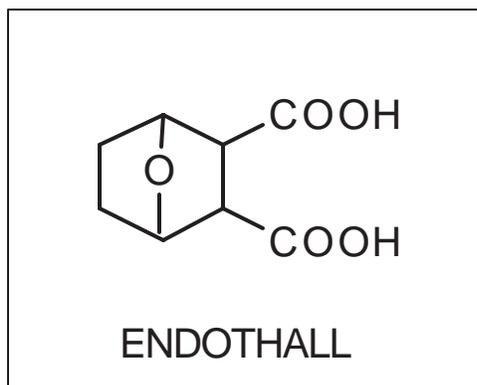


### III.6 ENDOTHALL



#### SUMMARY

Endothall (7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acid) is a relatively water-soluble contact herbicide, primarily used for the control of submersed weeds. Endothall exhibits a relatively short persistence time in the aquatic environment, usually undergoing complete degradation by microbial action in 30-60 days (USEPA, 1992a). Endothall does not adsorb to sediments nor does it bioconcentrate in aquatic organisms to any appreciable degree.

Two derivatives of endothall are available for aquatic weed control. These include the mono(N,N-dimethylalkylamine) salt and the dipotassium salt. Formulations containing the monoamine salt are particularly effective against filamentous algae but are more toxic to fish; thus they should not be used in areas where fisheries resources are important. Formulations containing the dipotassium salt exhibit a lower organism toxicity and are more appropriate for use in important fisheries areas.

The aquatic herbicidal properties of endothall were first suggested in the mid 1950s by its manufacturer at the time, Pennwalt Corporation. Actual development of endothall for this use started in 1958 (Elf Atochem, 1993a).

Endothall toxicity as noted in animal studies ranges from dermal and eye irritation, respiratory failure and hemorrhaging of the gastrointestinal tract upon exposure to high concentrations for a short period of time to effects on the liver and kidney upon longer-term exposure. There is no conclusive evidence indicating that endothall is either teratogenic, fetotoxic, mutagenic or carcinogenic.

Many studies have been conducted with the various endothall formulations addressing both toxicity and environmental fate and persistence. The U.S. Environmental Protection Agency (EPA) requires that endothall be reregistered under the 1988 amendments to FIFRA (Federal Insecticide, Fungicide and Rodenticide Act). Endothall is currently still under review. A number of studies relating to the toxicity of endothall to aquatic organisms as well as to its environmental persistence were submitted to EPA to fulfill some of the requirements of the reregistration process. The results of many of these studies are cited in this report; however, none of these studies has been critically reviewed by Massachusetts.

#### REGISTERED PRODUCTS IN MASSACHUSETTS

The current list of aquatic herbicides containing endothall that are registered in Massachusetts can be accessed at <http://www.state.ma.us/dfa/pesticides/water/aquatic/aquatic/profile.htm> on the Massachusetts Department of Agricultural Resources (DAR) Aquatic Pesticide Website. The DAR updates this list regularly with changes. In addition, the DAR can be contacted directly at (617) 626-1700 for more specific questions regarding these products.

## ENDOTHALL USES AND APPLICATION

Both the monoamine salt formulation and the dipotassium salt formulation are manufactured for use in lakes and ponds to control aquatic vegetation. For specific information on recommended application rates for a particular product, the product label should be consulted. The USEPA Office of Pesticide Programs (OPP) has a link to a database of product pesticide labels at <http://www.epa.gov/pesticides/pestlabels/>. A list of the weeds that these products control, which has been compiled from the Environmental Protection Agency (EPA) registration labels for these products, is contained in Table III.6-1.

Endothall applications should be made soon after emergence of new vegetative growth. Water temperature should be at least 65° F (18° C) prior to application. Although the EPA registration labels for these products do not recommend that any specific adjuvants be used during application, the following adjuvants have been suggested elsewhere: with salt formulations, polymeric adjuvants are recommended to aid in sinking the herbicide for underwater applications (e.g., with dipotassium salt formulations, Nalquatic and with monoamine salt formulations, Nalcotrol II). For the liquid formulations of these herbicides, invert emulsions are recommended to improve spreading and penetration of droplets, resist washoff and reduce evaporation and drift (Aquatic Plant Identification and Herbicide Use Guide, 1988).

## MECHANISM OF ACTION

Endothall's herbicidal mode of action is not clear. Several mechanisms have been postulated. It is known that endothall interferes with plant protein synthesis in some way (Aquatic Plant Identification and Herbicide Use Guide, 1988). In addition, endothall affects lipid synthesis and dipeptidase and proteinase activities (Mann and Pu, 1968; Mann *et al.*, 1965 as cited in MacDonald *et al.*, 1993). 5 µg/l of endothall caused an approximate 40% inhibition of incorporation of malonic acid into the lipid fraction of hypocotyl segments of the hemp plant (*Sesbania exaltata*) (Mann and Pu, 1968 cited in USEPA, 1988). It has been suggested that endothall produces a number of cell membrane changes that cause drying and wilting of leaf tissue and an increased respiratory rate in plants (Maestri and Currier, 1966 cited in USEPA, 1988). It has also been postulated that endothall acts to inhibit respiration. This was noted in a study in which the effect from endothall is greater in the dark, indicating the mechanism of action is not light-dependent. Under light conditions, photosynthesis provides some energy for respiration; however, all energy under dark conditions is produced via respiration. Thus, it was suggested that this effect may be due to respiratory inhibition by endothall (MacDonald *et al.*, 1993). It is also postulated that endothall interferes with metabolism of molecules involved in genetic coding (e.g., mRNA metabolism) (MacDonald *et al.*, 1993).

