./L LOEC: 9.2 mg a.i./L	Hoberg 1992f, MRID 42396406
Duckweed (<i>Lemna gibba</i>)	Hydrothol 191 (23.4% a.e.)	EC ₅₀ : 430 µg a.e./L NOEC: 50 µg a.e./L	MRID 44127806 Hoberg, 1994
Duckweed (<i>Lemna gibba</i>)	Hydrothol 191 (23.4% a.e.)	EC ₅₀ : 740 µg a.e./L NOEC: 150 µg a.e./L	MRID 44949402 Drott et. al. 1999

A5 Table 2: Efficacy Studies on Endothall Applications			
Species	Exposure	Response	Reference
<i>Elodea canadensis</i>	Hydrothol 191 (23.4% a.e.) in open channel treatments at concentrations of 3.4 ppm to 6.9 ppm. The form of endothall in the concentrations used to characterize the treatments is unclear.	Substantial decreases in biomass of target species at 2 to 21 weeks after application.	Bowmer and Smith 1984
Mixed aquatic macrophytes including Hydrilla, watermilfoil, ellgrass and southern naiad.	Hydrothol 191, 3 mg/L to experimental pools. Observations followed for 280 days.	Obvious signs of damage to macrophytes – discoloration and death within 2 days. Secondary effects on water quality associated with decomposing vegetation. No remarkable effect on phytoplankton.	Carter and Hestand 1977
Cladophora, Spirogyra, and sago pondweed (<i>Potamogeton pectinatus</i> L.).	Hydrothol 191, seven applications at 2 week intervals at 0.2 ppm following labeled directions. This would be 0.2 ppm a.e.	Marked reductions in sago pondweed. Effects on other species not detailed. Concentration of endothall was variable in 1 to 20 mile sections downstream, 0.03 to 0.32 ppm (Table 2 of paper).	Corbus 1982
Mixed species of macrophytes	Liquid formulations of 5% disodium endothall at 2 ppm	Good control of several species but poor control of <i>Najas guadalupensis</i> , <i>Potamogeton nodosus</i> , and <i>Zannichellia palustris</i> .	Houser and Gaylor 1962

Appendix 5: Toxicity to aquatic plants (continued)

A5 Table 2: Efficacy Studies on Endothall Applications			
Species	Exposure	Response	Reference
Mixed species of macrophytes	Granular formulations of 5% disodium endothall applied at 1 ppm or 2 ppm	Good control in 3/5 whole pond treatments at 2 ppm. No observed mortalities in fish.	Houser and Gaylor 1962
<i>Cladophora</i> sp.	Disodium salt of endothall, partial lake treatments at 2 ppm (a.i.).	No significant effect.	McLarty 1960
Giant salvinia (<i>Salvinia molesta</i>)	Aquathol and Hydrothol 191 liquid formulations. Applications expressed as kg a.e./ha to 80 L trashcans holding the target vegetation. Cannot convert to ppm.	Aquathol K at 5.04 kg/ha offer better control than Hydrothol 191 at 2.24 kg/ha.	Nelson et al. 2001
Eurasian Watermilfoil (<i>Myriophyllum spicatum</i>) and <i>Hydrilla verticillata</i>	Aquathol K. All exposures expressed in units of mg a.e./L. Concentration x time relationships. Observation period of 28 days.	1 mg a.e./L: NOEC for damage to hydrilla for exposures of up to 72 hours (maximum used in study). Eurasian watermilfoil was more sensitive. A longer-term NOEC of about 0.25 ppm a.e. can be estimated from Figure 5 in paper.	Netherland et al. 1991
Curlyleaf pondweed (<i>Potamogeton crispus</i>)	Aquathol K treatments at 10°C, 15°C, and 20°C at concentrations of 0.45 to 1.4 ppm a.e.	All treatments evidenced damage to some degree depending on the application rate and time after treatment. Endothall efficacy was inhibited as water temperature decreased.	Netherland et al. 2000
Mixed plant community including Eurasian watermilfoil (target species)	Aquathol-K at 1.5 mg/L a.i. (≈1 mg/L a.e.)	Good control of milfoil. Adverse effect on large-leaf pondweed (<i>Potamogeton amplifolius</i>), a nontarget species. Beneficial effect on elodea, muskgrass, and bladderwort. Increases may reflect the decreased competition from milfoil.	Parsons et al. 2004
Curlyleaf pondweed (<i>Potamogeton crispus</i>)	Aquathol K, Target concentrations of 1 to 2 mg a.i./L (0.71 to 1.42 mg a.e./L) at temperatures of 15 to 20°C.	All treatments caused signs of visual damage as well as decreases in biomass.	Poovey et al 2002
Mixed population of macrophytes	Hydrothol 191 applied to irrigation canals. Units appear to be in a.e./L but this is not explicitly stated.	Good control of target weeds at concentrations of 3 to 4 ppm for 3 hours. A concentration of 1 ppm for 9 hours did not provide uniform control – i.e., Haber's Law does not apply.	Price 1994
Mixed plant community in 0.3 ha (0.77 ac) pond	5 mg a.i./L dipotassium salt	Substantial mortality in macrophytes within two weeks – i.e., <i>Myriophyllum exalbescens</i> , <i>Ceratophyllum demersum</i> , <i>Potamogeton zosteriformis</i> , and <i>Potamogeton crispus</i> .	Serns 1977

