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

001001

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

DATE: September 11, 1981

SUBJECT: Endothall; EPA Reg.#4581-174; 4581-204; PP#1F1105, 2H5016; Revised Sec. B & Sec. F. CASWELL#421; Accession#245680; 070275-277

FROM: William Dykstra, Toxicologist
Toxicology Branch/HED (TS-769)

WRD 9/12/81

TO: Richard Mountfort (23)
Registration Division (TS-767)

Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

Recommendations:

1. The requested tolerances are not toxicologically supported. The requested tolerances result in 135.70% of the ADI. The significant increase from 0.20% of the ADI from published tolerances to 135.90% of the ADI from the current action is too great an increment and is not supported by the available toxicity data base. Endothall was considered teratogenic at 40 mg/kg/day in the mouse teratology study, although in view of the severe maternal toxicity observed at this level (greater than 30% mortality occurred) a possibility that other factors may also have been involved cannot be excluded. This finding triggers an RPAR criterion. A repeat of the rat teratology study may address this issue.

   Endothall was not oncogenic to mice in the study submitted. A valid rat chronic/oncogenic feeding study is required. Endothall was not mutagenic in the sister chromatid exchange mutagenicity study. An in vivo cytogenetic mutagenicity study is required.

   It should be noted that even the submission of the above requested toxicity data (rat teratology, rat chronic/oncogenic feeding, mutagenicity) may not be sufficient to support the requested tolerances due in part to the triggered RPAR criterion and the percent of the ADI utilized.

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Review:

1. Revised Section F

A food additive tolerance of 3 ppm is proposed for residues of the algicide/herbicide endothall (7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acid) in potable water as a result of the application of the potassium, sodium, di(N,N-dimethylalkylamine) and mono(N,N-dimethylalkylamine) salts, wherein the alkyl groups of the N,N-dimethylalkylamine salts are the same as in the fatty acid of coconut oil, of this chemical to slow-moving or quiescent fresh water in canals, ditches, rivers, lakes, and ponds and fast-roving fresh water in irrigation canals and ditches for the control of aquatic plants.

Pesticide tolerances are proposed for residues of the pesticide endothall (7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acid) resulting from application of its potassium, sodium, di(N,N-dimethylalkylamine) and mono(N,N-dimethylalkylamine) salts, wherein the alkyl group is the same as in the fatty acid of coconut oil, in or on the following raw agricultural commodities:

Fish	0.1 ppm
Meat, Fat, and Meat By-Products of cattle, sheep, goats, swine, and horses	0.02 ppm
Poultry	0.02 ppm
Eggs	0.02 ppm
Milk	0.02 ppm
Sugar Beet Roots	0.1 ppm
Sugar Beet Tops	0.1 ppm

Pesticide tolerances for irrigated crops are proposed for residues of the pesticide endothall (7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acid) resulting from application of its potassium, sodium, di(N,N-dimethylalkylamine) and mono(N,N-dimethylalkylamine) salts, wherein the alkyl group is the same as in the fatty acid of coconut oil, to slow-moving or quiescent fresh water in canals, ditches, rivers, lakes, and ponds and fast-moving fresh water in irrigation canals and ditches for aquatic plant control at 0.1 ppm in or on the crop groupings: citrus, cucurbits, fruiting vegetables, grain crops, nuts, pome fruits, root crop vegetables, seed and pod vegetables, small fruits, stone fruits, and on the individual crops avocados, cottonseed, and hops; at 0.5 ppm in or on leafy vegetables; and at 3.0 ppm on forage grasses and forage legumes. Where tolerances are established at higher levels from other uses of endothall on the subject crops the higher tolerance applies also to residues resulting from the aquatic use cited above.

2. Exhibit E. Evaluation of the Mutagenic Potential of Aquathol K by the Induction of Sister Chromatid Exchanges in Human Lymphocytes in vitro (N.V. Vigfusson, Dept. of Biology, Eastern Washington University, Cheney, Wash., April 22, 1981)

Mutagenicity of the aquatic herbicide Aquathol K has been evaluated by the use of the sister chromatid exchange test in human lymphocytes in vitro.

Four concentrations of Endothall acid equivalent (10 mcg/ml, 1.0 mcg/ml, 0.1 mcg/ml and 0.01 mcg/ml), with 10 mcg/ml of medium being the highest non-toxic dose, were tested with and without metabolic activation.