## ENVIRONMENTAL FATE/TRANSPORT

The fate and transport patterns of endothall in aquatic environments are similar for both the potassium and monoamine salt formulations (Aquatic Plant Identification and Herbicide Use Guide, 1988). Endothall is generally reported to be stable to oxidation, chemical hydrolysis and photolysis and not very volatile. However, in one study by the manufacturer, <sup>14</sup>C-labeled technical endothall, which was found to be stable to photolysis by xenon at pHs of 7 and 9, had a half-life of less than 24 hours at a pH of 5 (although the labeled endothall could not be accounted for). In another study by the manufacturer, the same compound exposed to xenon was stable at pH 5. In addition, the manufacturer also found that while technical endothall is stable to hydrolysis at pHs of 5 and 9, it breaks down with a half-life of 2825 days at pH 7. The above studies were all submitted by the manufacturer to the EPA to fulfill requirements for reregistration. These studies have not been reviewed by Massachusetts (Atochem, 1991a, 1991b, 1992a).

Endothall is also not expected to bioaccumulate or adsorb to suspended solids or sediments as indicated by very low octanol/water partition coefficients ( $K_{ow}$ ). (See Table III.6-3: Properties of

Endothall). The dominant fate processes affecting endothall in the aquatic environment are biotransformation and biodegradation via microbial action. A three phase clearance mechanism for endothall in the environment has been postulated. These include an initial, rapid rate where the endothall is temporarily adsorbed to sediments. The second phase, involving microbial metabolism, is considerably slower. The third phase consists of an intermediate rate of disappearance attributed to the proliferation of microorganisms with the ability to degrade endothall (Sikka and Rice, 1973 as cited in Aquatic Plants Management Program for Washington State, 1992).

Under aerobic conditions, endothall biodegrades rapidly in the aquatic environment, with a half-life of about one week or less (HSDB, 1994). Under anoxic conditions, the biodegradation half-life is longer. The manufacturer has determined a half-life of 10 days for the biodegradation of endothall dipotassium salt in water under anaerobic conditions (Atochem, 1993a). Other factors that affect endothall biodegradation include the presence of organic matter, plant tissue and microorganism populations (State of Wisconsin, 1990 as cited in Aquatic Plants Management Program for Washington State, 1992). Biotransformation of endothall occurs mainly by the tricarboxylic acid cycle after splitting of the oxabicyclo ring. Glutamic acid is the primary breakdown product. Minor metabolites include aspartic and citric acids, alanine, phosphate esters (not positively identified) and an unidentified product (HSDB, 1994 as cited in Sikka and Saxena, 1973). The importance of microbial action on endothall breakdown was illustrated in a study in which 2 ppm of endothall added to pond water resulted in no apparent degradation of endothall in autoclaved (sterilized) water after 9 days; yet the same amount added to non-autoclaved water resulted in 50% degradation after 4 days (Sikka and Rice, 1973 as cited in HSDB, 1994).

**Table III.6-1. List of Weeds Controlled by Endothall**

Bass Weed ( <i>Potamogeton amplexifolius</i> )	<i>Potamogeton diversifolius</i>
Bur Reed ( <i>Sparganium, spp</i> )	<i>Potamogeton filiformis</i>
Coontail ( <i>Ceratophyllum spp</i> )	<i>Potamogeton pusillus</i>
Milfoil ( <i>Myriophyllum spp</i> )	Water Star Grass ( <i>Heteranthera spp</i> )
Bushy Pondweed ( <i>Najas spp</i> )	Water celery ( <i>Vallisneria americana</i> )
Curly-leaf Pondweed ( <i>Potamogeton crispus</i> )	Canadian Waterweed ( <i>Elodea</i> )
Flat-Stem Pondweed ( <i>Potamogeton zosteriformis</i> )	Filamentous Green Algae ( <i>Cladophora, Pithophora, Spirogyra</i> )
Floating-Weed Pondweed ( <i>Potamogeton natans</i> )	Stonewort, Muskgrass ( <i>Chara</i> )
Horned Pondweed ( <i>Zannichellia spp</i> )	
Sago Pondweed ( <i>Potamogeton pectinatus</i> )	
<i>Potamogeton nodosus</i>	

Endothall applied to ponds at rates ranging from 0.3-10 ppm was undetectable after an average of 2.5 days and a maximum of 4 days (Simsiman *et al.*, 1976 as cited in HSDB, 1994). Fifty-five percent of a 1.2 ppm application of endothall added to another pond was removed after 12 days (Frank, 1972 as cited in HSDB, 1994). In other studies, an overall half-life of 4 days was reported in experimental greenhouse pools treated with 0.3 to 1.4 ppm endothall (Reinert *et al.*, 1985). In farm reservoirs, about 71% of

endothall applied at rates ranging from 0.3-1.4 ppm was removed after 12 days (Simsiman *et al.*, 1976 as cited in HSDB, 1994). Endothall added to the water of irrigation supply ponds at a concentration of 2 ppm decreased linearly with the predicted concentration of zero at 26 days (half-life 12 days) (Langeland and Warner, 1986 as cited in HSDB, 1994). Only 28% removal of endothall was achieved 30 days after addition of endothall to anoxic water (Simsiman *et al.*, 1976 as cited in HSDB, 1994).

Endothall does not significantly bioconcentrate in organisms. Consistently low endothall levels have been observed in many laboratory and field studies. Based on a water solubility of 100,000 mg/l at 20°C, a bioconcentration factor (BCF) of <1 was estimated for endothall as a function of its octanol-water partition coefficient ( $K_{ow}$ ) (Lyman *et al.*, 1982). A BCF of 10 for mosquito fish was observed in a modified Metcalf model ecosystem (Insensee, 1976 as cited in Reinert and Rodgers, 1987). In a field study, a 5 mg/l dipotassium endothall water concentration resulted in BCFs ranging from 0.003-0.008 in bluegills. After 72 hrs in the above study, no endothall residue was detected in the fish flesh (Serns, 1977 as cited in Reinert and Rodgers, 1987). In several organisms, it was noted that endothall concentrations exceeded the water concentration of endothall by more than an order of magnitude. Calculated BCF values of 150 for the water flea, 63 for green algae and 36 for a snail; however, the residue concentrations were transient and were not passed along trophic levels (Insensee, 1976 as cited in Reinert and Rodgers, 1987).

