5-26-83
BC-694

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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

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

THRU: William Burnam, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

SUBJECT: PP#1F1105 & 2H5016; Evaluation of Rat Teratology Study and Request for tolerances of Endothall in Water, Irrigated Crops, Meat, Milk, Other Animal Organs, Poultry, Eggs and Fish
CASWELL#421

Registrant: Pennwalt Agchem
Three Parkway
Philadelphia, PA 19102

Action Requested/Background Information: The registrant originally had requested the establishment of a tolerance for endothall at 3 ppm acid equivalent in drinking water. However, as noted in the letter of January 10, 1983 from Edwin L. Johnson to Gerald Roseberry, the evaluation of the safety of pesticide residues in drinking water will continue though the formal establishment of food additive tolerances for pesticides in drinking water will not occur. Proposed EPA policy in this area was outlined in the Federal Register notice of June 15, 1982. Thus the action to be considered is the approval of the use of endothall as an aquatic herbicide without the formal establishment of a tolerance for drinking water.

Recommendation:

Toxicology Branch cannot recommend favorably for the requested uses. Data gaps include the chronic rat study (due to the invalidation of an IBT study) and the chronic dog study (based on a rereview of a previously submitted study, see Review of Data). If an ADI is based on the 3 generation study, the requested use will utilize 42% or 126% of the ADI for adults or children, respectively.

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Discussion:

The memo of January 18, 1983 from J. Reinert of EFB assessed total dietary exposure i.e. drinking water and f.a.c.s based on three possible models:

1) Assuming a constant concentration of 3 ppm in water.

2) Assuming an initial concentration of 3 ppm after application and taking into account the half-life of endothall in water and a high use pattern (once every two weeks).

3) Assuming an initial concentration of 3 ppm after application and taking into account the half-life of endothall in water and a less frequent use pattern (4 times per year).

The 3 models yield the following EFB estimates of exposure for adults:

Example 1: 0.10 mg/kg/day
Example 2: 0.12 mg/kg/day
Example 3: 0.021 mg/kg/day

For children, the relative exposure will be increased due to a greater consumption of water on a ml/kg basis. A 10 kg child has been estimated to consume 1 liter of water compared to the consumption of 2 liters by a 60 kg adult. A 10 kg child thus consumes 3 times the amount of water that an adult does on a ml/kg basis and dosage, in mg/kg, will also be increased threefold. For children, estimates of exposure of the three examples will result in the following dosages:

Example 1: 0.300 mg/kg/day
Example 2: 0.360 mg/kg/day
Example 3: 0.063 mg/kg/day

Adequate chronic and subchronic studies upon which an ADI can be established are not available. The mouse oncogenicity study found compound related effects at each dose level (lowest dose tested = 300 ppm, see review of 9/25/81 by W. Dykstra). Thus the only study upon which a NOEL can be established is the 3 generation rat reproduction study (originally reviewed on 11/21/66 by R. Coberly, rereviewed on 9/25/81 by W. Dykstra).

For adults the % of the ADI (ADI = .05 mg/kg) utilized by predicted residues of endothall in drinking water and the diet is 200%, 240% and 42% for examples 1-3, respectively. For children the % of ADI utilized by predicted residues is 600%, 720% and 126%, respectively. The majority (greater than 95%) of residue contribution to the % of ADI utilized is by drinking water.

Review of Data:

1) Range-finding Teratology, Rats. Conducted by Science Applications, Inc., La Jolla, California, Study#1182005, reported dated November 11, 1982. Submitted by Pennwalt.

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Sprague-Dawley-derived FBR rats weighing between 229 and 284 grams (females) and 350 to 400 grams (males) were bred randomly. Evidence of mating in the form of sperm observed in a vaginal rinse resulted in the females being removed, weighed and that day designated as day 0 of gestation. Six females per group were dosed on days 6-19 of gestation at levels of 0, 10, 20, 30, 40 or 50 mg/kg of Endothall technical (disodium salt) in distilled water. Animals were observed daily, weighed on days 6-19, and asphyxiated with CO_2 on day 20 of gestation.

The dams were necropsied by examination of the thoracic and abdominal cavities and reproductive organs. The number of corpora lutea and live or dead fetuses recorded. Fetuses were examined externally, weighed and sexed.

