BO-694

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY 000668

DATE: October 25, 1978

SUBJECT: Request for permanent tolerances for endothall. EPA Registration#4581-204 Caswell#[redacted]

FROM: William Dykstra, Ph.D
TOX/HED TS-769 10/25/78 WHD

TO: Henry M. Jacoby
Product Manager#25

Pesticide Petition No. 1F1105

Food Additive Petition: 2H5016

Petitioner: Pennwalt Corporation

Request by Petitioner:

(A) Permanent tolerances of 3.0 ppm in potable water (FAP 2H5016)
0.1 ppm in or on fish
0.1 ppm in or on sugar beets
3.0 ppm in or on forage grasses and forage legumes
0.5 ppm in or on leafy vegetables
0.10 ppm in or on citrus, curcurbits fruiting vegetables, small grain, pome fruits, root crop vegetables, seed and pod vegetables, small fruits and stone fruits.
0.02 ppm in meat, milk poultry and eggs

(B) Up-date label with respect to directions for use, restrictions, and new EPA label formats.

Chemistry Residue Considerations: The memo of Robert J. Hummel (6/26/75) concludes that the metabolism of endothall in animals is not adequately defined. Therefore, toxicological considerations relating to potential hazards of unknown residues in mean and milk must be reserved until new metabolism studies are reviewed by Chemistry Branch.

Recommendations:

(1) Recommend against establishment of permanent tolerances at this time. Further toxicological testing is needed. The Teratogenic study is regarded as inadequate to support tolerance. The Mutagenic studies submitted are acceptable, but further mutagenic testing is required, including Ames test with and without metabolic activiation. Final report of 18 month oncogenicity study of disodium endothall in mice is required for permanent tolerances. The ADI is based on a two year rat feeding study conducted by IBT (6/3/75) and this study is required to be validated before permanent tolerances can be established.

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EPA FORM 1320-6 (REV. 3-76)

2. Some studies are by IBT and need to be validated.

3. Label amendments are acceptable with respect to EPA, directions for use and restrictions. Crop grouping: The aforelisted crop groupings are defined in the 40 CFR 180.34 as follows:

Group	Commodities therein
Citrus fruits	Citrus citron, grapefruit, kumquats, lemons, limes, oranges, tangelos, tangerines, and hybrids of these.
Cucurbits	Cantaloups, casabas, crenshaws, cucumbers, honey balls, honeydew melons, melon hybrids, muskmelons, Persian melons, pumpkins, summer squash, watermelons and their hybrids, winter squash.
Forage Grasses	Any grasses (either green or cured) that will be fed to or grazed by livestock, all pasture and range grasses, all grasses grown for hay or silage, small grains grown for hay, grazing, or silage.
Forage Legumes	Any crop belonging to the family Leguminosae that is grown for forage (hay, grazing, silage, etc.), alfalfa, beans (for forage), clovers, cowpeas (for forage), peanut hay, peas (for forage), pea vine hay, trefoil, velvet beans (for forage), vetch soybeans (for forage), soybean hay.
Fruiting Vegetables	Egg plants, peppers, pimentos, tomatoes.
Grain Crops	Any crop belonging to the family Graminae that produces mature seed that are used for food or feed narley, buckwheat, corn (field corn, sweer corn, and popcorn), milo, oats, rice, rye, sorghums (grain), wheat.
Leafy Vegetables	Anise (fresh leaf and stock omly), beet greens (tops), broccoli, broccli raab, brussels sprouts, cabbage, cauliflower, celery, Chinese cabbage, collards, dandelion, endive, escarole, fennel, kale, kohlrabi, lettuce, mustard greens, parsley, rhubarb, salsify tops, spinach, sugar beet tops, Swiss chard, turnip green (tops), watercress.
Pome Fruits	Apples, crabapples, pears, quinces.

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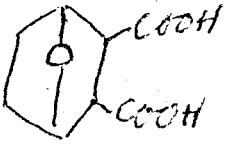
Root Crop Vegetables	-	Beets, carrots, chicory, garlic, green onions, horseradish, Jerusalem artichokes, leeks, onions, parsnips, potatoes, radishes, rutabagas, salsify, shallots, spring onions, sugar beets, sweet potatoes, turnips, yams.
Seed and Pod Vegetables	-	Black-eyed peas, cowpeas, dill, edible, soybeans, field beans, field peas, garden peas, green beans, kidney beans, lima beans, navy beans, okra, peas, pole beans, snap beans, string beans, wax beans, other beans and peas (except dried beans and peas).
Small Fruits	-	Blackberries, blueberries, boysenberries, cranberries, currants, dewberries, elderberries, gooseberries, grapes, huckleberries, loganberries, raspberries.
Stone Fruit	-	Apricots, cherries (sour and sweet), damson, nectarines, pawpaws, peaches, plums, prunes.

