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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

AUG 2 0 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: Endothall: Review of Acute Toxicology Studies with Technical Endothall (Aquathol K™)

FROM: Steven L. Malish, Ph.D., Toxicologist S. L. Malish 8/19/93
Tox. Branch II, Review Section IV
HED (H7509C)

TO: Kathryn Davis, Product Manager (52);
Ernestine Dobbins - PM Team Reviewer
Registration Division (H7508W)

THRU: Jess Rowland. M.S., Acting Section Head Jess Rowland 8/19/93
Tox. Branch II, Review Section IV
HED (H7509C)

and

Marcia van Gemert, Ph.D., Branch Chief Marcia van Gemert 8/19/93
Tox Branch II; HED (H7509C)

Task Identification: Submission: S5417778 DP Barcode: D178232
P.C. Code: 038901 Caswell No.: 421

ACTION REQUESTED: Review acute toxicity studies MRID No(s). 422829-01, -02, -03 and -04] for guidelines 81-1. -2, -4 and -5 with Endothall.

Response:

A Data Evaluation Report for the above referenced studies are attached. A summary is provided below.

Endothall Technical: (81.1% a.i.)

1. 81-1 Acute Oral Toxicity Study/Rodent
MRID No.: 422829-01

The acute oral LD_{50} using male and female rats was determined to be 45.4 mg/kg. For male rats, the LD_{50} was 50.2 mg/kg, while in female rats the LD_{50} was 44.4 mg/kg. Necrospy of animals that died during the study showed fluid filled and/or distended intestines and stomachs and pale kidneys. Terminal necropsies showed mottled kidneys in some instances. TOX. CATEGORY = I.

CORE CLASSIFICATION: Guideline; this study satisfies the data requirement [81-1] for an Acute Oral Study in rodents and is acceptable for regulatory purposes.

2. 81-2 Acute Dermal Toxicity Study/Non-Rodent
MRID No.: 422829-02

The acute rabbit dermal LD_{50} for Endothall Technical was determined to be greater than 2,000 mg/kg. TOX. CATEGORY = III

CORE CLASSIFICATION: Guideline; this study satisfies the data requirement [81-2] for an Acute Dermal Toxicity Study in non-rodents and is acceptable for regulatory purposes.

3. 81-4 Primary Eye Irritation Study/Non-rodent
(MRID No. 422892-03)

Under conditions of this study, Endothall Technical was found to be a strong eye irritant and was systemically toxic when instilled into the eyes of rabbits. TOX. CATEGORY = I.

CORE CLASSIFICATION: Guideline; this study satisfies the data requirement [81-4] for a Primary Eye Irritation Study in non-rodents and is acceptable for regulatory purposes.

4. 81-5 Acute Primary Skin Irritation Study/Non-rodent
MRID No.: 422892-04

Endothall Technical was found not to be a dermal irritant (Primary Irritation Index = 0.0) to the skin of rabbits. TOX.CATEGORY = IV.

CORE CLASSIFICATION: Guideline; this study satisfies the data requirement [81-5] for a Primary Dermal Irritation Study in non-rodents and is acceptable for regulatory purposes.

010507

DATA EVALUATION REPORT

Endothall, Technical

Study Type: Primary Eye Irritation Study in Rabbits (81-4)

Prepared for:

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Chemical Hazard Evaluation Group
Biomedical and Environmental Information Analysis Section
Health Sciences Research Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831

Primary Reviewer:
H. T. Borges, Ph.D., MT(ASCP)

Signature: H.T. Borges
Date: 8/11/93

Secondary Reviewer:
Robert H. Ross, M.S., Group Leader

Signature: Robert H Ross
Date: 8-11-93

EPA Reviewer: Steven Malish, Ph.D.
Review Section IV, Toxicology Branch/HED

Signature: Steven J. Malish
Date: 8/17/93

EPA Section Head: Jess Rowland, M.S.
Review Section IV, Toxicology Branch/HED

Signature: Jess Rowland
Date: 8/16/93

DATA EVALUATION REPORT

STUDY TYPE: Primary Eye Irritation Study in Rabbits (81-4)

EPA IDENTIFICATION NUMBERS:

Tox. Chem. Number: 421
MRID Number: 422892-03

TEST MATERIAL: Endothall, Technical

SYNONYMS: None known or reported

SPONSOR: Atochem North America, Three Parkway, Philadelphia, PA

STUDY NUMBER: PH 421-ANA-002-91

TESTING FACILITY: Pharmakon Research International, Inc., Waverly, PA

TITLE OF REPORT: Primary Eye Irritation with Endothall Technical

AUTHOR: Victor T. Mallory, B.S., RLAT

STUDY COMPLETED: 11/20/91

CONCLUSION: Under the conditions of this study, Endothall Technical was found to be a strong eye irritant and was systemically toxic when instilled into the eyes of rabbits.

TOXICITY CATEGORY: I

CORE CLASSIFICATION: Guideline. This study meets the data requirement [81-4] for a primary eye irritation study in rabbits and is acceptable for regulatory purposes.

A. MATERIALS

1. Test Material

Test material: Endothall Technical
Receipt: 1/14/91
Physical description: Off-white crystalline solid
Active Ingredient: Endothall, 81.1%
Inactive Ingredient: Not reported
Lot number: J19A
pH: Not reported
Stability: No apparent change in the physical state of Endothall Technical was observed during administration.