## **PHARMACOKINETICS**

Very little information exists regarding the pharmacokinetics of endothall in mammals. In rats given a single oral dose of about 5 mg/kg  $^{14}\text{C}$ -labeled endothall, approximately 3% of the endothall was recovered as carbon dioxide in urine while 90% was recovered in the feces and 7% in the urine (Soo *et al.*, 1967 as cited in USEPA 1988). The rats had received 5 mg/kg of unlabeled endothall in the diet for two weeks prior to treatment with  $^{14}\text{C}$ -labeled endothall. These results suggest that little gastrointestinal absorption took place. Studies in which deaths were induced in rabbits exposed to endothall directly in the eye or on the skin indicate the potential for absorption by these routes (Pharmacology Research, Inc., 1975a, 1975b as cited in USEPA, 1988, 1992a).

In rats receiving a single oral dose of 1.0 mg/kg  $^{14}\text{C}$ -labeled endothall, the highest levels of  $^{14}\text{C}$  after one hour were detected in the stomach and intestines (~ 95%), liver (~1.1%) and kidney (0.9%) and 0.02-0.1% in heart, lung, spleen and brain). Within 48-72 hours, endothall levels in all tissues fell to below detection. Total excretion of the  $^{14}\text{C}$  was over 95% complete after 48 hours and over 99% complete after 72 hours. In addition, no radioactivity was detected in rat pups of dams who had been given oral doses of  $^{14}\text{C}$ -endothall. Thus, endothall is not expected to accumulate. The metabolism of endothall has not been determined (Soo *et al.*, 1967 as cited in USEPA 1988). Another study also demonstrated that endothall was poorly absorbed via the oral route. In rats given a single oral dose of endothall, approximately 89-98% of the dose remained in the gut and was excreted in the feces unchanged (Hallifax, 1990 as cited in WSDOE, 2001). Regardless of whether rats received a single dose or a dose delivered subchronically for fifteen days, both the absorbed and unabsorbed chemical were not metabolized but were excreted in urine and feces. Bile was a very minor excretory route for endothall (Hallifax, 1990 as cited in WSDOE, 2001).

## **HEALTH EFFECTS**

### **Avian:**

Several acute or short-term toxicity studies have been conducted with endothall to fulfill EPA registration requirements. These studies have not been reviewed by this office. An oral LD50 value of 344 mg/kg was determined in a 21-day study conducted with mallard ducks and a formulation of the dipotassium salt (Atochem, 1992b). 8-day acute dietary studies conducted using a dipotassium salt

formulation with both bobwhite quail and mallard ducklings indicated that the acute oral LD50 and the NOEL values were both greater than 5,000 ppm (Elf Atochem, 1994c, 1994d). Two 20-week oral toxicity and reproductive studies conducted using the technical acid of endothall with bobwhite quails and mallard ducks yielded NOELs of 250 ppm for quail and 50 ppm for duck (Elf Atochem, 1992d, 1992e).

### **Mammalian:**

#### **Acute/Subchronic:**

The only available information in the literature addressing acute health effects of endothall to humans is a case history of a young male suicide victim who ingested 7-8 g of endothall in solution (about 100 mg endothall ion/kg). Effects included repeated vomiting, focal hemorrhages and edema in the lungs and gross hemorrhages of the gastrointestinal tract (Allender, 1983 as cited in USEPA, 1988).

Effects noted in animals exposed to high levels of endothall for a short period of time include cardiac arrest or respiratory failure as causes of death in dogs and rabbits injected with endothall at a concentration of at least 5 mg/kg (Goldstein, 1952; Srensek and Woodard, 1951 as cited in USEPA, 1988). The acute toxicity of the endothall acid appears to be greater than that of the salt forms usually used in herbicides. Acute oral LD50s in rats were reported to be 35-51 mg/kg for the acid form and 182-197 mg/kg for the sodium salt (Simsiman et al., 1976; Tweedy and Houseworth, 1976 as cited in USEPA, 1988).

Rats receiving about 40 or 400 mg/kg/day endothall ion in food for four weeks had slight liver degeneration and focal hemorrhaging in the kidney. Most of the rats receiving 400 mg/kg/day endothall died within a week (Brieger, 1953a as cited in USEPA, 1988).

Dogs that received 1-50 mg of disodium endothall/kg/day (0.8-40 mg endothall ion/kg/day) for 6 weeks died within 11 days (Brieger, 1953b as cited in USEPA, 1988). In the group given 20 mg/kg/day, vomiting and diarrhea occurred. Other health effects including pathological changes in the gastrointestinal tract (congested and edematous stomach walls and edematous upper intestines) were seen in all dogs. Erosion and hemorrhages of the stomach were noted with doses of at least 20 mg/kg/day.

Application of a 1% solution of endothall to the skin of rabbits resulted in no effects in unbroken skin and mild skin lesions in scarified skin. Application of 10% and 20% endothall solutions resulted in more serious effects, including necrosis and some animal deaths (Goldstein, 1952 as cited in USEPA, 1988). Dermal exposure of 6 rabbits to 200 mg endothall technical/kg resulted in the deaths of all of the rabbits within 24 hours of treatment (Pharmacology Research, Inc., 1975a as cited in USEPA, 1988).

Application of technical endothall to the eyes of rabbits produced severe eye irritation. Several rabbits died upon treatment, indicating that absorption of endothall took place through the eye (Pharmacology Research, Inc. 1975b as cited in USEPA, 1988). A number of acute and shorter-term toxicity studies in mammals have been conducted to fulfill EPA registration requirements. These studies have not undergone review by the Department. The studies are listed in Table III.6-2.