Appendix 5: Toxicity to aquatic plants (continued)

A5 Table 2: Efficacy Studies on Endothall Applications			
Species	Exposure	Response	Reference
<i>Hydrilla verticillata</i>	Aquathol K. Treatments of 0.25, 0.5, and 1.25 mg a.e./L at exposure period of 96 hours.	Transient stimulation of shoot mass at lowest concentration. By DAT 21, significant inhibition at 1.25 mg/L only. By DAT 42, clear dose-related decrease in shoot mass at all concentrations.	Shearer and Nelson 2002
Non-target species: Illinois pondweed (<i>Potamogeton illinoensis</i>), American pondweed (<i>Potamogeton nodosus</i>), vallisneria (<i>Vallisneria americana</i>),	Aquathol K. Treatments of 0.25 and 0.5 mg a.e./L at exposure period of 96 hours	Decreases in dry weight at DAT 21 and DAT 42 for all nontarget species. Nontarget plants are more sensitive than target species.	Shearer and Nelson 2002
Curlyleaf pondweed (<i>Potamogeton crispus</i>)	Disodium salt of endothall. Treatment rates appear to be in units of a.i. but this is not explicit. Application rates of 1, 3, and 5 ppm to small ponds.	Effective treatment rates were estimated as low as 0.6 ppm. Applications of 5 ppm were “100% effective” and application rates of 3 ppm were nearly completely effective.	Simes 1961
Sago pondweed (<i>Potamogeton pectinatus</i>)	Aquathol K in treatments of high flow canals at metered target concentration of 0.3 to 0.4 mg/L for 84 hours.	Highly effective control of sago as well as other macrophytes for up to 28 DAT. Working Note: Metered applications are included on the product labels.	Sisneros et al. 1998
Sago Pondweed (<i>Stuckenia pectinata</i>) ^a	Aquathol K at 1 to 10 mg a.i./L for 3 to 24 hours in flowing water.	Significant decreases in shoot biomass at 28 DAT with treatments as low as 1 ppm for 3 hours (See Figure 1 of paper. Could evaluate Haber’s Law). Recovery after 4 weeks.	Slade et al. 2008
Sago Pondweed (<i>Stuckenia pectinata</i>) ^a	Hydrothol 191 at 0.5 to 5 mg a.i./L for 3 to 24 hours in flowing water.	Significant decreases in shoot biomass at 28 DAT with treatments as low as 0.5 ppm for 3 hours. (See Figure 1 of paper. Could evaluate Haber’s Law). Recovery after 4 weeks.	Slade et al. 2008
Sago pondweed (<i>Potamogeton pectinatus</i>)	Aquathol K at 0.5, 1, and 2 mg a.i./L for 24 hours. Observation period of 35 days.	Significant decrease in biomass at all concentrations. No remarkable difference between 1 and 2 mg/L (See Figure 1 of paper).	Sprecher et al. 1998
<i>Hydrilla verticillata</i>	Dipotassium salt, concentrations of 0.5 to 5 ppm. Units of concentration not clear. Single application but the duration of treatment is not clearly specified	Substantial damage at all concentrations from 7 DAT to 70 DAT.	Steward and Van 1987

Appendix 5: Toxicity to aquatic plants (continued)

