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April 19, 1967

File: 9F0555

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Treflan (trifluralin (a,a,a-trifluoro-2,6-dinitro-N,N-dipropyl-p-toluidine).
0.05 ppm trifluralin in or on whole, unpeeled carrots.
0.05 ppm trifluralin in or on, whole unwashed cantaloupes and cucumbers.

PESTICIDE PETITION NO. 7F-0555

Elanco Products Company
Division of Eli Lilly & Co.
Indianapolis, Indiana
(AP 9-577)

Toxicity data of Treflan in support of the safety of a temporary tolerance of 0.05 ppm in or on sugar beets, Pesticide Petition No. 6F-0494 was evaluated in May 26, 1966 memorandum.

The following evaluation is of the completed long term studies referred to in the May 26, 1966 memorandum, some completed and the remainder in an interim status at that time.

Rat feeding study: Petitioner's Study No. 131-61.

Groups of Charles Strain rats, 5 of each sex were fed 0, 20, 200, 2000 and 20,000 ppm Treflan diets for 2 years.

Observations for effects included:

1. Growth
2. Mortality
3. Food intake
4. Food efficiency utilization
5. Hemograms including hematocrits, hemoglobin and erythrocyte counts.
6. Necropsy to search for compound related gross organ and tissue effects.
7. Microscopic examination of skeletal muscle, heart, lungs, liver, spleen, pancreas, salivary gland, thymus, thyroid, adrenal, mesenteric lymph node, GI tract and genitourinary system.

Results:

Rats consuming the 20,000 ppm Treflan diets were affected as revealed by decreased growth, food intake and food utilization. Slight focal bile duct proliferation was recorded in one of the 20,000 ppm rats that the petitioner relates to compound ingestion.

Effects were absent in the other diet groups. Two thousand ppm was

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...nstrated on a no-effect level.

Petitioner's rat feeding study No. K 62 031: Groups of Cox strain albino rats, 25 of each sex, were fed 0, 200, 1000 and 2000 ppm Treflan diets for ... years.

...tions for effects included:

1. Weekly weights.
2. Food consumption.
3. Necropsy of succumbing animals.
4. Hematology, at experiment termination of all survivors included hematocrits, hemoglobin, erythrocyte and leucocyte counts, leucocyte differential counts and prothrombin time.
5. Blood glucose and SGPT was measured in about ½ of the survivors.
6. Weights of liver, kidneys, heart, spleen, thyroid, adrenal, prostate and reproductive organs were determined.
7. Microscopic examination of specimens of heart, lung, liver, spleen, thymus, GI tract, genitourinary system, mammary gland, adrenal and thyroid from survivng rats.

...ults.

...mpound related influences were not revealed by the observations made. ...ese data demonstrate rats can consume 2000 ppm Treflan diets for two ... without effects.

Treflan dog studies: Petitioner's study No. ... 31-61: Groups of mongrel dogs, 1 of each sex were orally dosed 7 days a week at 2.5, 5 and 25 mg/kg rates for two years. Two females were similarly dosed at 10 mg/kg for two ...

...etailed observations including behavior, body weight, blood studies, ...inary function, organ weights, biochemical tests, gross and micro-...ple organ and tissue examination did not reveal compound related ...fluences.

...e female on 10 mg/kg was bred to a male on 25 mg/kg at the 17th ...th. Gestation was normal and 3 healthy pups were born; 3 ...lived to weaning.

Petitioner's study ... 3-19-62: Groups of purebred beagle dogs were ...ally dosed 0 mg/kg (2 of each sex), 1 mg/kg (2 of each sex), 2.5 mg/kg ... of each sex), 5 mg/kg (2 males) and 10 mg/kg (2 males) with Treflan for ...

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liver lesions not evident previously these were for the mongrel dog study. Effects were not revealed by observations made.

Petitioner's dog study No. H-24-63 (should be 63?) Groups of purebred beagle dogs were orally administered 0.4 mg/kg (3 of each sex), 10 mg/kg (3 of each sex) and [illegible] (3 of each sex) of Reilly for three years.

Observations for mortality were similar to those in the other dog studies.

Compound related changes in the 10 mg/kg group were described as centrilobular necrosis and a trend toward heavier livers.

Lipochrome pigment found in the livers of the Reilly dosed dogs was discounted as significant by the investigators. Disregarding the liver lipochrome pigment, 400 ppm can be judged as the no effect level in this study.

Justification for not considering the pigment as an effect, is based on this pigment being found in dogs livers without known cause, this pigment not associated with degenerative liver changes in the test dogs, this pigment not being found in the livers of the dogs in the two other long term feeding experiments and the lack of evidence of liver damage in rats fed 2000 ppm diets for two years.

The data demonstrates dogs can be dosed daily with 10 mg/kg of Reilly for three years without effect.

breeding experiments: Petitioner's dog study [illegible]. After approximately two years on the experiment each female was bred to a male within her group.