Related Petitions: 6G0503, 7F0570, 7G068, 2H5016, 0F0972, 1F1057, 1F1105, 3F1416, 4G1449, 4G1510.

Existing Tolerances: § 180.293, 0.1 ppm in or on cottonseed and potatoes.

A. Substance Identification

1. Chemical Structure:



2. Synonyms: Aquathol, Aquathol K, Aquathol granular, Hydrothol 191 liquid, Hydrothol 191 granular, Hydrothol 47, Hydout, Des-I-Cate/Accelerate Herbicide 282, Herbicide 283.

3. Chemical Name: Endothall (7-oxabicycyclo [2.2.1] heptane-2,3-dicarboxylic acid)

B. Background Information:

1. Pesticide Petition No. 6G0503 was originally submitted in support of a request for the stablishment of a temporary tolerance of 0.1 ppm in raw cottonseed. Toxicity data supported the temporary tolerance request but not a permanent tolerance, since a more complete chronic rat study was needed (see momo of GEWhitmore, 7-14-66).

Residues chemists (see memo of R.S. Quick 8-19-66) indicated that questions regarding metabolism, distribution of residues in the hulls, detection of Endothall with existing methods of analysis and the possibility of transfer over into milk and meat through animal feeding had to be resolved before granting a tolerance.

2. Pesticide Petition No. 7F0570 consituted a "Substantive Amendment" to petition#6G0503 and consisted of additional data in support of a reduced tolerance of 0.01 ppm in cottonseed. The request was withdrawn, however, because of analytical problems.

3. Pesticide Petition No. 7G0608 requested a temporary tolerance of 0.01 ppm in or on potatoes; this was refused on the grounds of inadequate residue data.

4. Pesticide Petition No. 0F0972 sought, and ulitmately was granted, a negligible residue tolerance in cottonseed of 0.1 ppm; residues, toxicity and chemical data were considered to be adequate for that purpose.

5. Pesticide Petition No. 1F1057 sought a tolerance of 0.2 ppm on potatoes. TB and CB recommended a tolerance of 0.1 ppm to be safe (DL Ritter 9-1-71).

6. Pesticide Petition No. 1F1105 sought a tolerance of 0.2 ppm in or sugar beets (roots and tops) and in water. TB deferred to CB on the sugar beet roots and tops because they are not human food. An interim tolerance of 0.2 ppm was established for potable water on April 17, 1973 in.21 CFR 121.1248 (time was extended until 1/4/75).

7. Pesticide Petition No. 3F1416 applied for a tolerance of 0.05 ppm in or on rice. TB found the use on rice to be safe.

8. Pesticide Petition No. 4G1449 requested a tolerance of 0.05 ppm in or on rice and 0.1 ppm on rice straw. TB had no objections.

9. Pesticide Petition No. 4G1510 requested a tolerance of 0.2 ppm in or on sugarcane. TB had no objections (Ritter 7/8/74). The temporary tolerance was established October 4, 1974 for a period of one year.

C. Formulation: Designation	% and Form of Active Ingredient	% Acid Equivalent	Registration No.	Use
Endothall* Technical		75-86	4581-257	
AQUATHOL(R) Aquatic Herbicide (Liquid)	19.2% disodium endothall	15.5	4581-139	Aquatic Herbicide
Endothall Turf Herbicide (Liquid)	19.2 disodium endothall	15.5	4581-79	Turf Herbicide