Approximately equivalent concentrations of ethylmethonesulfonate were also tested as positive controls as well as a negative control with only solvent (H_2O) added to the culture medium.

Results:

Results of the analysis showing mean SCE frequencies for the 50 cells counted and the standard deviations are presented in Table I. The positive control, EMS, differs significantly ($p = .001$) from the control only at the highest concentration of 1.335×10^{-4} M. This is in agreement with previous data from this lab. It should be pointed out that EMS concentration of 1.335×10^{-4} M is the approximate molar equivalent to the highest concentration of endothall used.

It is evident from the data that the test compound does not induce SCE in human lymphocytes in vitro.

TABLE I

Mean SCE frequencies in human lymphocytes after in vitro exposure to various concentrations of Aquathol "K" (endothall acid) with and without metabolic activation with S9 liver extract.

Treatment	Mean SCE ± SD
None (Control)	22.04 ± 5.16
1.335×10^{-8} M EMS	22.71 ± 5.01
1.335×10^{-7} M EMS	21.45 ± 5.88
1.335×10^{-6} M EMS	21.70 ± 4.35
1.335×10^{-5} M EMS	23.31 ± 5.12
1.335×10^{-4} M. EMS	25.72 ± 5.01
0.01 mcg/ml Endothall	19.62 ± 4.64
0.10 mcg/ml Endothall	21.00 ± 4.90
1.0 mcg/ml Endothall	24.21 ± 6.12
10.0 mcg/ml Endothall	22.79 ± 4.13
S9 Mix (Control)	33.03 ± 7.09
0.1 mcg/ml Endothall + S9	31.16 ± 4.70
0.10 mcg/ml Endothall + S9	33.32 ± 4.95
1.0 mcg/ml Endothall + S9	33.86 ± 6.17
10.0 mcg/ml Endothall + S9	35.86 ± 7.42

Conclusion:

Aquathol K was not mutagenic in the sister chromatid exchange test.

Classification: Acceptable

3. Teratology Study in Mice (IRDC#470-006; July 2, 1981)

Test Material: Endothall

Groups of 25 pregnant Charles River CD-1 mice were used in this study to determine the teratogenic potential of Endothall. Dosage levels of 0, 5, 20, and 40 mg/kg/day were administered orally by gavage as a single daily dose on days 6 through 16 of gestation at a constant volume of 5 ml/kg. The control group received the vehicle only, blended whole egg/deionized water (4:1 volume/volume), on a comparable regimen. Cesarean sections were performed on all surviving females on gestation day 17.

Results:

There were no biologically meaningful differences in appearance or behavior of mice in the 5 mg/kg/day treatment group when compared to the control group. Two females in the 20 mg/kg/day group died on gestation day 7. Eight mice died during the treatment period in the 40 mg/kg/day group; one each on gestation days 8, 10, 13 and 17 and two each on gestation days 7 and 9. The cause of death was attributed to an intubation error for dam#65881 (40 mg/kg/day group); the remaining nine animals died of unknown cause. The uterine contents of dam#65858 in the 40 mg/kg/day group consisted of early resorptions only whereas normally developing implantations were noted in the remainder of these females. The intestinal contents of a majority of these mice were reported as liquid in form and tan or brown in color upon gross internal examination.

Remarkable postmortem findings at Cesarean section included one 5 mg/kg/day female (#65811) with hydrometra. At the 40 mg/kg/day level, a cystic ovarian bursa was observed on the right ovary of dam #65862 and on both ovaries of dam #65879. All other females examined at Cesarean section were internally normal.

There were no biologically meaningful differences in mean maternal body weight in any of the Endothall treated groups when compared to the control group throughout the entire gestation period. The mean adjusted body weight gain (dam body weight exclusive of the uterus and contents) for all treated groups was comparable to the control value.

There were no biologically meaningful differences in the mean numbers of corpora lutea, viable fetuses, early or late resorptions, postimplantation loss, total implantations, the fetal sex distribution or mean fetal body weight in any of the Endothall treated groups when compared to the control group. Statistically significant increases in the mean number of corpora lutea ($p < 0.05$) occurred in the 5 and 20 mg/kg/day groups and a significant ($p < 0.01$) increase in the mean number of total implantations and viable fetuses was observed in the 20 mg/kg/day group. However, since ovulation and implantation occur prior to initial test article administration in this species, the findings were attributed to random occurrence. Nonviable fetuses were not observed in control or in any of the Endothall treated groups.