A5 Table 2: Efficacy Studies on Endothall Applications			
Species	Exposure	Response	Reference
<i>Hydrilla verticillata</i>	Mono-amine salt, concentrations of 0.5 to 5 ppm. Units of concentration not clear. Single application but the duration of treatment is not clearly specified	Substantial damage at all concentrations from 7DAT to 70 DAT. At lower concentrations, the mono-amine salt appears to allow for more rapid recovery (see Fig 1 of paper).	Steward and Van 1987
<i>Hydrilla verticillata</i> and parrotfeather (<i>Myriophyllum brasiliense</i>)	Endothall (NOS) at concentrations of 0.5 and 5 ppm.	Significant phytotoxicity at 5 ppm but mixed results at 0.5 ppm.	Sutton et al. 1971
Mixed macrophytes	Single applications to pond farms at target concentrations of 0.3 to 2 mg/L of dipotassium or disodium salts.	Weeds not controlled by endothall: American elodea, common duckweed, nitella (<i>Nitella clavaia</i>), and common stonewort (<i>Chara vulgaris</i>).	Yeo 1970
^a Sago pondweed may be designated as <i>Potamogeton pectinatus</i> (POPE6), <i>Stuckenia pectinatus</i> (STPE12), or <i>Coleogeton pectinatus</i> (COPE9). See http://plants.usda.gov/java/profile?symbol=STPE15 .			

A5 Table 3: Toxicity of Technical Grade Endothall Acid to Algae			
Species	Exposure	Response	Reference
<i>Chlorococcum</i> sp.	10 days	EC ₅₀ (growth): 50 mg a.e./L	Walsh 1972
<i>Dunaliella tertiolecta</i>	10 days	EC ₅₀ (growth): 50 mg a.e./L	Walsh 1972
<i>Isochrysis galbana</i>	10 days	EC ₅₀ (growth): 24 mg a.e./L	Walsh 1972
<i>Phaeodactylum tricornutum</i>	10 days	EC ₅₀ (growth): 15 mg a.e./L	Walsh 1972

A5 Table 4: Toxicity of Dipotassium Salt to Algae			
Species	Exposure	Response	Reference
<i>Chlorococcum</i> sp.	10 days, material specified as the dipotassium salt of endothall. Values converted to a.e. equivalents using the factor of 0.71 a.e./a.i. (Table 2 of current Forest Service risk assessment.)	EC ₅₀ (growth): 1,500 mg/L or 1065 a.e./L.	Walsh 1972
<i>Dunaliella tertiolecta</i>		EC ₅₀ (growth): 1,500 mg/L or 1065 a.e./L.	Walsh 1972
<i>Isochrysis galbana</i>		EC ₅₀ (growth): 3,000 mg/L or 2130 mg a.e./L.	Walsh 1972
<i>Phaeodactylum tricornutum</i>		EC ₅₀ (growth): 500 mg/L or 355 mg a.e./L.	Walsh 1972

Appendix 5: Toxicity to aquatic plants (continued)