2. Controls

Materials: Not needed
Animals: Left eye not instilled with Endothall Technical

3. Test Animals

Species: Rabbits
Strain: New Zealand White
Source: CAMM Research Lab Animals, Wayne, NJ
Receipt Date: 7/11/91
Sex: Male and female
Numbers: Three male and three female
Housing: Rabbits were housed individually in cages, acclimated for a minimum of five days, and adjusted to a 12-hour light/dark cycle. The room temperature was controlled at 20°C ± 3°C with a relative humidity of 50% ± 20%.
Age: Adult
Weight: 2.5-3.3 kg
Feeding: Purina Lab Rabbit Chow H.F.® and fresh tap water provided ad libitum.
Assignment: Animals randomly assigned to groups based on sex, body weight, and general health.
Location of raw data: All raw data is recorded and retained by Pharmakon Research International, Inc. in laboratory notebook #1455, pages 145-147.

4. Exposure

Route of administration: Ocular
Dose level: 100-103 mg/treated eye

B. TEST PERFORMANCE

Treatment. Both eyes of each rabbit selected for testing were examined 24 hours prior to the start of the study. Any rabbit having eye irritation, ocular defects or pre-existing corneal injury was not used. Endothall Technical (100-103 mg) was instilled into the conjunctival sac of the right eye of each rabbit after the lower lid was gently pulled away from the eyeball. The lids were gently held together after instillation for approximately 1 second to limit loss of Endothall Technical. The left eye of each rabbit in the study was not treated and served as the control.

The eyes of each rabbit were examined 1 and 24 hours postinstillation. The ocular irritation score was recorded after each examination. The rabbits were examined for clinical signs of Endothall Technical toxicity 5 hours and 24 hours postinstillation. The body weight of each rabbit was recorded at the start of the study and at death or termination of the study.

Scoring and Classification of Ocular Irritation. Ocular irritation was scored according to the scheme shown in Table 1A. Reactions considered positive in the study included the following: ulceration of the cornea (other than a fine stippling); opacity of the cornea (other than a slight dulling of the normal luster); inflammation of the iris (other than a slight hyperemia of the circumcorneal blood vessels); or an obvious swelling in the conjunctivae (excluding the cornea and iris) with partial eversion of the eyelids and a diffuse crimson color with individual vessels not easily discernible. Ocular irritation was scored according to the scheme shown in Table 1B.

C. RESULTS AND STUDY AUTHOR'S CONCLUSIONS

The individual ocular irritation scores recorded 1 hour and 24 hours postinstillation of Endothall Technical for each rabbit in the study are shown in Table 2. The summary incidence scores for primary irritation are shown in Table 3.

One hour postinstillation of Endothall Technical, all male and female rabbits had scores of 2 for the cornea (easily discernible translucent areas with details of the iris slightly obscured) and iritis (no reaction to light, hemorrhage, and/or gross destruction). All six rabbits had conjunctival scores for redness of 3 (diffuse beefy red) and 5/6 had chemosis scores of 4 (eyes swollen half to fully closed). The remaining rabbit had a conjunctival chemosis score of 3. Because of the death of 4/6 rabbits and the severe chemosis (score of 4) in the two surviving rabbits, only the conjunctival scores were recorded 24 hours postinstillation (Table 2). No data was reported nor could information be found in the laboratory notes concerning the ocular irritancy scores of the contralateral (control) eye.

All rabbits in this study showed clinical signs of Endothall Technical-related toxicity 5 hours post-instillation (Table 4). These signs included decreased activity (2 male, 2 female), abnormal gait (2 male, 2 female), abnormal stance (2 male, 2 female), dyspnea (2 male, 2 female), and prostration (1 male and 1 female). In addition, a red discharge was found in the catch pans of one male and one female rabbit. Prior to the 24 hour observation, 3/3 male rabbits and 1/3 female rabbits died. At necropsy, 3/3 male and the female rabbit had ascites, 1/3 male and the female had a red fluid-filled bladder, and 1 male rabbit had a dark red liver (Table 5). At the sponsor's request, the two surviving female rabbits were sacrificed after the 24-hour observation period. At the time of sacrifice, one female rabbit showed no clinical signs of Endothall Technical toxicity, while the other female had decreased activity and an abnormal gait and stance

(Table 4). At necropsy, one female rabbit had ascites while the other had pale kidneys (Table 5).

Based on the results of this study, the author concluded that Endothall Technical was an eye irritant that was systemically toxic when instilled into the eyes of rabbits.

D. REVIEWER'S COMMENTS

This study was terminated 24 hours after eye instillation because of the severe ocular and systemic toxicity of Endothall Technical. The two surviving rabbits were euthanatized. All rabbits used in the study developed severe chemosis within one hour of treatment and 4/6 rabbits died within 24 hours of Endothall Technical instillation. While no data was located concerning the irritancy scores of the contralateral control eye in this study, because of the severe toxicity and irritancy of Endothall Technical to the eyes of rabbits in this study, the information may be irrelevant. The description of the methods used for the preliminary screen of the rabbit's eye is not sufficiently detailed to evaluate its usefulness. Based on the results of this study, Endothall Technical is an eye irritant that is systemically toxic following instillation into the eyes of rabbits.

E. COMPLIANCE

A signed and dated Quality Assurance Unit Statement was provided.
A signed and dated Good Laboratory Practice (GLP) statement was provided.