An increase (although not statistically significant) in both the number of litters and fetuses with malformations was observed at the 40 mg/kg/day level. The total number of fetuses (and litters) affected were 16 (6) and 4 (3) from the 40 mg/kg/day and control groups, respectively. Vertebral anomalies, primarily involving malformed atlas and/or axis bones, were observed in all Endothall treated groups as well as the control group. However, the reported incidence was markedly increased at the 40 mg/kg/day level over control values with respect to the number of fetuses and litters affected. In addition, the occurrence of fused, malformed, absent and/or extra vertebral arches (which occurred with associated rib anomalies) was noted in 6 fetuses from 2 litters and fused ribs were confirmed in 2 fetuses from 2 litters. The extremely low incidence of these types of anomalies in control fetuses in the IRDC laboratory suggests that Endothall induced a positive teratogenic response at the 40 mg/kg/day level. However, in view of the severe maternal toxicity observed at this level (greater than 30% mortality occurred) a possibility that other factors may also have been involved cannot be excluded.

There were no biologically meaningful or statistically significant differences in the number of litters with malformations in the 5 or 20 mg/kg/day groups when compared with the control group. A slight increase in the percentage of fetuses and litters with misaligned sternebrae (with or without fusion) occurred in all treated groups and the reported values at the 40 mg/kg/day level exceeded the range of the historical control. All other genetic and developmental variations observed were comparable to the respective control values.

Conclusions:

The number of litters with malformations in the 5 and 20 mg/kg/day groups were comparable to control; there were no statistically significant differences. An increase (although not statistically significant) in both the number of litters and fetuses with malformations was observed at the 40 mg/kg/day level. The anomalies which occurred most frequently were of skeletal origin and included the following defects: vertebral anomalies, fused ribs and fused, malformed, absent or extra vertebral arches (which occurred with associated rib anomalies). The extremely low incidence of fused ribs and scoliosis in control fetuses in the IRDC laboratory suggests that Endothall induced a positive teratogenic response. However, in view of the severe maternal toxicity observed at this level (greater than 30% mortality occurred) the possibility that other factors may also have been involved cannot be excluded.

Based upon a comparison with concurrent and historical control data it was concluded that treatment with Endothall at the toxic dosage level of 40 mg/kg/day induced a teratogenic effect in Charles River CD-1 mice. However, the lack of a teratogenic response was clearly demonstrated at dosage levels of 20 mg/kg/day or less. The NOEL for fetotoxicity is considered to be 20 mg/kg/day.

Classification: Core-Minimum Data

4. Range-finding Teratology Study in Mice with Endothall (IRDC#470-005)

Pregnant Charles River CD-1 mice were used to determine dosage levels of Endothall for a teratology study. Dosage levels of 5, 10, 20, 40 and 60 mg/kg/day were administered orally by gavage as a single daily dose on days 1 through 16 at a constant volume of 5 ml/kg. The control group received the vehicle only, blended whole egg/deionized water (4:1 volume/volume) on a comparable regimen at a constant volume of 5 ml/kg. Uterine examinations were performed on all surviving females on gestation day 17.

Results:

There were no abnormalities noted in the appearance or behavior of any female in any of the treatment groups or in the control. Survival was 100% in the control group and in the 5, 10, 20, and 40 mg/kg/day dosage groups. Two deaths occurred during the treatment period in the 60 mg/kg/day dosage group and a cause of death could not be determined for either female at necropsy. Postmortem examination did not reveal any remarkable findings in any female in the control group or in the 5, 10, 20, 40 or 60 mg/kg/day dosage groups. There were no biologically meaningful

differences in mean maternal body weight gains over the entire gestation period or in the mean uterine examination observations in the 5, 10, 20 or 60 mg/kg/day dosage groups when compared to the control group.

A slight reduction in mean maternal body weight gain occurred in the 40 mg/kg/day dosage group and was due to one dam with reduced body weight throughout gestation (having hydrometra and 11 early resorptions at uterine examination).

Conclusion:

Based on these results, dosage levels of 5, 20 and 40 mg/kg/day were selected for the teratology study in mice with Endothall.