Table III.6-2. Acute/Short-Term Studies Submitted to the U.S. EPA (Elf Atochem)

SPECIES	DURATION	TYPE	RESULTS	REFERENCE
Dipotassium salt formulation:				
Rat	one dose	acute oral	LD50 = 99.5 mg/kg	Atochem, 1991c
rabbit	one dose	acute dermal	LD50 > 2,000 mg/kg	Atochem, 1991d
Rat	one dose	acute inhal.	LC50 = 0.83 mg/l (liquid aerosol)	Atochem, 1992c
rabbit	one dose at 0.1 ml	eye irrit.	Class I irrit.; one death	Atochem, 1991e
rabbit	one dose at 0.5 ml	skin irrit. (intact)	not irrit. at 0.5 ml	Atochem, 1992d
guinea pig	3 6-hr applies	dermal hypersensitivity	delayed contact hypersensitivity when induced at 5%, challenged and re-challenged at 2% in 80% ethanol	Atochem, 1991f
rat	1x/d; 5 d/wk; 21 d	dermal toxicity	40 mg/kg	Atochem, 1992e
rat	1x/d; 5 d/wk; 21 d	dermal toxicity	3 deaths at 80 mg/kg; 10 deaths each at 200 mg/kg and 500 mg/kg	Elf Atochem, 1993b
Monoamine salt formulation:				
rat	one dose	pharmacokinetic	half-life (blood) at 0.9 mg/kg - 1.8 hrs (M) and 2.5 hrs (F); at 4.5 mg/kg - 13.9 hrs (M)	Pennwalt Corp., 1990a
rat	one dose	dermal tox.	<7% of applied doses were absorbed into systemic circulation	Pennwalt Corp., 1990b

**Chronic:**

A 2-year toxicity study conducted with sodium endothall in beagle dogs yielded no adverse effect at 2 mg endothall ion/kg/day and an increase in organ weights and organ/body-weight ratios of the stomach and small intestine at the mid- and high-dose groups (6 and 16 mg ae/day for 24 months, respectively). The effect at the mid-dose was considered to be due to the irritation potential of the chemical (Keller, 1965 as cited in USEPA, 1988). A similar 1-year toxicity study in beagle dogs produced changes in the portal tract of the liver and dose-related changes in stomach mucosa at 14.4 mg ion/kg/day. At 4.8 mg ion/kg/day, there were no observed effects on the liver and marginal injury to the stomach (Greenough *et al.*, 1987 as cited in USEPA, 1992a).

No adverse effects were reported in female rats given 100 mg ion/kg/day for 2 years (Brieger, 1953b as cited in USEPA, 1988).

A number of longer-term toxicity studies using disodium endothall have been conducted to fulfill EPA registration requirements. These studies have not been reviewed by Massachusetts for this report and are summarized as reported by the manufacturer. A series of range-finding tests and a 2-year toxicity study were conducted in beagle dogs. A overall dose-response chart was developed by the authors of these studies with doses ranging from a NOEL of 4 mg/kg/day, to a LOEL of 6 mg/kg/day with increasingly severe health effects, up to a dose level of 120 mg/kg/day producing severe anorexia, vomiting, decreased body weight and decreased food consumption, leading to sacrifice of the animals after 4 days due to their poor condition (Elf Atochem, 1992e).

The selection of the NOEL in both the above study and another study on carcinogenicity discussed below are based on stomach changes in the dog (Elf Atochem, 1992c). Thickening of the stomach wall was not considered a significant effect by the toxicologist evaluating the results of these studies based on the fact that such thickening was consistent with stomach findings produced by long-term treatment with prostaglandins. The toxicologist concluded that the effect was an adaptive response to the irritating properties of the constant ingestion of endothall and not an adverse effect (Elf Atochem, 1992c).

In rats fed 0, 5.3, 10.5, 31.5 or 63 mg ae/kg/day disodium endothall (12.6% endothall acid equivalent) for 24 months, rats in the three highest dose groups had dose-related decreases in body weight and body weight gains and decreased glucose levels. Gross necropsy revealed an increased incidence of thickening of both the glandular and non-glandular stomach at the three highest dose groups. Acanthosis and keratosis were seen in the gross stomach lesions. The LOAEL was 31.5 endothall acid equivalent/kg/day and the NOAEL was 10.5 mg endothall ae/kg/day (Plankenhorn, 1990 as cited in WSDOE, 2001).

In an oral dietary study conducted in VD-1 6-week old mice over 92 weeks, NOELs of 100 ppm for males and 300 ppm for females were determined; however, the results from this study are questionable based on a possible miscalculation of dose calculations in feed (Atochem, 1990).

### **Developmental/Reproductive:**

A three-generation study in rats was conducted in which groups of male and female rats were fed diets containing 0, 4, 12 or 100 mg endothall ion/kg/day until they were 100 days old and then mated. Three successive generations of offspring were kept on the same test diet and then mated to produce the next test generation of offspring. No adverse effect was noted in the 4 mg/kg/day pups. Pups in the 12 mg/kg/day group had decreased body weights. Pups in the 100 mg/kg/day group did not survive more than one week (Scientific Associates, 1965 as cited in USEPA, 1988).

A short-term teratology study in rats indicated that no developmental effects were produced in offspring at endothall concentrations that were lethal to dams. Groups of 25 or 26 female rats were mated and then orally dosed with 0, 8, 16 or 24 mg endothall ion/kg/day of aqueous endothall technical on days 6 to 19 of gestation. Two dams died at the 16 mg/kg/day dose and ten dams died at the 24 mg/kg/day dose. The study suggests that the dams are more susceptible to endothall than are embryos or fetuses (Science Applications, Inc., 1982 as cited in USEPA, 1988).

In another study conducted in mice, endothall was administered via gavage to 4 groups of 25 pregnant mice on gestation days 6 through 16 at doses of 0 (control), 5, 20 and 40 mg/kg bw/day. Two dams died at the 20 mg/kg/day dose and two dams died at the 40 mg/kg/day dose. The incidence of vertebral and rib malformations in the offspring was increased although it was not statistically significant. The authors suggested that the results of this study are nevertheless significant since the usual incidence of vertebral and rib malformations is low in their laboratory;

however, they acknowledged that the influence of maternal toxicity in producing the reported malformations could not be ruled out (IRDC, 1981 as cited in USEPA, 1992a).