F. CORE CLASSIFICATION

Guideline. This study meets the data requirement [81-4] for a primary eye irritation study in rabbits and is acceptable for regulatory purposes.

TABLE 1A. SCALE FOR SCORING OCULAR LESIONS[a]

Cornea	Score
(A) *Opacity - Degree of density (area most dense taken for reading)*	
No opacity	0
Scattered or diffuse areas, details of iris clearly visible	1[b]
Easily discernible translucent areas, details of iris slightly obscured	2
Opalescent areas, no details of iris visible, size of pupil barely discernible	3
Opaque, iris invisible	4
IRIS	
(A) Values	
Normal	0
Folds above normal; congestion, swelling, circumcorneal injection (any or all of these or combination of any thereof) iris is still reacting to light (sluggish reactions are positive)	1[b]
No reaction to light, hemorrhage, gross destruction (any or all of these)	2
CONJUNCTIVAE	
(A) Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)	
Blood vessels normal	0
Blood vessels definitely injected above normal	1[b]
More diffuse, deeper crimson red, individual vessels not easily discernible	2
Diffuse beefy red	3
(B) Chemosis	
No swelling	0
Any swelling above normal (includes nictitating membrane)	1
Obvious swelling with partial eversion of lids	2[b]
Swelling with lids about half closed	3
Swelling with lids about half closed to completely closed	4

[a]Illustrated Guide for Grading Eye Irritation Caused by Hazardous Substances. Directorate for Engineering and Science, U.S. Consumer Product Safety Commission, Washington, D.C.
[b]Lowest grade considered positive under the Federal Hazardous Substance Act Regulations at 16 CFR 1500.42.

TABLE 1B. TOXICITY CATEGORIES FOR EYE IRRITATION[c]

Evaluation Criteria	Irritation Rating
Corrosive (irreversible destruction of ocular tissue) or corneal involvement or irritation persisting for more than 21 days	I
Corneal involvement or irritation clearing in 8-21 days	II
Corneal involvement or irritation clearing in 7 days or less	III
Minimal effects clearing in less than 24 hours	IV

[c]Addendum 2 of Pesticides Assessment Guidelines - Eye Irritation (U.S.) Environmental Protection Agency, Washington, D.C., January, 1988.

TABLE 2. PRIMARY EYE IRRITATION OCULAR SCORES FOR ENDOTHALL TECHNICAL[a]

Rabbit Number/Sex	Endothall Technical Instilled (mg)	Primary Eye Irritation Scores					
		Cornea		Iris		Conjunctivae (A/B)	
		1 Hour	24 Hour	1 Hour	24 Hour	1 Hour	24 Hour
4070/M	101	2	d	2	d	3/3	d
4071/M	103	2	d	2	d	3/4	d
4072/M	100	2	d	2	d	3/4	d
4073/F	101	2	d	2	d	3/4	d
4074/F	103	2	a	2	a	3/4	3/4[b]
4075/F	101	2	a	2	a	3/4	3/4[b]

[a]*Pharmakon Research International, Inc., (1991). Primary Eye Irritation with Endothall Technical, Study Number PH 421-ANA-002-91, page 16.*
Cornea = Degree of opacity
Iris = Degree of iritis
Conjunctivae = A - redness/B - chemosis
a = Scoring prohibited due to excessive chemosis
b = Animal sacrificed at sponsor's request following 24 hour observation period
d = Animal died during study

TABLE 3. INCIDENCE OF PRIMARY EYE IRRITATION POSITIVE SCORES FOR ENDOTHALL TECHNICAL[a]

	Hours Postinstillation	
	1	24[b]
Corneal Opacity	6/6	NS
Iritis	6/6	NS
Conjunctivae		
Redness	6/6	2/2
Chemosis	6/6	2/2

[a]Pharmakon Research International, Inc., (1991). Primary Eye Irritation with Endothall Technical, Study Number PH 421-ANA-002-91, page 17.
[b]N = 2 because four animals died during study
NS = Not scored because of excessive chemosis

TABLE 4. SUMMARY OF ENDOTHALL TECHNICAL CLINICAL OBSERVATIONS[a]

Clinical Signs	Sex	Hours Postinstillation	
		5[b]	24[c]
No signs	M	0	-
	F	0	1
Decreased Activity	M	2	-
	F	2	1
Abnormal Gait	M	2	-
	F	2	1
Abnormal Stance	M	2	-
	F	2	1
Dyspnea	M	2	-
	F	2	0
Prostration	M	1	-
	F	1	0
Red Discharge in Cage Pan	M	1	-
	F	1	-

[a]Pharmakon Research International, Inc., (1991). Primary Eye Irritation with Endothall Technical, Study Number PH 421-ANA-002-91, page 18.
[b]All rabbits alive (3 males and 3 females)
[c]The remaining two rabbits were sacrificed following the 24 hour observation period at the sponsors request.
- Denotes all rabbits died during study.

TABLE 5. INCIDENCE OF LESIONS FOUND AT NECROPSY FOLLOWING EYE INSTILLATION OF ENDOTHALL TECHNICAL TO RABBITS[a]

Observation	Interim Death		Terminal Necropsy	
	Male	Female	Male	Female
No Visible Lesions	0/3	0/1	NA	0/2
Ascites	2/3	0/1	NA	1/2
Red Ascites	1/3	1/1	NA	0/2
Red Fluid-filled Bladder	1/3	1/1	NA	0/2
Pale Kidneys	0/3	0/1	NA	1/2
Dark Red Liver	1/3	0/1	NA	0/2

[a]Pharmakon Research International, Inc., (1991). Primary Eye Irritation with Endothall Technical, Study Number PH 421-ANA-002-91, page 19.