Rat No.	Dose Schedule	Number pups born M	Number pups born F	Number pups reared M	Number pups reared F	
[illegible]		3	0	3	0	
172	0	1	4	1	4	
170	0	3	2	3	2	
[illegible]						
[illegible]	400 ppm	4	2	4	2	
[illegible]	400 ppm	3	3	0	0	Accident at birth drowning & death fro exposure to col d wa
[illegible]	1000 ppm	2	1	2	1	
[illegible]	1000 ppm	[illegible]	[illegible]	2	3	1 male suffocated
[illegible]	1000 ppm	2	[illegible]	2	4	1 runt-dead-24 hrs.

reproduction studies:

[illegible] Groups of [illegible] strain rats, 6 males and 12 females per group were fed 0, 200 and 4000 ppm Treflan [illegible] in a 3-generation (2 litters each) reproduction study.

[illegible] (see next page)

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Reproduction Study Indexes

F_0 Generation

Indexes	Fertility		Gestation		Viability		Lactation	
Litters	a	b	a	b	a	b	a	b
Diet ppm								
0	93	100	96	13	66	55	94	85
200	73	100	90	92	73	63	100	85
2000	53	72	100	77	63	63	94	70

F_1 Generation

0	20	[illegible]	60	76	100	27	100	56
200	61	61	93	97	91	89	96	93
2000	60	57	100	100	71	76	95	99

F_2 Generation

0	43	100	68	93	35	77	15	90
200	73	73	91	100	60	96	72	96
2000	0	20	0	94	0	31	0	100

F_3 Generation

0	57	92	100	100	83	67	93	67
200	100	[illegible]	96	97	87	75	93	88
2000	100(*rat)	100(*rat)	100	100	92	100	100	92

* 1 rat

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F0 generation-continuous breeding

Intake	Fertility	Gestation	Viability	Lactation
[illegible] ppm				
0	7.7	[illegible]	77.[illegible]	89.1
200	64.3	94.0	90.7	85.1
2000	69.2	92.6	76.8	83.8

Approximate average of 8 litters each per female

Number of parent rats necropsied

[illegible]	1st	2nd	3rd	4th
[illegible] 0 ppm	6	3	12	4
[illegible] ppm	8	8	12	12
[illegible] ppm	1	9	[illegible]	11
[illegible] ppm	[illegible]	[illegible]	[illegible]	6
200 ppm	5	6	6	6
2000 ppm	[illegible]	6	[illegible]	3

Stillbirths

[illegible] ppm	0		200		2000	
	No. litters	No. still b.	No. litters	No. still b.	M.L	MSB
[illegible] No. litter	25	23	21	13	22	11
[illegible] No. litter	7	4	22	9	16	0
[illegible] No. litter	12	15	12	9	2	11
[illegible] No. litter	12	0	22	11	2	0
Original Parents continuous breeding	31	65	62	37	54	33

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Microscopic examination of skeletal muscle, heart, lungs, liver, spleen, pancreas, salivary gland, thymus, thyroid, adrenal, lymph node, [illegible] and genitourinary system of the parents of the offspring did not reveal compound related effects.

[illegible] weights of the liver, kidneys, thyroid, adrenals and salivary reproductive organs of the parent rats did not reveal compound influences.

This data demonstrates reproduction performance was uninfluenced during production of 3 generations with a 200 ppm treflan diet. The 2000 ppm diet was without influence for production of approximately 3 continuous litters in the original parent group.

Too few animals were bred in the 2000 ppm group for production of the third and fourth generation for a valid conclusion of possible effects. The lack of available females was related to environmental conditions. The petitioner related an episode of moving the experimental rats when the F1 females were pregnant for their second litters. As a consequence, only one 2000 ppm female was available for breeding for the fourth generation.

The petitioner described a change of quarters involving a 30 mile [illegible], followed by extreme inconsistency in heating temperatures from a heating system malfunction during severe winter weather.

Rabbit Teratology Study: Groups of mated New Zealand White does were [illegible] Treflan from the 6th thru the 18th day of pregnancy.

Treatment	No. pregnant	Viable pups	Dead pups	Resorption sites
Control	7	49	3	15
[illegible]/kg	7	47	9	2
[illegible]/kg	7	65	6	1
[illegible]/kg	7	33	10	24

On the 29th day of gestation the does were killed, fetuses removed and examined for viability and malformation and implantation sites were examined.

Visible signs of fetal malformation were not found except for 2 fetuses from one 225 mg/kg dose. Their appearance was described as underdeveloped hind legs and hind quarters. Four normal fetuses were part of the same litter.

The increased number of visibly dying and increased number of absorption sites in the 1000 mg/kg groups could not be related to the administered compound. Assuming they are related to compound effects, 100 mg/kg can be assigned as the no effect level.

Summary of investigations - no-effect levels:

2000 ppm, 2 year rat feeding studies.
200 ppm, 4 generation rat reproduction study.
2000 ppm, continuous breeding, approximately 4 litters from each female.
100 ppm, two, 2 year dog feeding studies.
20 ppm, one, three year dog feeding study.
500 ppm, dog breeding study.
100 mg/kg-rabbit teratology study.

CONCLUSION:

The petition data supports the safety of the requested residue tolerances.

Recommended:

cc: FDA
FFE
FOI
CIR (Y. Jacobson)
PP No. 7F-0533

Typed 4-19-67

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