Designation	% and Form of Active Ingredient	% Acid Equivalent	Registration No.	Use
Endothall Weed Killer (Liquid)	19.2% disodium endothall	15.5	4581-79	Sugar Beet Herbicide
AQUATHOL "G" (Granular)	5.0% disodium endothall	3.6	4581-138	Aquatic Herbicide
Endothall Harvest Aid (Liquid)	6.3% disodium endothall	5.1	4581-147	Disccant
AQUATHOL "K" (Liquid)	40.3% dipotassium endothall	28.6	4581-204	Aquatic Herbicide
Herbicide 273 (Liquid)	40.3% dipotassium emdothall	28.6	4581-223	Sugar Beet Herbicide
AQUATHOL Granular	10.1% dipotassium endothall	7.2	4581-201	Aquatic Herbicide
HYDROTHOL(R) 191 Aquatic Algicide & Herbicide (Liquid) (TD-191, HY-191)	53.0% mono (N,N-dimethylalkylamine*) salt of endothall	23.36	4581-174	Aquatic Herbicide
ACCELERATE(R) Cotton Harvest Aid (Liquid)	15.9% mono(N,N-dimethylalkylamine) salt of endothall	5.5	4581-284	Harvest
DES-I-CATE(R) Harvest Aid (Liquid)	15.9% mono (N,N-dimethylalkylamine) salt of endothall	5.5	4581-206	Desiccant
HYDROTHOL 191 Granular	11.2% mono (N,N-dimethylalkylamine) salt of endothall	5.0	4581-172	Aquatic Herbicide
HYDOUT™** Aquatic Herbicide (Pellet)	22.4% mono(N,N-dimethylalkylamine) salt of endothall	10.0	State Registered	Aquatic Herbicide

*N,N-dimethylalkylamine as derives from coconut oil is referred to in the text as cocoamine.

Designation	% and Form of Active Ingredient	% Acid Equivalent	Registration No.	Use
HYDROTHOL 47 (Liquid) (TD-47, HY-47)	66.7% di (N,N-dimethylalkylamine) salt of endothall	18.8	4581-173	Aquatic Herbicide
HYDROTHOL 47 Granular	17.5% di (N,N-dimethylalkylamine) salt of endothall	5.0	4581-175	Aquatic Herbicide
Herbicide 283 (Liquid)	54.7% mono (N,N-dimethylalkylamine) salt of endothall	23.9	4581-243	Sugar Beet Herbicide
Herbicide 282 (Liquid)	68% di(N,N-dimethyltridecylamine) salt of endothall	19.2	4581-232	Sugar Beet Herbicide

1. This concentration is acheived by easing 4.0-7.5 gallons for an entire pond or large area.

2. Slow Flowing or static water (0.25 mph) 1, 2 and 3 ppm - This concentration is acheived by using 2.5-27.0 gallon depending on width of ditch or canal. Uses of endothall alone.

3. Invert Spray System.

4. Rate per Surface Area.

(7. Uses Proposed)
A. Weedy Controlled
a. Susceptible weeds. (continue at bottom)
1.06-2.13 ppm (acid equivalent)

Three to four gallons of Aquathol K plus two to four pounds of a copper ion complex in sufficient water to apply 30 to 50 gallons total spray. Use only copper-containing products which are registered for this use. If retreatment is necessary, wait 10 to 14 days before reapplication.

Review

A. Toxicology Studies

1. Toxicity Data: The following data have been reviewed in connection with prior petitions:

Animal	Route		Results Mg/Kg
Rat (Endo-acid)	PO	LD_{50} 51 (tech)	----------
Rat (Disodium endo)	PO	LD_{50} 38	LD_{50} -198 (15.5% Formulation)
Rat (Di-K Endothall)	PO	LD_{50} 50	LD_{50} - 125 (40.3% Formulation)
Rat (Accelerate)	PO	_____	LD_{50} - 610 (Formulation)

b. Highly susceptible weeds, 0.36-1.42 ppm (acid equivalent)

Animal	Route		Results Mg/Kg
Rat (Hydrothal)	PO	LD_{50} 206	LD_{50} - 309 (Formulation)
Rabbit (Hydrothal)	PO	MLD 24-47	MLD 36-70 (Formulation)
Fish (Di-Na Endothall)	Ambient Conc	MLD 80-680 ppm	----------
Fish (Accelerate)	Ambient Conc	----------	LC_{50} - 9 ppm
Rabbit (Accelerate)	Dermal	LD_{50} - 143	----------
Rabbit (Hydrothal)	Dermal	MLD 47-70	----------
Rat (Di-Na Endothall)	Inhalation	200 mg/M^3 -	no ill effect
Guinea Pig (Di-Na Endothall	Topical	1-10%	Aqueous Sol'n - Irritation no sensitization
Rabbit (Di-Na Endothall)	Topical	Neat -	severe skin irritation 1% aqueous - no irritation
Rabbit (Di-Na Endothall)	Topical eye	1 - 4% Sol'n -	Transient eye irritation
Rabbit (Hydrothal 47)	Topical eye	Undiluted -	severe damage 1% Aqueous minimal transient irritation.