NA = Not Applicable

010507

DATA EVALUATION REPORT

Endothall, Technical

Study Type: Acute Dermal Toxicity Study in Rabbits (81-2)

Prepared for:

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Chemical Hazard Evaluation Group
Biomedical and Environmental Information Analysis Section
Health Sciences Research Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831

Primary Reviewer:
H. T. Borges, Ph.D., MT(ASCP)

Signature: H.T. Borges
Date: 8/11/93

Secondary Reviewer:
Robert H. Ross, M.S., Group Leader

Signature: Robert H Ross
Date: 8-11-93

EPA Reviewer: Steven Malish, Ph.D.
Review Section IV, Toxicology Branch/HED

Signature: Steven Malish
Date: 8/17/93

EPA Section Head: Jess Rowland, M.S.
Review Section IV, Toxicology Branch/HED

Signature: Jess Rowland
Date: 8/16/93.

DATA EVALUATION REPORT

STUDY TYPE: Acute Dermal Toxicity Study in Rabbits (81-2)

EPA IDENTIFICATION NUMBERS:

Tox. Chem. Number: 421
MRID Number: 422892-02

TEST MATERIAL: Endothall, Technical

SYNONYMS: None known or reported

SPONSOR: Atochem North America, Three Parkway, Philadelphia, PA

STUDY NUMBER: PH 422-ANA-002-91

TESTING FACILITY: Pharmakon Research International, Inc., Waverly, PA

TITLE OF REPORT: Acute Exposure Dermal Toxicity with Endothall Technical

AUTHOR: Victor T. Mallory, B.S., RLAT

STUDY COMPLETED: 11/19/91

CONCLUSION: The acute rabbit dermal LD_{50} for Endothall Technical was determined to be greater than 2000 mg/kg.

TOXICITY CATEGORY: III

CORE CLASSIFICATION: Guideline. This study satisfies the data requirement [81-2] for an acute dermal toxicity study in rabbits and is acceptable for regulatory purposes.

A. MATERIALS

1. Test Material

Test material: Endothall Technical
Receipt: 1/14/91
Physical description: Off-white crystalline solid
Active Ingredient: Endothall, 81.1%
Inactive Ingredient: Not reported
Lot number: J19A
pH: Not reported
Stability: No apparent change in the physical state of the test article during administration

2. Controls

Materials: Not needed
Animals: Not needed

3. Test Animals

Species: Rabbits
Strain: New Zealand White
Source: CAMM Research Lab Animals, Wayne, NJ
Receipt Date: 6/27/91
Sex: Male and female
Numbers: 5 males and 5 females
Housing: Rabbits were housed individually in cages, acclimated for a minimum of five days, and adjusted to a 12-hour light/dark cycle. The room temperature was controlled at 20°C ± 3°C with a relative humidity of 50% ± 20%.
Age: Adult
Weight: 2.1-2.6 kg
Feeding: Purina Rabbit Chow H.F.® and fresh tap water provided ad libitum.
Assignment: Animals randomly assigned to groups based on sex, body weight, and general health.
Location of raw data: All raw data is recorded and retained by Pharmakon Research International, Inc. in laboratory notebook #1497, pages 170-172.

4. Exposure

Route of administration: Dermal
Dose level: 2000 mg/kg

B. TEST PERFORMANCE

Depilation was done 24 hours prior to the test by shaving an area greater than 10% of the total body surface area on the dorsal trunk. Care was taken not to abraid the skin. Endothall Technical, 2000 mg/kg, was moistened with 1 ml/g saline and held in contact with the skin with a porous gauze dressing and nonirritating tape for 24 hours. The test site was further covered (method not described) to ensure that the rabbits could not ingest the test substance. After 24 hours of exposure, the wrappings were removed and residual Endothall Technical removed with water and gauze. The rabbits were observed for Endothall Technical toxicity and the data recorded throughout the 14-day observation period. The body weights of the rabbits were recorded on day 0, 7, and 14. The mean and standard deviation of body weights were calculated using Systat by Systat, Inc., Version 4.1. All rabbits were sacrificed (method not described) on day 14, necropsy done, and the results recorded.

C. RESULTS AND STUDY AUTHOR'S CONCLUSIONS

Diarrhea was observed in one female rabbit on days 7-10. No other clinical signs of Endothall Technical toxicity were observed during the study period. Necrosis of the skin at the application site was observed in all rabbits throughout the entire study period. A decrease in the mean body weight of male and female rabbits relative to the body weight recorded on day 0 was observed (Table 1). By day 14, however, the mean body weight had increased to greater than prestudy values. No deaths occurred during the study period nor were lesions observed in any rabbits at necropsy.

D. REVIEWER'S COMMENTS

Based on the results of this acute dermal toxicity study of Endothall Technical, the author has correctly interpreted the data. The dermal LD_{50} of Endothall Technical in male and female rabbits is greater than 2000 mg/kg, corresponding to Toxicity Category III.

E. COMPLIANCE

A signed and dated Quality Assurance Unit Statement was provided.
A signed and dated Good Laboratory Practice (GLP) statement was provided.