Results:

No maternal clinical signs of toxicity were noted. Two dams died at 40 mg/kg and two died at 50 mg/kg. No gross pathologic indications of toxicity were noted at any dose level. Maternal body weight gain was decreased in all groups. Although the data was not statistically analyzed by this reviewer or the registrant, clear weight gain depression was observed at dose levels of 30 mg/kg and greater and slight body weight depression was observed at 20 mg/kg. Actual mean body weight gain on days 6-20 was 92.7, 87.8, 78.0, 61.8, 68.7 and 70.8 grams for the 0, 10, 20, 30, 40 and 50 mg/kg groups, respectively.

No compound related effects were observed on the rate of implantation or the mean number of live fetuses per litter. Mean live fetal weights were slightly decreased in the 40 and 50 mg/kg groups. External examinations found one fetus with an umbilical hernia in the control group and one fetus in the 50 mg/kg classified as a runt.

Core-Classification: Supplementary Data

Maternal toxicity was most evident at dose levels of 30 mg/kg and greater though a slight decrease in body weight gain was observed at 20 mg/kg. The NOEL for maternal toxicity was 10 mg/kg. Slight fetotoxicity in the form of decreased weight was observed at dose levels of 40 and 50 mg/kg.

2) Teratology with Post-Natal Phase, Rats. Conducted by Science Applications, Inc., La Jolla, Ca. (Study #1182006), reported dated November 11, 1982. Submitted by Pennwalt.

Sprague-Dawley-derived FBR rats weighing between 202 and 273 grams were randomly mated. Evidence of mating in the form of sperm observed in a vaginal rinse or plugs resulted in the female being removed, weighed and that day designated as day 0 of gestation. Twenty-five females per group were dosed by gavage at levels of 0, 10, 20 and 30 mg/kg of Endothall technical (disodium salt) in distilled water. Animals were observed daily, weighed on days 6-20 and those dams not selected for the post-natal phase were asphyxiated with CO_2 on day 20. Sacrificed dams were necropsied by making an incision in the abdominal wall and the thoracic and abdominal cavities were examined in situ. The reproductive organs were examined grossly, the number of corpora lutea recorded and the number of live and dead fetuses and sites of resorption counted. Each fetus was examined for external abnormalities and weighed. Approximately 1/2 of the fetuses in each litter were randomly selected, decapitated and the heads fixed in Bouin's solution. Heads were then examined using the Wilson's slicing method. Each fetus was carefully examined viscerally, fixed in ethanol and stained with Alizarin Red, and then examined for skeletal abnormalities.

Between 11 and 13 dams per group were randomly designated to deliver pups for behavioral testing. On the day of delivery, 5 males and 5 females from each litter were randomly selected and observed for the following: day of eye opening, surface righting reflex, pivoting locomotion and "general health and survival". All pups were weighed on day 0, 4, 14 and 21 and were sacrificed on postnatal day 21.

Results:

At 30 mg/kg, 10 maternal deaths were observed and at 20 mg/kg, 2 dams died. The report stated that none of these dams showed clinical signs of toxicity prior to death or gross lesions indicative of toxicity after necropsy. Mean body weight change was depressed in a dose related manner (93.9, 88.5, 81.0 and 75.9 grams weight gain on days 6 through 20 of gestation for the control, 10, 20 and 30 mg/kg groups, respectively). Implantation rate, mean number of live fetuses per litter, resorption rate and fetal weights were similar in all groups. Two dead fetuses were found in the high dose

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group whereas no fetal mortality was observed in other groups. A variety of malformations were observed including micrognathia, dome shaped skull, curved tail, bifurcated ribs and absent vertebral centra. However, the incidences of these malformations were low and no apparent effect of treatment is noted. A slight increase in the overall rate of skeletal variations was observed in the 20 and 30 mg/kg groups. The increase was due primarily to incomplete ossification of various sternebra. An increased incidence of rudimentary 14th ribs was also observed in the high dose group. The rates of selected variations and the combined incidence of skeletal variations is shown in the following table:

Table: Skeletal Variations

	Dose Level (mg/kg)			
	0	10	20	30
All Skeletal Variations*	0.068 ±0.080	0.074 ±0.105	0.165 ±0.273	0.244 ±0.309
Rudimentary 14th Ribs**	.5%	.7%	.9%	5.2
Absent Sternebra 6**	.5%	0	2.5%	5.2
Incomplete Ossification of Sternebra 6**	.8%	1.8%	4.1%	10.2

*Mean proportion of viable fetuses per litter with at least one variation.

**Mean percentage per litter of fetuses with a given variation.

The number of days to eye opening ranged from 14.5 to 15.2 for all groups and did not appear to be affected by treatment. Surface righting ability also did not appear to be affected by treatment. Pivoting ability was examined as follows:

"Pups were placed on a wood board marked with a circle (diameter = 25 cm) divided into quadrants to test pivoting for a 1 minute trial on PN 9 and 11. Pivoting was defined as a change in compass direction of the body midline produced by forelimb movements. The rat's rear legs provided the pivot point. The amount of time spent pivoting, the number of uninterrupted 90° turns and the number of exists from the circle were recorded in the one minute session."