B. Subacute and Chronic Toxicity Data

See memo of GEWhitmore, 7/14/66, Pesticide Peition No. 6G0503.

SUMMARY OF DATA

No-effect level in 16-Week Dog Feeding Study was 103 ppm (highest level tested).

No-effect level in 2-Year Dog Feeding Study was 300 ppm.

No-effect level in 3 Generation Rat Study was 100 ppm.

No-effect level in 2 year rat feeding study was 1000 ppm. but was judged to be inadequate for purposes of establishing a permanent tolerance on the basis of poor survival and small number of rats used.

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Acute Rat Oral LD_{50} (19.2% formulation) - Pharmacology Res. 4/3/72.

The material tested was identified as a 19.2% disodium endothall formulation (EPA No. 4581-139).

The undiluted test material was administered undiluted to five starves males per level in a range of from 125 to 500 mg/kg.

Results: LD_{50} = 210 mg/kg. All deaths occurred 4 to 24 hours after dosage.

Rabbit Eye Irritation (19.2 formulation) - Pharmacology Res. 4/3/72.

The material tested was identified as a 19.2% disodium endothall formulation (EPA No. 4581-139).

One-tenth ml was instilled into one eye of each of three rabbits.

Results: Moderate to severe irritation was reported for the first two days. Normally returned in four to six days. No corneal involvement was reported.

Acute Rat Oral LD_{50} (15.9% formulation) - Pharmacology Res.

The material tested was identified as a 15.9% mono (N,N-dimethylalkylamine) salt of endothall (Accelerate-Des-I-Cate).

The undiluted test material was administered undiluted to five starved males per level in a range of from 320 to 1600 mg/kg.

Results: LD_{50} = 650 mg/kg. No deaths occurred within 24 hours of treatment.

Rabbit Dermal LD_{50} (15.9% formulation) - Pharmacology Res. 10/15/71.

The material tested was identified as a 15.9% mono (N,N-dimethylalkylamine) salt of endothall (Accelerate-Des-I-Cate).

The test material was applied as a 10% w/v dilution in distilled water to each of six rabbits at the level of 250 mg/kg.

Results: LD_{50} is greater than 250 mg/kg.

Acute Rat Oral LD_{50} (54.7% formulation) - Pharmacology Res. 10/15/71.

The material tested was identified as a 54.7% mono (n,N-dimethyltridecylamine) salt of endothall.

An aqueous dilution of the test material was administered to ten male CFN rats at the single level of 50 mg/kg.

Results: LD_{50} is greater than 50 mg/kg. No mortality was reported.

Acute Rabbit Dermal LD_{50} (54.7% formulation) - Pharmacology Res. 10/15/71.

The material tested was identified as 54.7% mono (N,N-dimethyltridecylamine) salt of endothall.

An aqueous dilution of the test material was applied to the trunk of each ten rabbits at the level of 200 mg/kg. Length of contact was 24 hours.

Results: LD_{50} is greater than 200 mg/kg. No mortality was reported.

21-Day Rat Oral - Industrial Bio-Test 7/3/72.

The material tested were identified as dipotassium endothall and disodium endothall.

Groups of fifteen rats were fed either dipotassium endothall, dipotassium endothall as a 10% aqueous solution, or disodium endothall at dietary levels of 2,400 ppm. Observations and tests for effects included body weights, food consumption, mortality and abnormal reactions.

No hematology or histopathological studies were included in this 21 day oral study.

Results: The body weight gains and food consumption of the groups receiving dipotassium endothall were significantly lower than the control value. The disodium endothall test group was unaffected.

A no effect level for this study will not be established because the parameters investigated do not permit comprehensive evaluation of possible effects.

Two Year Rat Feeding - Industrial Bio-Test 6/3/75.

The test materials were identified as dipotassium endothall monhydrate (NB. 58-36) or disodium endothall (NB. 58-63-1). The test material was changed from dipotassium endothall monohydrate to disodium endothall after 20 weeks of testing at the suggestion of our Dr. C. Williams.