F. CORE CLASSIFICATION

Guideline. This study satisfies the data requirement [81-2] for an acute dermal toxicity study in rabbits and is acceptable for regulatory purposes.

TABLE 1. BODY WEIGHTS (g) OF RABBITS FOLLOWING ACUTE DERMAL EXPOSURE TO 2000 mg/kg ENDOTHALL TECHNICAL[a]

Male Rabbit Number	Initial	Day 7	Day 14	Female Rabbit Number	Initial	Day 7	Day 14
4161	2316	2198	2192	4166	2345	2157	2535
4162	2433	2311	2535	4167	2076	1932	2144
4163	2505	2568	2648	4168	2172	2094	2298
4164	2282	2217	2478	4169	2280	2137	2460
4165	2637	2706	2854	4170	2320	2142	2537
Mean	2434.6	2400.0	2541.4		2238.6	2092.4	2394.8
S.D.	144.29	225.87	242.5		112.40	92.67	170.59

[a]Pharmakon Research International, Inc., (1991). Acute Exposure Dermal Toxicity with Endothall Technical, Study Number PH 422-ANA-002-91, page 16.

DATA EVALUATION REPORT

Endothall, Technical

Study Type: Acute Oral Toxicity Study in Rats (81-1)

Prepared for:

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Chemical Hazard Evaluation Group
Biomedical and Environmental Information Analysis Section
Health Sciences Research Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831

Primary Reviewer:
H. T. Borges, Ph.D., MT(ASCP)

Signature: H.T. Borges
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Secondary Reviewer:
Robert H. Ross, M.S., Group Leader

Signature: Robert H Ross
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EPA Reviewer: Steven Malish, Ph.D.
Review Section IV, Toxicology Branch/HED

Signature: Steven Malish
Date: 8/19/93

EPA Section Head: Jess Rowland, M.S.
Review Section IV, Toxicology Branch/HED

Signature: Jess Rowland
Date: 8/16/93.

DATA EVALUATION REPORT

STUDY TYPE: Acute Oral Toxicity Study in Rats (81-1)

EPA IDENTIFICATION NUMBERS:

Tox. Chem. Number: 421
MRID Number: 422892-01

TEST MATERIAL: Endothall, Technical

SYNONYMS: None known or reported

SPONSOR: Atochem North America, Three Parkway, Philadelphia, PA

STUDY NUMBER: PH 402-ANA-002-91

TESTING FACILITY: Pharmakon Research International, Inc., Waverly, PA

TITLE OF REPORT: Acute Exposure Oral Toxicity in Rats with Endothall Technical

AUTHOR: Victor T. Mallory, B.S., RLAT

STUDY COMPLETED: 11/20/91

CONCLUSIONS: The acute oral LD_{50} using male and female rats was determined to be 45.4 mg/kg. For male rats, the LD_{50} was 50.2 mg/kg, while in female rats the LD_{50} was 44.4 mg/kg. Necropsy of animals that died during the study showed fluid-filled and/or distended intestines and stomachs and pale kidneys. Terminal necropsy showed mottled kidneys in some instances.

TOXICITY CATEGORY: I

CORE CLASSIFICATION: Guideline. This study satisfies the data requirement [81-1] for an acute oral toxicity study in rats and is acceptable for regulatory purposes.

A. MATERIALS

1. Test Material

Test material: Endothall Technical
Receipt: 1/14/91
Physical description: Off-white crystalline solid
Active Ingredient: Endothall (81.1%)
Inactive Ingredient: Not reported
Lot number: J19A
pH: Not reported
Stability: No apparent change in the physical state of the test article during administration

2. Controls

Materials: Not needed
Animals: Not needed

3. Test Animals

Species: Rats
Strain: Sprague-Dawley
Source: Charles River Laboratories, Inc., Wilmington, MA
Receipt Date: 6/6/91 - Dose-range-finding Study One; 8/1/91 - Dose-range-finding Study Two; 8/18/91 - Definitive LD_{50} Study
Sex: Male and female
Numbers: Dose-range-finding Study One - 3 male, 3 female; Dose-range-finding Study Two - 2 male, 2 female; Definitive LD_{50} Study - 25 male, 25 female
Housing: Rats were housed individually in stainless steel cages, acclimated for a minimum of five days, and adjusted to a 12-hour light/dark cycle. Attempts were made to control the room temperature at 22°C ± 3°C with a relative humidity of 50% ± 20%. During the study, however, the temperature reached 26.6°C on one day and the relative humidity was 72-78% on 14 days. According to the author of the study, these excursions from the specified temperature and relative humidity ranges did not adversely effect the validity of the study.
Age: Young adult
Weight: Dose-range-finding Study One: 191 - 382 grams; Dose-range-finding Study Two: 200 - 341 grams; Definitive LD_{50} Study: 170 - 238 grams; The weight variation of rats used in both studies did not exceed ± 20% of the mean weight for each sex.
Feeding: Ad libitum Certified Purina Rodent Chow® and Wayne Teklad Lab Blox®. Fresh tap water provided ad libitum.
Assignment: Animals randomly assigned to groups based on sex, body weight, and general health.
Location of raw data: All raw data is recorded in laboratory notebook #1497; pages 239-240, 242-243, and 245-256, retained by Pharmakon Research International, Inc.