Classification: Supplementary Data

5. 24-Month Study of Endothall (15.8% active) in CD Mice (Final Histopathology Report; Donald A. Willigan, D.V.M.)

A total of 400 mice, approximately four weeks of age, were obtained from the Charles River Laboratories, Inc., Wilmington, Mass. The weight range of experimental animals at week 0 was 23.3 ± 0.24 gm for female and 28.4 ± 0.34 gm for males. When received, each animal was ear-tagged and was identified by a unique number. If this tag was lost, the animal was identified by a unique combination of ear punches. Animals were then housed by sex in groups of 5.

Test animals were randomly assigned to one four treatment groups as shown below:

Group	Dose Level (ppm)	Number of Animals	
		Males	Females
I	0	50	50
II	300	50	50
III	600	50	50
IV	1200	50	50

All animals were examined daily for general physical appearance, palpable masses and pharmacotoxic signs. All body weights were recorded at weekly intervals through week 12, and monthly thereafter for the duration of the study. Means per cage were used as the base of measure, resulting in each cage having a representative animal weight expressed in grams.

Food consumption was recorded at weekly intervals through week 13, and monthly thereafter for the duration of the study. Consumption was recorded as the mean value per cage, in grams.

The heart, kidneys, spleen and gonads of each animal surviving to termination were weighed to the nearest 1×10^{-3} gm. Liver weight measurements were overlooked and were not taken. These measurements were also represented as an index obtained by dividing the organ weight by the final body weight.

Gross necropsies were performed pm all non-autolyzed or non-canibalized animals. Tissues for histopathology were removed from animals surviving to termination, sacrificed in extremis, or found dead, but not autolyzed (a total of 201 animals). Additionally, some tissues were taken from animals found dead but partially autolyzed (a total of 129 animals). No tissues were available from 64 animals (totally autolyzed) and 6 animals (totally cannibalized). After gross pathological examination, all available tissues were preserved in 10% neutral buffered formalin for future microscopic examination.

adrenal
bone marrow (sterum)
brain (3 levels)
duodenum
esophagus
eye and Harderian gland
gall bladder
heart
kidney
liver
lung
lymph nodes
mammary glands
ovary/testes
pituitary
pancreas
prostate/uterus
salivary gland
sciatic nerves
skin
small & large intestines
spinal cord
spleen
stomach
thymus
thyroid/parathyroid
trachea
urinary bladder
gross lesions
Vertibra Tibia Femoral Joint

Also, the nasal cavity, tongue, oral cavity, nasopharynx and middle ear were removed from ten survivors per sex group. If fewer than ten animals survived, all animals alive at termination in that group had these tissues removed,

Statistical analyses of the data were performed.

Results:

No effect of the test material on survival was apparent in either males or females. At week 70, approximately 20% of the males had died in each group. This pattern continued through week 103, at which time 14% (controls), 12% (300 ppm), 6% (600 ppm) and 26% (1200 ppm) of the male had survived. Females followed a similar pattern through week 79 although the total number of females surviving at termination appeared to be somewhat greater than that of the males; 38% (control), 24% (300 ppm), 34% (600 ppm) and 50% (1200 ppm) of the females had survived.

Males did not appear to exhibit obvious differences in frequencies of pharmacotoxic signs of treatment. The time at which these signs were first noted also appeared to be similar. Likewise, the frequency, time of recognition and duration of pharmacotoxic signs in females did not appear to differ among treatment groups.

Thickened conjunctiva, however, were noted in 34 males but only 6 females, and lacerations were seen in 23 males versus nine in females.

Masses were found in the stomachs of females treated with test material on 15 occasions. The stomachs of control females appeared normal in all cases. Similarly, pancreatic masses were evident in five test material treated females; however only one mass on the pancreas of control females was found. Masses of the lung were seen in ten females receiving 1200 ppm of test material in the diet compared with frequencies of 4, 5 and 7 for females receiving control, 300 and 600 ppm diets, respectively.

Summing over sex, high dose animals exhibited nearly twice as many internal masses as controls (50 high-dose animals vs 30 control animals).

Significant differences were found in body weights among females at various times throughout the 24-month study. However, these differences were sporadic. A more clear pattern ~~of pattern~~ of differences was seen in the body weights of males. Animals treated with the test material frequently weighed less than controls through week 77. The body weight of controls showed marked fluctuations from week 77 through termination at week 103.