Fifty Charles River rats of each sex were used per level of 0, 600, 1,200, and 2,400 ppm. Observations and tests for effects included body weight, food consumption, mortality, abnormal reactions, tumor incidence and the following hematologic and clinical chemistry studies from ten rats of each sex in both the control and 2,400 ppm level after 3, 6, 10 and 24 months:

Total leukocyte count	BUN
RBC	SAP
Hemoglobin Conc.	SGOT
Differential leukocyte count	SGPT
Hematocrit	Urinalysis

Terminal studied included organ weights of the liver, kidneys, heart, spleen, gonads, and brain, and a histopathological exmination of the following tissues from ten rats of each sex from the control and 2400 ppm groups:

Heart	Colon
Trachea	Spleen
Lung	Kidney
Liver	Testis
Prostate	Brain
Pituitary	Eye
Adrenal Gland	Mesentary
Ovary	Uterus
Salivary Gland	Skin
Mammary Gland	Skeletal Muscle

Results: The body weight losses which occurred during the first 20 weeks among both sexes in all treated levels receiving dipotassium endothall monohydrate overshadows the possible effects of disodium endothall. At 12 months the 600 ppm males managed to neutralize their body weight gain inhibition. The body weight gain inhibition among the other test groups (except the 1,200 ppm males) was increased at the 12 month period.

In the priod between 6-12 and 6-24 months the following body weight gains were reported:

Male	6-12 Months	6-24 Months
Control	66	0
600	114	105
1200	95	86
2400	64	39
Female.		
Control	70	89
600	65	83
1200	53	94
2400	28	78

These values do not lend themselves easily to the establishment of a firm no effect level. However, it does appear that the 2400 ppm level animals exhibits a body weight gain inhibition. The corresponding food consumption of the test animals was also lower than the control value.

The other parameters investigated showed normal biological variations.

The no effect level for this study is 1200 ppm. This is the study on which the ADI is based.

Exhibit 181 Report Teratologic Evaluation of Endothall in Rats - Food & Drug Research Laboratories, Inc. - Nov. 11, 1976.

Test Material: Endothall technical; 89.5% acid equivalent; tan granules.

Method: Virgin, adult female albino rats (Wistar derived Stock) were individually housed in mesh botton cages in temperature controlled quarters. Each rat had free access to food and fresh tap water. They were mated with young adult males and detection of the vaginal sperm plug was considered to occur on day 0 of gestation. Beginning on day 6 and continuing daily through day 15 of gestation, each female received the appropriate quantity of Endothall to acheive a final dose of 0, 0.01, 0.15 or 2.00 mg/kg /day. The gavage vehicle was water. Aspirin (250 mg/kg/day) was given to a positive control group. Body weights were recorded on days 0, 6, 11, 15 and 20 of gestation. All animals were observed daily for appearance and behavior with particular attention to food consumption and weight, in order to rule out any abnormalities which may have occurred as a result of anorexic effects.

On day 20 of gestation, each dam was sacrificed by chloroform overdose and subjected to Caesarean section. The uterine contents were examined and the number of implantation sites for each uterine horn were recorded along with the number of live pups, dead pups and resorption sites.

The weight of each pup and the number of corpora lutea were recorded. The urogenital tract was examined for signs of gross abnormality.

One third of the pups in each litter were randomly chosen and fixed in Bouin's examined for soft tissue abnormalities using the Wilson freehand slicing technique. All pups showing any gross abnormality were included in this preparation. The remaining pups were fixed in 70% isopropyl alcohol and arranged in ice cube trays to maintain their identities as to location in the uterus. They were cleared in KOH, stained with Alizarin Red S, and individually stored in glycerin and then subjected to a detailed skeletal examination under low powder magnification. All observations of skeletal abnormalities were recorded. All animals were evaluated according to normally accepted degrees of development for a 20 day old fetus.

Rates of appearance of abnormalities were compared statistically by published methods.

Results: The average body weights of dams during gestation was significantly less in the positive (aspirin) control group than the control (22%) and significantly less in the intermediate and high dosage (endothall) treatment groups (9.5% and 9.7%; respectively) than the lowest treatment group. This weight loss is accepted as evidence of significant maternal toxicity in the treatment (endothall) groups.