4. Exposure

Route of administration: Gavage
Dose level: Dose-range-finding Study One: 500, 2500, and 5000 mg/kg Endothall Technical in deionized water.
Dose-range-finding Study Two: 50 and 200 mg/kg Endothall Technical in deionized water.
Definitive Study: 2, 8, 25, 40, and 60 mg/kg Endothall Technical in deionized water.

B. TEST PERFORMANCE

Dose-range-finding Study. In Dose-range-finding Study One, three groups of rats, each composed of one male and one female, were fasted overnight prior to receiving a single oral gavage dose of Endothall Technical suspended in deionized water at concentrations of 500, 2500, or 5000 mg/kg body weight. In Dose-range-finding Study Two, two groups of rats, each composed of one male and one female, were fasted overnight prior to receiving a single oral gavage dose of Endothall Technical suspended in deionized water at concentrations of 50 or 200 mg/kg body weight. The rats were observed at approximately 1, 4, and 24 hours after dosing for pharmacological and toxicological effects and these observations recorded. The body weight of each rat was recorded at the start of the study and at the time of death.

Definitive Study. Five groups, each composed of five male and five female rats, were fasted overnight prior to receiving a single oral gavage dose of Endothall Technical suspended in deionized water at concentrations of 2, 8, 25, 40, or 60 mg/kg body weight. The rats were observed at approximately 1, 4, and 24 hours after dosing and once daily thereafter for pharmacological and toxicological effects during the 14-day study. Viability of the rats was checked daily. The body weight of each rat was measured and recorded on days 0, 7, and 14 or when found dead. All surviving rats were asphyxiated by CO_2 on day 14 of the study and necropsies done.

C. RESULTS AND STUDY AUTHOR'S CONCLUSIONS

Dose-range-finding Study. All rats in all treatment groups showed signs of Endothall Technical toxicity that consisted of decreased activity, diarrhea, abnormal stance, abnormal gait, piloerection and dyspnea. Male and female rats treated with 2500 or 5000 mg/kg Endothall Technical by gavage were dead within one hour. The male and female rat treated with 500 mg/kg Endothall Technical and a male rat treated with 200 mg/kg Endothall Technical died prior to the 4-hour observation period. The remaining female rat, treated with 200 mg/kg Endothall Technical, and the male and female rat treated with 50 mg/kg Endothall Technical died prior to the 24-hour observation period.

Definitive Study. The effects of Endothall Technical treatment on rats are summarized in Tables 1 - 3. No clinical signs of toxicity or deaths were recorded in groups of male and female rats that received either 2 or 8 mg/kg Endothall Technical by gavage. No grossly observable lesions were found at terminal necropsy.

Decreased activity and diarrhea for up to 24 hours post-treatment were observed in male and female rats that received 25 mg/kg Endothall Technical. After 24 hours, clinical signs of toxicity

were not observed. No rats in this treatment group died prior to the end of the study and grossly observable lesions were not found at terminal necropsy.

Male and female rats treated with either 40 or 60 mg/kg Endothall Technical by gavage had the following clinical signs of toxicity: decreased activity, diarrhea, abnormal gait, abnormal stance and dyspnea. Four of ten rats (2/5 males, 2/5 females) treated with 40 mg/kg Endothall Technical died within 2 days of the start of the study. The remaining rats (3 males and 3 females) in this treatment group survived until the termination of the study. Of the rats in the 40 mg/kg treatment group that died prior to the end of the study, 2/2 male and 2/2 female had fluid-filled stomachs and 1/2 males and 1/2 females had distended intestines. Except for one male rat that had mottled kidneys, the remaining male and female rats treated with 40 mg/kg Endothall Technical that survived the 14-day study period had no grossly observable lesions at necropsy.

Eight of ten rats (3/5 males, 5/5 females) treated with 60 mg/kg Endothall Technical died within 1 day of treatment. The remaining two male rats survived the 14-day study period. All rats treated with 60 mg/kg Endothall Technical that died prior to the end of the study (3/5 males, 5/5 females) had fluid-filled stomachs. In addition, 1/3 male rats and 1/5 female rats had distended intestines, 1/5 female rats had fluid-filled intestines, and 1/5 female rats had pale kidneys. Of the two male rats that survived the duration of the study, one had no visible lesions while the other had mottled kidneys at necropsy. All surviving rats gained weight during the study.

Statistical analysis of the study results was by the method of Litchfield and Wilcoxon via the Pharmacologic Calculation System, version 4.1. Based on the study results, the author concluded that the acute oral LD_{50} of Endothall Technical in male and female rats was 45.4 mg/kg with a 95% confidence limit of 37.7-54.6 mg/kg. The acute oral LD_{50} in male rats was 50.2 mg/kg with a 95% confidence interval of 33.1-76.3 mg/kg. The acute oral LD_{50} in female rats was 44.4 mg/kg with 95% confidence interval of 34.0-58.1 mg/kg.

D. REVIEWER'S COMMENTS

Based on the results of this acute oral toxicity study on Endothall Technical, the author has correctly interpreted the data. The oral LD_{50} of Endothall Technical in male and female rats is 45.4 mg/kg, corresponding to Toxicity Category I. Based on EPA guidelines, the acute oral LD_{50} of Endothall Technical was determined using a protocol that exceeded specified requirements.

E. COMPLIANCE

A signed and dated Quality Assurance Unit Statement was provided.
A signed and dated Good Laboratory Practice (GLP) statement was provided.

F. CORE CLASSIFICATION

Guideline. This study satisfies the data requirement [81-1] for an acute oral toxicity study in rats and is acceptable for regulatory purposes.