A developmental/reproductive study was conducted by the manufacturer in which rats were dosed with disodium endothall in drinking water during organogenesis (days 6-15) of pregnancy and sacrificed on day 20. A NOAEL of 12.5 mg/kg/day was determined for maternal effects and a NOAEL of 25 mg/kg/day was determined for fetal effects (Elf Atochem, 1993c). In another study, rats were given disodium endothall in the diet until completion of breeding, a 2-generation reproductive study was conducted and a NOAEL of 150 ppm for maternal reproductive effects was identified (Elf Atochem, 1993d).

Another, more recent two-generation study was conducted in which rats were fed endothall disodium salt at 1.2, 6 or 36 mg ae/kg/day endothall. No treatment-related effects were noted in terms of pregnancy rates, fertility, reproductive performance or offspring viability and survival. The only significant adverse effect noted was decreased body weight in parents and offspring in the high dose group. The NOAEL for the study was 6 mg ae/kg/day endothall (Trutter, 1993 as cited in WSDOE, 2001).

### **Mutagenicity:**

A number of short-term mutagenicity studies have been conducted with various forms of endothall as the test agent. The results of these studies are mixed. Endothall was not mutagenic in studies conducted with bacteria, fungus, mammalian cells or *Drosophila*. Assays conducted with in vivo somatic or male germinal-cells using the disodium salt did not induce any mutagenic effects. Endothall did not produce aneuploidy in plants and dipotassium endothall did not induce the frequency of sister chromatid exchange in human lymphocytes. the dipotassium salt formulation did induce mutagenic effects in BALB/3T3 both in the presence and absence of rat primary hepatocytes; however the validity of these studies is questionable (USEPA, 1992a).

Several mutagenicity assays, conducted by the manufacturer, including two Ames assays, one assay in Chinese hamster ovary cells and one in vivo test conducted in mouse bone marrow erythropoietic cells yielded all negative and one set (Ames) of equivocal results (Elf Atochem, 1993e, 1993f, 1994e). Endothall produced positive results in a chromosome aberration study in *Allium cepa* (Mutation Research, 1982 as referenced in GENETOX, 1995).

### **Carcinogenicity:**

Limited studies have been conducted which address the potential carcinogenicity of endothall. 10 male and 10 female rats were exposed to endothall in the diet at various concentrations up to 2,500 mg disodium endothall/kg food (about 100 mg endothall ion/kg/day) for 2 years. Two of the treated rats had lung tumors; however, based on the small sample size used for this investigation and the lack of information obtained on tumor type and dose group, the statistical validity of these findings was not evaluated (Brieger, 1953b as cited in USEPA, 1988). A 2-year oral cancer study in rats found no carcinogenic response at doses up to 1800 ppm (Atochem North America, 1990). The present database is inadequate to assess the animal or human carcinogenic potential of endothall. Based on a review of the available chronic feeding studies and results of mutagenicity tests, there are no definitive data indicating that endothall is carcinogenic. The primary histopathological findings have been attributed to the high irritation potential of endothall to the gastro-intestinal tract (WSDOE, 2001). The U.S. EPA Office of Pesticide Programs (OPP) has designated endothall as a Group E carcinogen under the old EPA cancer classification system. Under the new EPA cancer classification system using descriptors, a Group E carcinogen corresponds to the descriptor “not likely to be carcinogenic to humans”.

**Available Toxicity Criteria:**

The Environmental Protection Agency (EPA) has developed several Drinking Water Health Advisories for endothall. Health Advisories are defined as concentrations of a substance in drinking water estimated to have negligible deleterious effects in humans, when ingested for a specified period of time. These values include a ten-day health advisory for a child of 0.8 ppm as well as a lifetime health advisory of 0.2 ppm for a child and 0.7 ppm for an adult (USEPA, 1988).

The EPA has also developed a Maximum Contaminant Level Goal (MCLG) of 0.1 mg/l for drinking water and has promulgated this value as a Maximum Contaminant Level (MCL) standard (USEPA, 1992b; USEPA, 1995a). Massachusetts has adopted this value as a drinking water standard, known as a Massachusetts Maximum Contaminant Level (MMCL).

In addition, the EPA Carcinogen Risk Assessment Verification Endeavor (RfD/RfC) Workgroup has developed an oral Reference Dose (RfD) of 0.02 mg/kg/day for endothall based upon the Keller (1965) two-year feeding study in dogs cited earlier. The EPA Office of Pesticide Programs (OPP) has calculated the same RfD value based on the same study (USEPA, 1995b). The RfD is an estimate, (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime (USEPA, 1992b).

**ECOLOGICAL TOXICITY****Aquatic Organisms :**

Limited information indicates that, in contrast to endothall absorbed by mammals in which it is excreted largely as the bound form, endothall absorbed by plants and fish is completely metabolized (Simsman *et al.*, 1976 as cited in HSDB, 1994). In acute and behavioral toxicity studies, goldfish did not avoid endothall at 0.17 ppm and 1.70 ppm, but avoided it at 17.0 ppm (Berry, 1984 as cited in HSDB, 1994). Rainbow trout avoided a dipotassium salt formulation at concentrations above 10 ppm (State of Wisconsin, 1990 as cited in WSDOE, 1992).

Most of the available information on the toxicity of endothall to aquatic organisms is based on acute exposure data obtained in laboratory studies. There are very few studies addressing longer-term exposures. One longer-term study evaluated the effects of a one-time application of dipotassium endothall over a three-year period on reproduction or survival of young-of-the-year bluegills. No difference in effects was noted but adult fish survival was found to be higher in the treatment pond. It was suggested that this finding might be due to slower growth in the treatment pond reflecting a greater biomass of fish present (State of Wisconsin, 1990 as cited in WSDOE, 1992).