The results of the pivoting ability test are presented in the following table:

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SUMMARY OF PIVOTING LOCOMOTION
IN OFFSPRING OF RATS EXPOSED TO ENDOTHALL TECHNICAL[a]

Dose Levels (mg/kg)	0	10	20	30
Day 9				
Amount of Time Spent Pivoting (Seconds)				
Males	10.88±3.82	14.46±3.66	12.75±5.99	11.71±4.26
Females	10.78±4.23	16.88±7.09	11.36±4.30	12.37±7.23
Number of Exits from Circle				
Males	0.0±0.1	0.2±0.2	0.1±0.2	0.3±0.3[b]
Females	0.2±0.3	0.2±0.2	0.1±0.2	0.1±0.1
Day 11				
Amount of Time Spent Pivoting (Seconds)				
Males	10.25±5.55	8.77±4.26	6.82±2.86	8.71±3.60
Females	10.55±5.34	10.42±4.92	5.04±3.68[b]	7.00±3.41
Number of Exits from Circle				
Males	0.4±0.5	0.5±0.6	0.4±0.4	0.6±0.3
Females	0.5±0.7	0.4±0.5	0.6±0.5	0.7±0.6

[a]Activity measured during one minute interval; mean ± one standard deviation.

[b]$p < .05$

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As can be seen in the table above, amount of time spent pivoting appears to be increased at day 9 and decreased at day 11 in treated animals. The number of exits from the circle is slightly increased at the high dose level on both days for males. However, a dose relationship is not apparent; neither sex is consistantly affected and the standard deviation in both cases is relatively large. A relationship to treatment is not considered to have been demonstrated.

Core Classification: Core-Minimum Data

The NOEL for maternal toxicity appears to be 10 mg/kg. Based on an increased incidence of skeletal variations, the NOEL for fetotoxicity also appears to be 10 mg/kg. No clear indication of behavioral toxicity is evident in the post-natal phase. A teratogenic potential is not demonstrated in this study.

NOTE: The following study was reexamined during the course of this review due to fact that it is the only chronic feeding study available for endothall, after the invalidation of the IBT chronic rat. It had not been reexamined since its initial submission.

3. Two-Year Chronic Feeding, Dog. Conducted by Scientific Associates, report date and number unknown. Submitted by Pennsalt Corp. (now Pennwalt) on January 13, 1966.

Three male and 3 female purebred beagle dogs per dose level were allowed to consume ad libitum dose levels of 0, 100, 300 and 800 ppm disodium endothall (unspecified purity) for two years. The high dose level was increased to 2000 ppm from month 19 to 24. Animals were housed individually observed daily, and body weights recorded weekly. Hematology samples were taken during the quarantine. Total and differential white cell count, hemoglobin and hematocrit were measured. Clinical chemistry consisted of SGOT and BSF measurement. Urine analyses were performed during the quarantine period and at 6, 12, 18 and 24 months. Specific gravity, color, pH, acetone, reducing sugar, protein and microscopic examination of sediment were observed. All surviving dogs were sacrificed at 24 months via injection of pentobarbital sodium. Gross necropsy was performed on each animal and the brain, liver, kidney, spleen, gonad, thyroid, adrenal, heart, small intestine, caecum, colon and stomach were weighed. The following tissues were excised and fixed:

Brain	Heart	Colon
Spinal cord	Aorta	Pancreas
Femoral nerve	Spleen	Liver
Skeletal muscle	Thymus	Gall bladder
Pituitary	Bone marrow	Kidney
Thyroid	Salivary gland	Testis (Ovary)
Parathyroid	Stomach	Prostate (or Uterus)
Adrenal	Small intestine	Lymph nodes
Lung	Cecum	

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These tissues were microscopically examined for the control and high dose animals. Stomach, small intestine and colon were microscopically examined from the low and mid dose groups.

Results:

Neither summary nor individual animal data was presented in the Final Report. Only summary statements were available such as the following: "Hematological, liver function and urine analysis values for the dogs generally remained within normal limits and were comparable for the control dogs."

Core Classification:

Invalid. Upon submission of individual animal data and identification of the test compound, this study may be upgraded.

Gary J. Burin 5/26/83

Gary J. Burin, Toxicologist
Toxicology Branch/HED (TS-769)

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