TABLE 1. SUMMARY OF CLINICAL OBSERVATION INCIDENCE FOLLOWING ACUTE ORAL EXPOSURE TO ENDOTHALL TECHNICAL[a]

Treatment Group	Clinical Signs	Hours			Day				
		1	4	24	2	3	4	7	14
2 or 8 mg/kg	No Signs	5M, 5F	5M,5F	5M, 5F	5M, 5F	5M, 5F	5M, 5F	5M, 5F	5M, 5F
25 mg/kg	No Signs	3M, 3F	3M, 2F	3M, 3F	5M, 5F	5M, 5F	5M, 5F	5M, 5F	5M, 5F
	Decreased Activity	2M, 2F	2M, 2F	2M, 2F	0M, 0F	0M, 0F	0M, 0F	0M, 0F	0M, 0F
	Diarrhea	0M, 0F	0M, 1F	0M, 0F	0M, 0F	0M, 0F	0M, 0F	0M, 0F	0M, 0F
40 mg/kg	No Signs	3M, 3F	1M, 3F	0M, 0F	0M, 0F	3M, 3F	3M, 3F	3M, 3F	3M, 3F
	Decreased Activity	2M, 2F	4M. 2F	3M, 4F	3M, 3F	0M, 0F	0M, 0F	0M, 0F	0M, 0F
	Diarrhea	0M, 0F	4M. 2F	0M, 0F	0M, 0F	0M, 0F	0M, 0F	0M, 0F	0M, 0F
	Abnormal Gait	0M, 0F	2M, 0F	3M, 2F	3M, 1F	0M, 0F	0M, 0F	0M, 0F	0M, 0F
	Abnormal Stance	0M, 0F	2M, 0F	3M, 2F	3M, 1F	0M, 0F	0M, 0F	0M, 0F	0M, 0F
	Dyspnea	0M, 0F	0M, 0F	3M, 2F	3M, 1F	0M, 0F	0M, 0F	0M, 0F	0M, 0F
60 mg/kg	No Signs	2M, 1F	1M, 1F	0M, -F	0M, -F	2M, -F	2M, -F	2M, -F	2M, -F
	Decreased Activity	3M, 4F	4M, 4F	2M, -F	2M, -F	0M, -F	0M, -F	0M, -F	0M, -F
	Diarrhea	0M, 0F	4M, 4F	0M, -F	0M, -F	0M, -F	0M, -F	0M, -F	0M, -F
	Abnormal Gait	0M, 1F	4M, 4F	2M, -F	2M, -F	0M, -F	0M, -F	0M, -F	0M, -F
	Abnormal Stance	0M, 1F	4M, 4F	2M, -F	2M, -F	0M, -F	0M, -F	0M, -F	0M, -F
	Dyspnea	0M, 0F	0M, 0F	2M, -F	2M, -F	0M, -F	0M, -F	0M, -F	0M, -F

[a]Pharmakon Research International, Inc., (1991). Acute Exposure Oral Toxicity in Rats with Endothall Technical, Study Number PH 402-ANA-002-91, adapted from pages 14 to 19.

- Denotes all animals within treatment group were dead

TABLE 2. SUMMARY OF MORTALITY FOLLOWING ACUTE ORAL EXPOSURE TO ENDOTHALL TECHNICAL[a]

Dose (mg/kg)	Sex	# of Rats	Days															Total Mortality
			0*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
2	M	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5
	F	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5
8	M	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5
	F	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5
25	M	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5
	F	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5
40	M	5	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	2/5
	F	5	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	2/5
60	M	5	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	3/5
	F	5	0	5	-	-	-	-	-	-	-	-	-	-	-	-	-	5/5

[a]Pharmakon Research International, Inc., (1991). Acute Exposure Oral Toxicity in Rats with Endothall Technical, Study Number PH 402-ANA-002-91, page 19.

* Includes 1st and 4th hour observations

- Denotes all animals within group were dead

TABLE 3. SUMMARY OF NECROPSY RESULTS FOLLOWING ORAL TREATMENT WITH *ENDOTHALL TECHNICAL*[a]

Lesion	2, 8, or 25 mg/kg		40 mg/kg				60 mg/kg			
	Death at Term		Interim Death		Death at Term		Interim Death		Death at Term	
	M	F	M	F	M	F	M	F	M	F
No Visible Lesions	5	5	0	0	2	3	0	0	1	-
Fluid-filled Stomach	0	0	2	2	0	0	3	5	0	-
Fluid-filled Intestines	0	0	0	0	0	0	0	1	0	-
Distended Intestines	0	0	1	1	0	0	1	1	0	-
Mottled Kidneys	0	0	0	0	1	0	0	1	0	-
Pale Kidneys	0	0	0	0	0	0	0	0	1	-

[a]Pharmakon Research International, Inc., (1991). Acute Exposure Oral Toxicity in Rats with Endothall Technical, Study Number PH 402-ANA-002-91, adapted from pages 25 to 27.