Acute flow-through type bioassays have been conducted with a number of freshwater and marine fish and invertebrates. In general, the dipotassium salt formulation is the least toxic to aquatic organisms, the technical acid is somewhat more toxic and the monoamine formulation is much more toxic. Typical acute LC50 values obtained in 96-hr static bioassays using a 40.3% dipotassium salt of endothall formulation (i.e., as a liquid) range from >150 ppm for channel catfish to 230-450 ppm for rainbow trout to 343-450 ppm for bluegills to 313 ppm for scuds. Typical LC50 values obtained in similar assays using a 53% formulation of endothall monoamine salt (i.e., as a liquid) are much lower ranging from 0.05 ppm for grass shrimp and stoneflies to 0.49 ppm for channel catfish to 0.94 for bluegills (Phipps, G.L., 1984 as cited in HSDB, 1994). In a series of studies conducted with freshwater (rainbow trout, bluegill sunfish, water flea) and marine (oyster, sheepshead minnow and mysid shrimp) species: For tests conducted with a formulation of 40.3% active ae, the LC50 values ranged from 240-740 ppm. The least sensitive species was the bluegill and the most sensitive species were the mysid shrimp and the water flea. For the

technical acid, the LC50 values ranged from 39-110 ppm. The least sensitive species was the sheepshead minnow while the most sensitive species was the mysid shrimp. For tests conducted using a monoamine salt formulation, the LC50 values ranged from 0.19-2.0 ppm with the least sensitive species being the bluegill and sheepshead minnow and the most sensitive species being the mysid shrimp and the water flea (Elf Atochem, 1993a).

Thus, the toxicity of endothall to aquatic organisms depends on the formulation used. The dipotassium salt of endothall is generally not toxic to aquatic organisms at recommended application rates of 0.5-5 ppm, whereas the monoamine salt formulation is lethal to many organisms at the same recommended application rate.

**Plants:**

Since endothall is effective in treating a large range of plants, it may have a widespread effect on non-target plants, especially when applied as a whole-pond treatment. In addition to direct toxic effects of the herbicide, treatment of a pond with endothall may also cause indirect impacts including dissolved oxygen depletion and habitat loss. These impacts may cause general weakening and/or death of plants on a large scale (WSDOE, 1992).

**Microorganisms :**

No significant differences were seen in zooplankton population over a 5-month period in a pond treated with 5.0 ppm dipotassium endothall as compared to a control pond. No significant impacts were noted on aquatic bacteria from the dipotassium salt at 5ppm (WSDOE, 1992).

Table III.6-3. Properties of Endothall

CAS #:	145-73-3
Synonyms	Hexahydro-3,6-endo-oxy-phthalic acid; 3,6-endo-Epoxy-1,2-cyclohexanedicarboxylic acid
Molecular formula	C <sub>8</sub> H <sub>10</sub> O <sub>5</sub>
Molecular weight	186.2
Physical properties	crystalline, white solid; odorless
Melting point	when heated rapidly at 144° C, decomposes into the anhydride and water
Density	1.43 g/ml
Vapor pressure	negligible
Photolysis half-life	stable
Hydrolysis half-life	stable
Biodegradation half-life	8.35 days
K <sub>ow</sub>	1.36 (potassium salt) 1.91 (acid)
K <sub>oc</sub>	110-138 ml/g
BCF	<1-1.1
Solubility:	(g acid monohydrate/100 g solvent)
Acetone	7.0
Benzene	0.01
Dioxane	7.6
Ether	0.1
Isopropyl Alcohol	1.7
Methanol	28.0
Water	10.0

(Aquatic Plant Identification and Herbicide Use Guide, 1988; WSSA, 1983)

### Endothall References

- Allender, W.J. 1983. Suicidal poisoning by endothall. *J Anal Toxicol* 7:79-82.
- Aquatic Plant Identification and Herbicide Use Guide. November, 1988. Volume I: Aquatic Herbicides and Application Equipment. Howard E. Westerdahl and Kurt D. Getsinger, eds. Environmental Laboratory. Department of the Army. Vicksburg, Mississippi.
- AQUIRE (Aquatic Toxicity Information Retrieval Database). 1995. Environmental Research Laboratory. U.S. Environmental Protection Agency.
- Atochem North America, Inc. May, 1990. Oncogenicity feeding study of disodium endothall in mice: project no. WIL-75009. WIL Research Laboratories. Ashland, Ohio.
- Atochem North America, Inc. October 22, 1991a. Hydrolysis of  $^{14}\text{C}$ -endothall dipotassium salt in water at pH 5, 7 and 9. Xenobiotics Laboratory, Inc. Princeton, N.J.
- Atochem North America, Inc. October 31, 1991b. Photogradation of  $^{14}\text{C}$  endothall in a buffered aqueous solution under artificial sunlight. Battelle. Columbus, Ohio.
- Atochem North America. November 20, 1991c. Acute exposure oral toxicity in rats with Aquathol K. Pharmakon Research International, Inc. Waverly, PA.
- Atochem North America. November 19, 1991d. Acute exposure dermal toxicity with Aquathol K. Pharmakon Research International, Inc. Waverly, PA.
- Atochem North America. November 20, 1991e. Primary eye irritation with Aquathol K. Pharmakon Research International, Inc. Waverly, PA.
- Atochem North America. November 22, 1991f. A comparative delayed contact hypersensitivity study in guinea pigs (Buehler) with Aquathol K. Pharmakon Research International, Inc. Waverly, PA.
- Atochem North America, Inc. October 22, 1992a. Photodegradation of  $^{14}\text{C}$  endothall in water under artificial light. Battelle. Columbus, Ohio.
- Atochem North America, Inc. May 15, 1992b. AQUATHOL K Aquatic Herbicide: 21-Day Acute Oral LD50 Study in Mallard Ducks. Bio-Life Associates, Ltd. Neillsville, WI.
- Atochem North America. April 22, 1992c. An acute inhalation toxicity study of Aquathol K in the rat. Bio/dynamics, Inc. East Millston, New Jersey.
- Atochem North America. January 14, 1992d. Primary dermal irritation study with Aquathol K. Pharmakon Research International, Inc. Waverly, PA.
- Atochem North America. January 23, 1992e. 21 day dermal toxicity study in rats - Aquathol K. Pharmakon Research International, Inc. Waverly, PA.
- Atochem North America, Inc. August 12, 1993a. Anaerobic aquatic metabolism of  $^{14}\text{C}$ -endothall dipotassium salt. Xenobiotic Laboratories, Inc. Plainsboro, N.J.
- Berry, C.R. Jr. 1984. Toxicity of the herbicides diquat and endothall to goldfish (*Carassius auratus*). *Environ Pollut Ser A Ecol Biol.* 34(3):251-258.