Neither aspirin nor endothall at any dose level interfered with pregnancy. Live litters were born to dams in all treatment groups. The endothall did not significantly affect the number of implantation sites, resorptions, or live fetuses per dam as compared to controls. Aspirin, on the other hand, induced a significant number

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of resorptions and dead fetuses, as expected.

Aspirin, the positive control, produced skeletal terata. Endothall did not produce dose related effects on skeletal development except possibly increasing the number of fetuses which developed more than 13 ribs. One of 180, 4/157 and 6/136 fetuses were affected in the low, mid and high endothall groups compared to 1/151 for the controls. In addition, incomplete closure of the skull was observed in 45/180, 23/157 and 13/136 of the low, mid and high endothall groups compared to 7/151 for the controls. The effect is inversely proportional to dose - the lowest level of endothall produced the greatest effect. No treatment related effects of endothall were observed during examination of soft tissue abnormalities of pups.

Conclusion: The occurrence of incomplete closure of the skull in all dose groups was significantly greater than the controls. Although, the inverse dose-effect relationship is difficult to explain, a pharmacological mechanism may exist such as maternal adaptation which could explain this inverse relationship. This explantation, however, is incumbent upon the registrant. It is concluded that endothall is possibly teratogenic in this study and this potential needs to be further explored. It is concluded that this study needs to be repeated and the questions raised have to be addressed.

Classification: Inadequate Study which does not support the registration.

Exhibit 182 Report - Mutagenicity Evaluation of Rat Dominant Lethal Assay - Disodium endothall - final report - Litton Bionetics, Inc. - Jan. 1977.

Test Material: Disodium endothall orange liquid, 15.8% acid ingredient.

Method: Random bred male & female rats were used, strain CRL: COBS CD (SD) Br. Ten random bred male rats, 10 weeks of age, from a closed colony were assigned to one of five groups. Three of these groups received different dose levels of the test compound (150 ppm, 300 ppm and 600 ppm), a fourth group received only the solvent (corn oil) and the fifth group received a known mutagen (triethylene melamine) and served as the positive control group. The test compound and the solvent control were administered in the feed for five consecutive days. Triethylene melamine (TEM) was used as the positive control and was given as a single intraperitioneal injection two days before the animals were mated. Following treatment each male was rested for two days and then caged with two unexposed virgin females. At the end of seven days, these females were replaced with two new unexposed females. This weekly mating sequence was continued for seven weeks. The two mated females were transferred to a new cage, and fourteen days after the midweek of being caged with the male, the females were killed with CO_2, and at necropsy, their uteri were examined for dead and living fetuses resportion sites and total implantations.

Results:

Toxic Signs: No signs of toxicity were seen in any of the treatment groups fed disodium endothall.

Body Weight and Food Consumption:

Body weight and food consumption data do not show any significant difference between treatment groups and controls.

Mutagenesis: Disodium endothall was administered to male rats in their fed for five consecutive days. Analysis of the uteri of unexposed females mated to the treated males did not reveal evidence of either pre - or post-implantation dominant lethality; where, the positive control compound TEM gave a strong dominant lethal during the first weeks. The data collected from these experiments have been evaluated statistically.

Conclusion: Disodium endothall did not induce significant dominant lethality in rats treated with the compound in their feed (up to 600 ppm) for five days, and can be considered non-mutagenic under the criteria of the dominant lethal assay.

Classification: Core-Minimum Data

Exhibit 183 - Report - Rat Bone Marrow Cytogenetic Analysis - Disodium Endothall - Final Report - Litton Laboratories, Inc. - Jan, 1977.

Test Material: Disodium endothall orange liquid, 15.8% acid equivalent.

Method: Five random bred male rats (CRL: CDBS CD (SD) Br strain) from a closed colony were assigned to each of five groups. Three of these groups received different dose level of the test compound (150, 300 and 600 ppm), a fourth group received only the solvent control (corn oil) and the fifth group received a known mutagen (triethylene melamine) and served as the positive control group. The test compound, disodium endothall, and the corn oil solvent were administered in the feed for five consecutive days. The positive control compound TEM was given as a single injection 24 hours before the animals were killed. On the fifth day, all animals were injected intraperitoneally (IP) with 4 mg/kg of colchicine and two hours later were killed with CO_2. The bone marrow was removed from the animals from the femurs and tibias of the lower limbs. Cells were centrifuged, fived in Carnoy's fixative and spread on a slide and stained with 5% giemsa. Slides were coded ans searched for metaphase according to a standardized pattern. Fifty spreads were located for each animal and when of suitable quality, the chromosomes were counted and evaluated for the presence of abnormalities - breaks, gaps, fragments, and chromosome rearrangements. The chromosomal aberrations were evaluated statistically.