A5 Table 5: Toxicity of Amine Salt to Algae			
Species	Exposure	Response ^a	Reference
Green algae (<i>Kirchneria subcapitata</i>)	Hydrothol 191 (23.4% a.e.)	EC ₅₀ : 2.3 µg a.e./L NOEC: 0.54 µg a.e./L	44949203 Drott et. al. 1999
Marine Diatom (<i>Skeletonema costatum</i>)	Hydrothol 191 (23.4% a.e.)	EC ₅₀ : 5.6 µg a.e./L NOEC: N/A	44127802 Hoberg, 1994
Bluegreen algae (<i>Anabaena flos-aquae</i>)	Hydrothol 191 (23.4% a.e.)	EC ₅₀ : 7 µg a.e./L NOEC: 0.5 µg a.e./L	44127803 Hoberg, 1994
Freshwater diatom (<i>Navicula pelliculosa</i>)	Hydrothol 191 (23.4% a.e.)	EC ₅₀ : 106 µg a.e./L NOEC: 5 µg a.e./L	44127805 Hoberg, 1994
Green algae (<i>Kirchneria subcapitata</i>)	Hydrothol 191 (23.4% a.e.)	EC ₅₀ : 1.9 µg a.e./L NOEC: 0.5 µg a.e./L	44127804 Hoberg, 1994
Marine Diatom (<i>Skeletonema costatum</i>)	Hydrothol 191 (23.4% a.e.)	EC ₅₀ : 22 µg a.e./L NOEC: 3.7 µg a.e./L	44976701 Drott et. al. 1999
Bluegreen algae (<i>Anabaena flos-aquae</i>)	Hydrothol 191 (23.4% a.e.)	EC ₅₀ : 40 µg a.e./L NOEC: 24 µg a.e./L	44949202 Drott et. al. 1999
Freshwater diatom (<i>Navicula pelliculosa</i>)	Hydrothol 191 (23.4% a.e.)	EC ₅₀ : 7.2 µg a.e./L NOEC: 2.3 µg a.e./L	44949201 Drott et. al. 1999
Filamentous algae (<i>Cladophora sp.</i>)	Hydrothol 191 (23.4% a.e.)	Product EC ₅₀ : 1000 µg /L NOEC: 250 µg/L Acid EC ₅₀ : 234 µg a.e./L NOEC: 58.5 µg/L	acc. 244122 USDI Bureau of Reclamation, 1964
Mixed phytoplankton	Hydrothol 191 (23.4% a.e.)	120-h LC ₅₀ : 0.35 mg a.e./L	Mudge et al. 1986
Blue-green algae (<i>Microcystis aeruginosa</i> Test 1)	Hydrothol 191 liquid. Toxicity values given in paper as a.i. and converted to a.e. using a factor of 0.44.	EC ₅₀ for cell density 24-h: 0.038 mg/L [8.9 µg a.e./L] 48-h: 0.045 mg/L [10.5 µg a.e./L] 96-h: 0.065 mg/L [28.6 µg a.e./L]	Ruzycki et al. 1998
Blue-green algae (<i>Microcystis aeruginosa</i> Test 2)	Hydrothol 191 liquid. Toxicity values given in paper as a.i. and converted to a.e. using a factor of 0.44.	EC ₅₀ for cell density 24-h: 0.081 mg/L [36 µg a.e./L] 48-h: 0.085 mg/L [37 µg a.e./L] 96-h: 0.114 mg/L [50 µg a.e./L]	Ruzycki et al. 1998
Blue-green algae (<i>Phormidium inundatum</i>)	Hydrothol 191 liquid. Toxicity values given in paper as a.i. and converted to a.e. using a factor of 0.44.	EC ₅₀ for cell density 24-h: 0.052 mg/L [23 µg a.e./L] 48-h: 0.088 mg/L [39 µg a.e./L] 96-h: 0.094 mg/L [41 µg a.e./L]	Ruzycki et al. 1998
Green algae (<i>Chlamydomonas noctigama</i>)	Hydrothol 191 liquid. Toxicity values given in paper as a.i. and converted to a.e. using a factor of 0.44.	EC ₅₀ for cell density 24-h: 0.522 mg/L [230 µg a.e./L] 48-h: 0.393 mg/L [173 µg a.e./L] 96-h: 0.273 mg/L [120 µg a.e./L]	Ruzycki et al. 1998
Green algae (<i>Chlorella vulgaris</i>)	Hydrothol 191 liquid. Toxicity values given in paper as a.i. and converted to a.e. using a factor of 0.44.	EC ₅₀ for cell density for 24 to 96 h: >0.600 mg/L [>264 µg a.e./L]	Ruzycki et al. 1998

Appendix 5: Toxicity to aquatic plants (continued)

A5 Table 5: Toxicity of Amine Salt to Algae			
Species	Exposure	Response ^a	Reference
Green algae (<i>Scenedesmus acuminatus</i>)	Hydrothol 191 liquid. Toxicity values given in paper as a.i. and converted to a.e. using a factor of 0.44.	EC ₅₀ for cell density 24-h: >0.6 mg/L [>264 µg a.e./L] 48-h: >0.6 mg/L [>264 µg a.e./L] 96-h: 0.417 mg/L [183 µg a.e./L]	Ruzycki et al. 1998
Diatom (<i>Synedra</i> sp.)	Hydrothol 191 liquid. Toxicity values given in paper as a.i. and converted to a.e. using a factor of 0.44.	EC ₅₀ for cell density for 24 to 96 h: >0.600 mg/L [>264 µg a.e./L]	Ruzycki et al. 1998
Green algae (<i>Cyclotella meneghiana</i>)	Hydrothol 191 liquid. Toxicity values given in paper as a.i. and converted to a.e. using a factor of 0.44.	EC ₅₀ for cell density 24-h: 0.272 mg/L [120 µg a.e./L] 48-h: 0.248 mg/L [109 µg a.e./L] 96-h: 0.232 mg/L [102 µg a.e./L]	Ruzycki et al. 1998