- Brieger, H. 1953a. Preliminary studies on the toxicity of endothall (disodium). EPA Pesticide Petition No. 6G0503, redesignated No. 7F0570, 1966. EPA Accession No. 246012.
- Brieger, H. 1953b. Endothall, long term oral toxicity test--rats. EPA Pesticide Petition No. 6G0503 redesignated No. 7F0570, 1966. EPA Accession No. 246012.
- Corte-Real, Lee. 1995. Personal Communication. Massachusetts Department of Food and Agriculture. Pesticide Bureau.
- Elf Atochem North America, Inc. February, 1992a. Aquathol K Aquatic Herbicide (EPA registration label).
- Elf Atochem North America, Inc. February, 1992b. Hydrothol 191 Aquatic Algicide and Herbicide (EPA registration label).
- Elf Atochem North America. August 28, 1992c. Endothall Acid and Salts Request for Toxicology meeting. Letter to Ms. Ernestine Dobbins from Gary R. Sandberg.
- Elf Atochem North America. September 8, 1992d. Endothall Technical: Toxicity and Reproduction Study in Bobwhite Quail. Bio-Life Associates, Ltd. Neillsville, WI.
- Elf Atochem North America. September 8, 1992e. Endothall Technical: Toxicity and Reproduction Study in Mallard Ducks. Bio-Life Associates. Neillsville, WI.
- Elf Atochem North America, Inc. March 24, 1993a. Technical Seminar "Endothal". Orlando, Florida.
- Elf Atochem North America, Inc. February 9, 1993b. Rat developmental toxicity study with disodium salt of endothall. Hazleton Washington, Inc. Vienna, VA.
- Elf Atochem North America, Inc. February 9, 1993c. Rat developmental toxicity study with disodium salt of endothall. Hazleton Washington, Inc. Vienna, Virginia.
- Elf Atochem North America, Inc. September 15, 1993d. Two-generation reproduction study in rats with disodium salt of endothall. Hazleton Washington, Inc. Vienna, Virginia.
- Elf Atochem North America, Inc. December 10, 1993e. Ames/Salmonella Plate Incorporation Assay on Technical Endothal Amine Salt Solution. Pharmakon Research International, Inc. Waverly, PA.
- Elf Atochem North America, Inc. December 10, 1993f. AS52/XPRT Mammalian Cell Forward Gene Mutation Assay on Technical Endothal Amine Salt Solution. Pharmakon Research International, Inc. Waverly, PA.
- Elf Atochem North America, Inc. March, 1994a. Aquathol Granular Aquatic Herbicide (EPA registration label).
- Elf Atochem North America, Inc. March 1994b. Hydrothol 191 Granular Aquatic Algicide and Herbicide (EPA registration label).
- Elf Atochem North America. March 1, 1994c. AQUATHOL K Aquatic Herbicide: 8-Day Acute Dietary LC50 Study in Bobwhite Quail. Bio-Life Associates, Ltd. Neillsville, WI.

- Elf Atochem North America. March 1, 1994d. AQUATHOL K Aquatic Herbicide: 8-Day Acute Dietary LC50 Study in Mallard Ducklings. Bio-Life Associates, Ltd. Neillsville, WI.
- Elf Atochem North America, Inc. January 7, 1994e. In vivo micronucleus test on technical endothal amine salt solution in mouse bone marrow erythropoietic cells. Pharmakon Research International, Inc. Waverly, PA.
- Frank, P.A. 1972. Adv Chem Ser. 111:135.
- GENETOX (Genetic Toxicology Database). 1995. U.S. Environmental Protection Agency.
- Goldstein, F. 1952. Cutaneous and intravenous toxicity of endothall (disodium-3-endohexahydrophthalic acid). Pharmacol. Exp. Ther. 11:349.
- Greenough, R.J., R.G. Goburdham and P. Howroyd. 1987. Disodium endothall: 52-week oral (dietary) toxicity study in dogs. Study performed by Inveresk Research International Ltd. Musselburg, Scotland for Pennwalt Corp. Philadelphia, PA. EPA MRID No. 40745202.
- Hallifax, D. 1990. Endothall: Absorption, distribution, metabolism and excretion study in the rat. Final report. Life Science Research Ltd, Eye, Suffolk IP23 7PX, England, LSR Report 89/0122.
- HSDB (Hazardous Substances Database). October 1994. Environmental Protection Agency.
- IRDC. International Research and Development Corporation. 1981. Teratology study in mice. Study No. 470-006. EPA Accession No. 070277.
- Isensee, A.R. 1976. Variability of aquatic model ecosystem-derived data. Int J Environ Stud. 10:35-41.
- Keller, J. 1965. Two year chronic feeding study of disodium endothall to beagle dogs. Scientific Associates report. EPA Pesticide Petition 6G0503, redesignated No. 7F0570, June 1966. EPA Accession No. 24601.
- Langeland, K.A. and J.P Warner. 1986. Persistence of diquat, endothall and fluridone in ponds. J Aquat Plant Manage. 24:43-6.
- Lyman, Warren J., William F. Reehl and David H. Rosenblatt. 1982. Chemical Property Estimation Methods - Environmental Properties of Organic Compounds. McGraw-Hill. NY. pp. 5-5.
- Maestri M. and H.B. Currier. 1966. Toxic effects of endothall. Plant Physiol Proc Ann Meeting. Abstract VII.
- MacDonald, G.E., D.G. Shilling and T.A. Bewick. 1993. Effects of endothall and other aquatic herbicides on chlorophyll fluorescence, respiration and cellular integrity. J Aquat Plant Manage. 31:50-54.
- Mann, J.D. and M. Pu. 1968. Inhibition of lipid synthesis by certain herbicides. Weed Sci. 16:197-198.
- Mutation Research. 1982. 99:273-291.
- Pennwalt Corporation Agrichemicals Division. September, 1990a. Endothall: absorption, distribution, metabolism and excretion study in the rat (final report). Life Science Research Ltd. Suffolk, England.