- Not Applicable

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DATA EVALUATION REPORT

Endothall, Technical

Study Type: Primary Dermal Irritation Study in Rabbits (81-5)

Prepared for:

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Chemical Hazard Evaluation Group
Biomedical and Environmental Information Analysis Section
Health Sciences Research Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831

Primary Reviewer:
H. T. Borges, Ph.D., MT(ASCP)

Signature: H.T. Borges
Date: 8/11/93

Secondary Reviewer:
Robert H. Ross, M.S., Group Leader

Signature: Robert H Ross
Date: 8-11-93

EPA Reviewer: Steven Malish, Ph.D.
Review Section IV, Toxicology Branch/HED

Signature: Steven Malish
Date: 8/17/93

EPA Section Head: Jess Rowland, M.S.
Review Section IV, Toxicology Branch/HED

Signature: Jess Rowland
Date: 9/16/93

DATA EVALUATION REPORT

STUDY TYPE: Primary Dermal Irritation Study in Rabbits (81-5)

EPA IDENTIFICATION NUMBERS:

Tox. Chem. Number: 421
MRID Number: 422892-04

TEST MATERIAL: Endothall, Technical

SYNONYMS: None known or reported

SPONSOR: Atochem North America, Three Parkway, Philadelphia, PA

STUDY NUMBER: PH 420-ANA-002-91

TESTING FACILITY: Pharmakon Research International, Inc., Waverly, PA

TITLE OF REPORT: Primary Dermal Irritation Study with Endothall Technical

AUTHOR: Victor T. Mallory, B.S., RLAT

STUDY COMPLETED: 1/14/92

CONCLUSION: Endothall Technical was found not to be a dermal irritant (Primary Irritation Index = 0.00) to the skin or rabbits.

TOXICITY CATEGORY: IV

CORE CLASSIFICATION: Guideline. This study satisfies the data requirement [81-5] for a primary dermal irritation study in rabbits and is acceptable for regulatory purposes.

A. MATERIALS

1. Test Material

Test material: Endothall Technical
Receipt: 1/14/91
Physical description: Off-white crystalline solid
Active Ingredient: Endothall, 81.1%
Inactive Ingredient: Not reported
Lot number: J19A
pH: Not reported
Stability: No apparent change in the physical state of the test article during administration

2. Controls

Materials: Not needed
Animals: Not needed

3. Test Animals

Species: Rabbits
Strain: New Zealand White
Source: CAMM Research Lab Animals, Wayne, NJ
Receipt Date: 6/27/91
Sex: Female
Numbers: Six
Housing: Rabbits were housed individually in cages, acclimated for a minimum of five days, and adjusted to a 12-hour light/dark cycle. The room temperature was controlled at 20°C ± 3°C with a relative humidity of 50% ± 20%.
Age: Adult
Weight: 2.2-2.9 kg
Feeding: Purina Lab Rabbit Chow® (H.F.) and fresh tap water provided ad libitum.
Assignment: Animals randomly assigned to groups based on sex, body weight, and general health.
Location of raw data: All raw data is recorded and retained by Pharmakon Research International, Inc. in laboratory notebook #1503, pages 2-3.

4. Exposure

Route of administration: Dermal
Dose level: 500 mg/animal

B. TEST PERFORMANCE

Depilation was done 24 hours prior to the test by shaving an area greater than 10% of the total body surface on the dorsal trunk free of fur. Care was taken not to abraid the skin. Endothall Technical, 500 mg, was applied to the shaved area of skin and moistened with approximately 500 µl saline. The test chemical was held in place by covering the site with a

porous 2" × 2" gauze dressing which in turn was covered with a dental dam. The dam was held in place by an elastic bandage and the entire application area secured with non-irritating tape. Four hours later, the wrappings were removed and the skin wiped with gauze moistened with water to remove excess chemical. The animals were scored for erythema and edema 30 - 60 minutes and 24, 48, and 72 hours following patch removal by the protocol shown in Table 1.

Dermal Irritation Scores were calculated and Endothall Technical categorized according to Addendum 3 of Pesticide Assessment Guidelines - Dermal Irritation (U.S.) Environmental Protection Agency, Washington, D.C., January, 1988.

C. RESULTS AND STUDY AUTHOR'S CONCLUSIONS

None of the rabbits had visible signs of erythema or edema at any time during the 72 hour observation period. All rabbits gained weight during the study.

D. REVIEWER'S COMMENTS

Since erythema or edema were not observed at any point, under the conditions of the study the author has correctly interpreted the results. The Primary Irritation Index for Endothall Technical is 0.00 which corresponds to Toxicity Category IV. Endothall Technical should be considered a nonirritant when applied to the skin of rabbits.

E. COMPLIANCE

A signed and dated Quality Assurance Unit Statement was provided.
A signed and dated Good Laboratory Practice (GLP) statement was provided.

F. CORE CLASSIFICATION

Guideline. This study satisfies the data requirement [81-5] for a primary dermal irritation study in rabbits and is acceptable for regulatory purposes.

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TABLE 1. DRAIZE[a] SCORING FOR DERMAL IRRITATION

Erythema and Eschar Formation (Most severely affected area graded):

No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4

Edema Formation (Most severely affected area graded):

No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well-defined by definite raising)	2
Moderate edema (raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond area of exposure)	4

[a]Draize, J.H. 1959. The Appraisal of Chemicals in Foods, Drugs and Cosmetics, Association of Food and Drug Officials of the United States, Austin, Texas, pp. 36-45.

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031103

Chemical:	**Endothall**
PC Code:	**038901**
HED File Code	**13000 Tox Reviews**
Memo Date:	**08/20/93**
File ID:	~~**DPD178232**~~ 010507
Accession Number:	**412-02-0010**

HED Records Reference Center
01/16/2002