Results:

Toxic Signs: No signs of toxicity were observed in treatment groups fed disodium endothall.

Body Weight and Food Consumption: Body Weight and food consumption were not significantly different between the treatment groups fed disodium endothall and the controls.

Mutagenicity: Disodium endothall treated groups do not show significant increases in the number of aberrations per dosage group above that of the negative controls and can be considered non-mutagenic under the conditions of this assay. However, TEN did produce a significant increase in chromosomal aberrations.

Conclusion: Disodium endothall did not induce significant abberrations in the chromosomes of rat bone marrow cells and can be considered non-mutagenic under the conditions of this assay.

Classification: Core-Minimum Data

(a) Further mutagenic testing is required, i.e., point mutation (bacterial Ames Test)

Exhibit 184 - Progress Report - 18 Month Oncogenicity Study of Disodium endothall in Mice - Cannon Laboratories, Inc. - July 28, 1977. 13 Week Progress Report in Mice.

Summary: The potential toxic effects of disodium endothall (15.9% active) in CD, mice is being evaluated. The compound was incorporated into NIH-07 laboratory feed at dose levels of 300, 600 and 1200 ppm. Each group consisted of 50 males and 50 females animals per group. A fourth group, consisting of 50 male and 50 female animals, formed the control group. Potential toxic effects were evaluated in terms of the following parameters: appearance and behavior, body weight, food consumption, ophthalmology and mortality.

Results: No untoward behavioral reactions were detected in this study among any of the groups. No mortality was observed in any of the groups. Body weight values are consistent in each group. Food consumption values are consistent in each group. Ophthalmology examination demonstrated no effects of test material on the transparency of the ocular media or the fundus of the eye as viewed by direct or indirect ophthalmoscope.

Conclusions: At 13 weeks, the no effect level in this experiment appears to be 1200 ppm in the diet.

Classification: Core-Minimum Data

Exhibit 185 Report - A primary dermal irritation study of Des-I-Cate 2/Accelerate on Abraded and non-abraded skin of New Zealand Albino Rabbits - Cannon Laboratories, Inc. - April 12, 1977.

Test Material: Des-I-Cate/Accelerate (N.B. 77-99-6)

Method: 0.5 ml of test material was applied dermally to intact and abraded skin sites on fur clipped trunks of six New Zealand albino rabbits, 2.0-2.5 kg, under an impervious cuff for 24 hours. Observations at 24 and 72 hours after exposure.

Results: 4/6 rabbits died at 72 hours. 2/6 showed erythema, eschar & edema on abraded and non-abraded skin sites. Moderate to Severe scored for two rabbits.

Classification: Core-Minimum Data

TOX Category II: WARNING

Section VIII

Domestic Animal Safety

Review : In order to establish a tolerance for endothall in water, it has been necessary to develop complete toxicological data. These include studies on domestic animals such as dogs, chickens, sheep and goats. Details of these studies are included in Section VII and Section IX of this submission.

Classification: Supplementary Data

Section XI: Accident Exposure Experience

Review: Practical experience in production, formulation and handling in the field of endothall products indicates that no special handling precautions other than those listed on the label are necessary. No serious, prolonged, or permanent injury have been reported during these years in the United States or foreign countires from the use of endothall procucts. In the case of irrigated crops, there will be no hazard to harvesting personnel or processors since residues of toxic significance do not occur.

Endothall formulations have been used as aquatic herbicides in swimming areas and no incidents of adverse effects on swimmers have been reported.

Classification: Supplementary Data

E. Evaluation of ADI

1. Prior tolerances

Previously Established Tolerances

Petitions and established tolerances for some of the above mentioned products are:

Endothall from use of its mono (N-N-dimethylalkylamine) salt	Petition No. 0F0972	Tolerance of 0.1 ppm in or on cottonseed.