Differences of average food consumption among females did occur; however, no clear dose-related response was obvious. Few differences were seen in food consumption among males.

The heart to body weight ratio in group III (600 ppm) females was lower than compared to group I (0 ppm), II (300 ppm) and IV (1200 ppm). Group IV males exhibited higher gonad weight to body weight ratios and gonad weights than males receiving 0, 300 or 600 ppm of test material in the diet. Males in groups III and V had lower kidney weights than those in group II and I. No other organ weight differences of statistical significance were observed.

Representative Summary of Tissues Examined

Exposure:	Control		Low		Mid		High	
Dose level (ppm):	0		300		600		1200	
Sex of Animals:	M	F	M	F	M	F	M	F
Animals per group:	50	50	50	50	50	50	50	50
Number Evaluated:								
Brain	26	30	20	27	27	27	34	39
Spinal cord	20	19	19	24	18	22	33	27
Peripheral nerve	14	12	20	25	21	24	25	27
Eye	29	35	26	33	29	29	37	40
Skin	28	32	26	32	27	28	37	39
Trachea	36	32	28	37	34	35	37	43
Lung	43	43	33	43	40	39	42	45
Heart	42	43	34	42	39	38	42	42
Liver	35	35	29	38	34	38	40	42
Pancreas	29	31	21	33	27	28	32	33
Stomach	31	32	22	38	29	29	38	42
Bone Marrow	34	37	31	36	35	34	38	42
Spleen	32	36	25	34	30	36	39	39
Kidney	34	36	28	40	33	40	40	42
Adrenal	24	25	24	31	30	31	29	32
Thyroid	30	30	26	37	31	35	35	36
Mammary gland	2	19	0	20	1	16	0	22
Testis	32	0	27	0	27	0	36	0
Uterus	0	32	0	34	0	34	0	39

There were other tissues examined which are not presented in the table above. It was considered that sufficient tissue were examined for evaluation of the study.

Neoplasms were apparent in test and control groups of mice. The total number (primary and metastatic) was as follows: control, 70; 300 PPM: 96; 600 PPM: 66; 1200 PPM: 103.

Primary neoplasms (i.e. neoplasms originating at a tissue site) comprised over 65 percent of the total number.

Number of Primary Tumors By Site

Tissue	Disodium Endothall (PPM) 0	300	600	1200
Lung	18	18	15	21
Liver	9	5	4	9
Spleen	6	6	6	12
Mammary gland	1	7	4	3
Uterus	3	7	3	9
Sub-total	37	43	32	54
Remaining tissues	14	20	15	22
Total Primary	51	63	47	76
Total Primary and Metastatic	70	96	66	103

Since the incidence of primary neoplasms by percent of the combined total number of primary and metastatic types is approximately equivalent among all test and control groups (control: 51/70, 72.9%; 300 PPM: 63/96, 65.6%; 600 PPM: 47/66, 71.2%; 1200 PPM: 76/103, 73.4%), the data suggest that no unusual number and/or types of neoplasms were induced specifically in tissues of mice exposed to disodium endothall, under conditions of this study. In other words, disodium endothall was not oncogenic.

Of the total number of primary neoplasms, over 68 percent originated in five tissues: lung, liver, spleen, mammary gland, and uterus (control: 37/51, 72.6%; 300 PPM: 43/63, 68.3%; 600 PPM: 32/47, 68.1%; 1200 PPM: 54/76, 71.1%). By type, neoplasms of the liver, lung, spleen, uterus, and mammary gland were not unusual and not unlike those normally encountered in untreated ageing Charles River CD-1 mice. Direct relationship to test exposure was not apparent. In the case of mammary neoplasms, the frequency of development was in inverse relationship to dose level of exposure.

The incidence of primary neoplasms, by type, in the lung, liver, spleen, mammary gland, and uterus is shown below:

Tissue/Neoplasm	Disodium Endothall (PPM)			
	C	300	600	1200
Lung				
bronchio-alveolar adenoma/carcinoma	20.9%	23.7%	19.0%	23.0%
Liver				
hepatic cell adenoma/carcinoma	11.4%	7.5%	5.6%	9.8%
cholangiocarcinoma	0.0%	0.0%	0.0%	1.2%
hemangiosarcoma	1.4%	0.0%	0.0%	0.0%
Spleen				
hemangioma/hemangiosarcoma	1.5%	1.7%	4.5%	3.8%
malignant lymphoma	7.4%	8.5%	4.5%	9.0%
reticulum cell sarcoma	0.0%	0.0%	0.0%	2.6%
Mammary gland				
adenoma/carcinoma	4.8%	35.0%	25.0%	13.7%
Uterus				
endometrial polyp	6.3%	17.7%	2.9%	12.8%
glomangioma	0.0%	0.0%	0.0%	2.6%
leiomyoma	0.0%	0.0%	0.0%	5.1%
hemangioma	3.1%	0.0%	0.0%	2.6%
fibrosarcoma	0.0%	0.0%	5.9%	0.0%
leiomyosarcoma	0.0%	2.9%	0.0%	0.0%

Evaluation regarding the oncogenic potential of primary neoplasms was undertaken with Toxicology Branch pathologist, Dr. L. Kasza.

Other neoplasms which occurred less frequently were by type and location identical to those normally encountered in ageing Charles River CD-1 mice. The neoplasms, unrelated to test exposure, were observed in the eye, Harderian gland, skin, trachea, lung, heart, liver, pancreas, salivary gland, stomach, duodenum, ileum, bone marrow, spleen, lymph nodes/mesenteric, lymph nodes (cervical/submaxillary), thymus, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, testis, prostate, ovary, uterus, skeletal muscle, shoulder (gross lesion), and tissue mass, gross lesions.

Neoplasms were not observed in the brain, spinal cord, peripheral nerve, nasal turbinates, aorta, gall bladder, tongue, esophagus, cecum, colon, epididymis, seminal vesicles, bone/femur, and costochondral junction.

Non-neoplastic responses attributable to disodium endothall were observed in the stomach, duodenum, jejunum, ileum, cecum, liver, lymph nodes (cervical/submaxillary), kidneys, adrenals, thyroids, seminal vesicles, and ovaries.

Disodium endothall was an irritant to the mucosa of the stomach, duodenum, jejunum, ileum, and cecum. Irritation took the form of gastritis/enteritis, glandular/epithelial hyperplasia, hyperkeratosis (cardia), and formation of mucosal and submucosal cysts. For the most part, the effects were dose-related. The colon was unaffected. Inflammatory changes in the mucosa and associated epithelial responses were most severe in the stomach. Fewer effects with lesser severity were observed progressively through the length of the small and large intestines.

At 1200 PPM, polyps were observed in the stomach (1/80, 1.3%) and duodenum (2/72, 2.8%). A gastric polyp was apparent in one control male (1/63, 1.6%). A mucosal adenoma occurred in the jejunum of one male (1/62, 1.6%). At 600 PPM, a carcinoma of the stomach developed in one male (adenosquamous) and in one female (squamous).

Tissue/Response	Disodium Endothall (PPM) 0	300	600	1200
Stomach				
gastritis	7.9%	50.0%	48.3%	67.5%
glandular/epithelial hyperplasia	23.8%	45.0%	56.9%	76.3%
keratosis (cardia)	9.5%	13.3%	36.2%	31.3%
mucosal cysts	9.5%	36.7%	41.4%	42.5%
submucosal cysts	0.0%	0.0%	13.8%	21.3%
(polyp	1.6%	5.0%	0.0%	1.3%)
(adenosquamous carcinoma	0.0%	0.0%	1.7%	0.0%)
(squamous cell carcinoma	0.0%	0.0%	1.7%	1.3%)
Duodenum				
enteritis	0.0%	0.0%	2.0%	9.0%
epithelial hyperplasia (mucosa)	0.0%	5.1%	12.2%	25.0%
mucosal cysts	0.0%	2.6%	0.0%	6.9%
(polyp	0.0%	0.0%	0.0%	2.8%)
Jejunum				
enteritis	0.0%	0.0%	2.3%	3.2%
(adenoma	0.0%	0.0%	0.0%	1.6%)
Ileum				
enteritis	0.0%	0.0%	0.0%	4.0%
Cecum				
enteritis	0.0%	0.0%	0.0%	6.7%

Inflammatory changes within the liver (chronic pericholangiolitis; hepatic cell necrosis) and kidney (chronic nephritis) were probably indirect effects of gastro-intestinal irritation. Lymph nodes (cervical/submaxillary) regional to the oral cavity were reactive (lymphoid cell hyperplasia) more frequently in the treatment groups but not in any dose-related sequence.