- Pennwalt Corporation Agrichemicals Division. July 6, 1990b. Dermal absorption of  $^{14}\text{C}$ -endothall monohydrate using male sprague-dawley rats. Battelle Columbus Division. Columbus, Ohio.
- Pharmacology Research, Inc. 1975a. U.S. EPA Pesticide Resubmission File 4581-EIE. Summary data on acute oral toxicity and dermal irritation in rabbits (endothall). EPA Accession No. 244125.
- Pharmacology Research, Inc. 1975b. U.S. EPA Pesticide Resubmission File. Summary data, primary eye irritation in the rabbit and inhalation toxicity in several species (endothall). EPA Accession No. 246012.
- Phipps, G.L. *et al.* 1984. *J Water Pollut Control Fed.* 56(6):725-58.
- Plankenhorn, L. 1990. Combined chronic toxicity and carcinogenicity study of disodium endothall in rats. Project HLA 6120-110, Phase 3 summary of MRID 00069054, Hazleton Labs America, Inc.
- Reinert, K.H., J.H. Rodgers Jr., M.L. Hinman and T.J. Leslie. 1985. Compartmentalization and Persistence of Endothall in Experimental Pools. *Ecotoxicol Environ Saf.* 10(1):86-96.
- Reinert, K.H. and J.H. Rodgers. 1987. Fate and persistence of aquatic herbicides. *Rev. Environ. Contamin. Toxicol.* 98:61-98.
- Science Applications, Inc. 1982. A dose range-finding teratology study of endothall technical and disodium endothall in albino rats. Resubmission of Pesticide Application for Aquathol K Aquatic Herbicide (EPA Registration No. 4581-174). EPA Accession No. 071249.
- Scientific Associates. 1965. Three generation rat reproductive study, disodium endothall. EPA Pesticide Petition No. 6G0503, redesignated 7F0570, 1966. EPA Accession No. 246012.
- Serns, S.L. 1977. Effects of dipotassium endothall on rooted aquatics and adult and first generation bluegills. *Water Res Bull.* 13:71-80.
- Sikka, H.C. and C.P. Rice. 1973. Persistence of Endothall in Aquatic Environment as Determined by Gas-Liquid Chromatography. *J. Agr. Food Chem.* 21:842-846 In: A. Protzed, *et al.* May 1990.
- Sikka H.C. and J. Saxena. 1973. *J Agric Food Chem.* 21:402
- Simsiman G.V., T.C. Daniel and G. Chesters. 1976. Diquat and endothall: Their fates in the environment. *Residue Rev.* 62:131-174.
- Sittig, Marshall. 1991. *Handbook of Toxic and Hazardous Chemicals and Carcinogens.* 3rd ed. vol. I. Noyes Publications. Park Ridge, N.J.
- Soo, A., I. Tinsley and S.C. Fang. 1967. Metabolism of  $^{14}\text{C}$ -endothall in rats. *J. Agric. Food Chem.* 15:1018-1021.
- Srensek, S.E., and G. Woodard. 1951. Pharmacological actions of "endothall" (disodium-3,6-endoxo-hexahydrophthalic acid). *Fed. Proc.* 10:337. (Abstract).
- State of Wisconsin. 1990, 3rd Edition. *Environmental Assessment Aquatic Plant Management (NR 107) Program.*

Tweedy, B.G. and L.D. Houseworth. 1976. Miscellaneous herbicides. In *Herbicides-chemistry, degradation and mode of action*. P.C. Kearney and D.D. Kaufman, eds. Chapter 17. New York: Marcel Dekker, Inc. pp. 815-833.

USEPA (U.S. Environmental Protection Agency). 1988. Endothall Health Advisory. Office of Drinking Water. Washington, D.C.

USEPA (U.S. Environmental Protection Agency). January 1992a. Final Drinking Water Criteria Document for Endothall. Health and Ecological Criteria Division. Office of Science and Technology. Office of Water. Washington, D.C.

Trutter, J.A.. 1993. Two-generation reproduction study in rats with disodium salt of endothall. Final report. Hazleton Washington, Inc. Laboratory Project Identification: HWA study no. 153-142.

USEPA (U.S. Environmental Protection Agency). August 1, 1992b. Integrated Risk Information System. Endothall - Reference Dose for Chronic Oral Exposure (RfD).

USEPA (U.S. Environmental Protection Agency). May, 1995. Drinking Water Regulations and Health Advisories. Office of Water. U.S. Environmental Protection Agency. Washington, D.C.

USEPA (U.S. Environmental Protection Agency). 9/10/95b. Office of Pesticide Programs Reference Dose Tracking Report.

(WSDOE) Washington State Department of Ecology. 1992. Aquatic Plants Management Program for Washington State. Vol 1: Final Supplemental Environmental Impact Statement and Responsiveness Summary; and Vol. 2: Final Supplemental Environmental Impact Statement: Vol. 2: Appendices. Olympia, Washington.

(WSDOE) Washington State Department of Ecology. February 2001. Herbicide Risk Assessment for the Aquatic Plant Management Final Supplemental Environmental Impact Statement – Appendix D -- Volume 2: Endothall.

WSSA (Weed Science Society of America). 1983. *Herbicide Handbook*. Weed Science Society of America. Champaign, Illinois.