Endothall from use of its mono (N,N-dimethylalkylamine) salt	Petition No. 1F1057	Tolerance of 0.1 ppm in or on potatoes.
"	Petition No. 3F1416 later designated Petition No. 4G1449	Tolerance of 0.05 ppm in or on rice grain and rice straw.
Endothall	Petition No. 1F1105	Tolerance of 0.2 ppm in or on sugar beets (interim)
Endothall from use of its potassium sodium, di (N,N-dimethylalkylamine) and mono (N,N-dimethyl-alkylamine) salts	Petition No. 1F1105 and Food Additive Petition No. 2H5016	Tolerance of 0.2 ppm in potable water (interim)

2. Determine ADI

A two year rat feeding no effect level of 1200 ppm was previously observed.

1200 ppm = 60 mg/kg/day

ADI = 60 mg/kg/day ÷ 100 = .6 mg/kg/day

MPI = .6 mg/kg/day X 60 kg = 36 mg/day

3. Determine impact of proposed tolerance in relation to ADI.

a. Theoretical exposure from present tolerances. The theoretical exposure from present tolerances on cottonseed, potatoes and rice contribute 0.02% of the ADI.

b. Comparison of Theoreical exposure to ADI.

The proposed tolerances on food and ptable water will contribute 16.99% of the ADI. The MTRC from proposed tolerances is 6.1154 mg/day. The MPI is 36.000 mg/day.

The combined proposed and present tolerances will contribute 17.01% of the ADI.

The Computer printout is included.

F. RPAR Criteria.

No RPAR criteria have been exceeded in these studies.

G. Conclusions and Recommendations:

Although the combined present and proposed tolerances contribute 17.01% of the ADI, it is recommended that the proposed tolerances not be granted at this time. The results of the teratology study show an inverse dose-response effect on skull closure and need to be explained. Further teratological testing is required. Due to the widespread exposure possible from use of this pesticide additional mutagenic evaluation is required incluing bacterial testing with and without metabolic activation. Also, the final report of the 18 month mouse oncogenicity study is required to assess this aspect of human safety. Chemistry branch concludes that the metabolism of endothall in animals is not adequately defined and therefore further toxicological considerations of potential hazards from unknown residues in meat and milk is reserved.

TOX/HED:th:REngler:10-21-78

Unverified Printout

ACCEPTABLE DAILY INTAKE DATA

RAT,Older NOEL mg/kg	ppm	S.F.	ADI mg/kg/day	TPI mg/day/60kg
60.000	1200.00	100	0.6000	36.0000

Published Tolerances

CROP	Tolerance	Food Factor	mg/day/1.5kg
Cottonseed(41)	0.100	0.15	0.00022
Potatoes(127)	0.100	5.43	0.00814
Rice(137)	0.050	0.55	0.00041

TPI	THRC	% ADI
36.0000 mg/day/60kg	0.0068 mg/day/1.5kg	0.02

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Current Action. FP 1F1105/2H50..6

CROP	Tolerance	Food Factor	mg/day/1.5kg
Potable Water(198)	3.000	133.33	0.00000
Fish,shellfish(59)	0.100	1.08	0.00162
Avocados(6)	0.100	0.03	0.00005
Citrus Fruits(33)	0.100	3.81	0.00572
Curcurbits(49)	0.100	2.84	0.00426
Fruiting Vegetables(60)	0.100	2.99	0.00449
Grapes, inc raisins(66)	0.100	0.49	0.00074
Grain Crops(84)	0.100	13.70	0.02056
Hops(73)	0.100	0.03	0.00005
Nuts(101)	0.100	0.10	0.00015
Pome Fruits(126)	0.100	2.79	0.00418
Root Crop Veg(138)	0.100	11.00	0.01649
Seed&Pod Veg(143)	0.100	3.66	0.00549
Small Fruit,berries(146)	0.100	0.83	0.00124
Stone Fruits(151)	0.100	1.25	0.00187
Sugar,cane&beet(154)	0.100	3.64	0.00546
Leafy Vegetables(80)	0.500	2.76	0.02069
Milk&Dairy Products(93)	0.020	28.62	0.00858
Meat,inc poultry(89)	0.020	13.85	0.00415
Eggs(54)	0.020	2.77	0.00083

TPI	THRC	% ADI
36.0000 mg/day/60kg	0.1154 mg/day/1.5kg	15.99

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Chemical:	**Endothall**
PC Code:	**038901** , 038904, 038905
HED File Code	**13000 Tox Reviews**
Memo Date:	**10/25/78**
File ID:	**TX000668**
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HED Records Reference Center
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