Tissue/Response	Disodium Endothall (PPM) 0	300	600	1200
Liver				
hepatic cell necrosis	8.6%	6.0%	6.9%	22.0%
chronic pericholangiolitis	0.0%	3.0%	15.3%	20.7%
hepatocysts	0.0%	0.0%	4.2%	8.5%
angiectasis	0.0%	0.0%	1.4%	9.8%
Kidney				
chronic nephritis	4.3%	0.0%	0.0%	7.3%
Lymph node (cervical/submaxillary)				
lymphoid cell hyperplasia	5.9%	31.3%	28.1%	26.1%

Certain non-inflammatory responses in the thyroid, adrenals, ovaries, and seminal vesicles were either induced or exacerbated by test exposure. None appeared to be associated with formation of neoplasms.

Tissue/Response	Disodium Endothall (PPM) 0	300	600	1200
Thyroid				
follicular cyst	6.7%	4.8%	10.6%	22.5%
Adrenals				
cortical lipidosis	0.0%	0.0%	0.0%	31.1%
Seminal vesicles				
distended with secretion	14.3%	57.1%	72.2%	58.8%
Ovaries				
follicular cyst	41.4%	65.6%	71.0%	54.5%
bursal cyst	17.2%	25.0%	19.4%	51.5%

Other non-neoplastic changes in various organs were identified as spontaneous events usually observed in ageing Charles River CD-1 mice. Such changes, unrelated to treatment, were evident in the brain, eyes, Harderian gland, skin/ear, skin, nasal turbinates, trachea, lung, heart, pancreas, salivary gland, tongue, esophagus, stomach, duodenum, cecum, colon, bone marrow, spleen, lymph nodes/mesenteric, lymph nodes (cervical, submaxillary), thymus, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, mammary gland, testis, epididymis, prostate, seminal vesicle, ovary, and uterus.

The spinal cord, perpheral nerve, aorta, bone/femur, and costochondral junction were unremarkable histologically.

Conclusion:

Endothall was not considered oncogenic to mice in this study. No NOEL for non-neoplastic histological lesions was established. The histological NOEL is less than 300 ppm.

Classification: Core-Minimum Data

6. Calculation of the ADI

The ADI is based on the NOEL of 300 ppm (7.5 mg/kg/day) in the 2-year dog feeding study. A 100-fold safety factor is used to calculate the ADI.

$$\text{ADI} = 7.5 \text{ mg/kg/day} \times \frac{1}{100}$$

$$\text{ADI} = .075 \text{ mg/kg/day}$$

The MPI for a 60 kg person is 4.5 mg/day

7. Published tolerances utilize 0.20% of the ADI.

The current action utilizes the ADI to 135.90%

Conclusions and Recommendations

The requested tolerances are not toxicologically supported. The requested tolerances result in 135.70% of the ADI. The significant increase from 0.20% of the ADI from published tolerances to 135.90% of the ADI from the current action is too great an increment and is not supported by the available toxicity data base. Endothall was considered teratogenic at 40 mg/kg/day in the mouse teratology study, although in view of the severe maternal toxicity observed at this level (greater than 30% mortality occurred) a possibility that other factors may also have been involved cannot be excluded. This finding triggers an RPAR criterion. A repeat of the rat teratology study may address this issue.

Endothall was not oncogenic to mice in the study submitted. A valid rat chronic/oncogenic feeding study is required. Endothall was not mutagenic in the sister chromatid exchange mutagenicity study. An in vivo cytogenetic mutagenicity study is required.

It should be noted that even the submission of the above requested toxicity data may not be sufficient to support the requested tolerances due in part to the triggered RPAR criterion and the percent of the ADI utilized.

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001001

File last updated 9/9/81

ACCEPTABLE DAILY INTAKE DATA

Dog mg/kg	NOEL ppm	S.F.	ADI mg/kg/day	MPI mg/day(60kg)
7.500	300.00	100	0.0750	4.5000

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

MPI	THEC	% ADI
4.5000 mg/day(60kg)	0.0088 mg/day(1.5kg)	0.20

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Current Action PP 1F1105/2H5016

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
Cucurbits(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(64)	0.100	13.79	0.02069
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

MPI	THEC	% ADI
4.5000 mg/day(60kg)	0.1155 mg/day(1.5kg)	135.90

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