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

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

FEB - 9 1995

#184

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Propazine; Request for Waiver of Chronic Dog Feeding Study (Guideline Requirement 83-1(b)); ID #: 285929; Griffin Corporation.

PC CODE : 080808
Tox.Chem No.: 184
MRID No.: None
DP Barcode No.: 206649
Submission No.: 471963

TO: Edward Allen, PM Team #25
Fungicide/Herbicide Branch
Registration Division (H7505C)

FROM: William Dykstra, Ph.D., Toxicologist
Review Section I
Toxicology Branch I
Health Effects Division (H7509C)
William Dykstra 1/31/95

THRU: Roger Gardner, Section Head, Toxicologist
Review Section I
Toxicology Branch I
Health Effects Division (H7509C)
Roger Gardner 2/7/95 KB 2/8/95

ACTION REQUESTED: The Griffin Corporation intends to support the reregistration of propazine, a canceled pesticide. In pursuit of the previously identified required studies, the Griffin Corporation requests the waiver of the chronic dog feeding study with propazine. Toxicology Branch (TB-I) has been requested to address this waiver request and recommend a conclusion to the Registration Division.

CONCLUSIONS: The chronic dog feeding study can be waived. TB-I has determined that toxicity data from a chronic dog study would probably not add any additional information necessary for an

adequate risk assessment for propazine. However, the uncertainty factor for the RfD for propazine should remain at 300 in the presence of a waived dog study. A comparison of the RfDs, the results of the 2-year rat feeding studies, and the results of the chronic dog feeding studies for atrazine, simazine, terbutryn, and propazine (minus the 1-year dog study), all of which are pesticides of the chlorinated s-triazine type, shows that the results of the 2-year rat feeding studies are the most sensitive endpoints and have been used to determine the RfDs and that the results of the dog studies are supportive evidence. Furthermore, the predominant finding in the 2-year rat studies for these pesticides is decreased body weight gain, which was also observed with propazine. Finally, the RfD for propazine will probably not change if the dog study requirement is waived, but the other studies required for reregistration remain in effect.

REVIEW: The results of the RfD, the 2-year rat studies and chronic dog feeding studies are summarized below.

Pesticide	**RfD** mg/kg/d	**UF**	**Rat Study** mg/kg/d	**Dog Study** mg/kg/d
Propazine	0.02	300	NOEL = 5 LEL = 50 Decr. Wt. Gn.	- - -
Atrazine	.035	100	NOEL = 3.5 LEL = 25 Decr. Wt. Gn.	NOEL = 4.95 LEL = 33.0 Dec. Wt. Gn. Sev. Syst Ef.
Simazine	.005	100	NOEL = .52 LEL = 5.3 Dec. Wt. Gn.	NOEL = 0.76 LEL = 3.64 Dec. Wt. Gn.
Terbutryn	.001	100	NOEL = 0.10 LEL = 15.0 Dec. RBC & Hb	NOEL = 10.0 LEL = 25.0 Sal. & Agita.

Structure-Activity Comparison of Chlorinated s-Triazines for Rat and Dog Studies			
Study	NOEL	LEL	Effects (Core Grade)
Terbutryn			
2-year rat	0.1	15	0.1, 15, 150 mg/kg/day: ↓ RBC's, HGB in females (tech.; minimum)
6-month dog	10	25	10, 25, 50 mg/kg/day: ↑ salivation, agitation (tech.; minimum)
Atrazine			
2-year rat	3.79	23	3.79, 23.01 mg/kg/day in ♀ Sprague-Dawley: decreased body weight gain (97% a.i.; minimum)
2-year rat	3.5	25	0.5, 3.5, 25, 50 mg/kg/day in ♀ Sprague-Dawley: decreased body weight gain (98.9% a.i.; minimum)
2-year rat	3.43	9.87	0.49, 3.43, 9.87, 20.47 mg/kg/day in males; females a little higher: decreased body weight gains (♂+♀; 97% a.i.; guideline)
1-year dog	4.95	33	0.48, 4.97, 33.65 mg/kg/day: death, cachexia, ascite, ↓ body weight and body weight gains, ↓ food consumption, irregular heart beats, ↑ heart rate, ↓ P-II value, atrial premature complexes & atrial fibrillation, cardiac lesions (dilation of atria and atrial degeneration (97% a.i.; minimum)
3-month dog	< 5	5	5, 15.8, 50 mg/kg/day: ↓ body weight gain (♂); at 15.8 and above in ♂, sl. ↓ RBC, HCT, HGB plus a mild to total arrest of spermatogenesis; at 50, ↓ food consumption (♂) and ↓ body weight, ↓ food consumption, sl. ↓ RBC, HCT, HGB (♀) (tech.; supplementary)

Structure-Activity Comparison of Chlorinated s-Triazines for Rat and Dog Studies			
Study	NOEL	LEL	Effects (Core Grade)
Simazine			
2-year rat	0.52	5.34	0.41, 4.17, 45.7 mg/kg/day in males; 0.52, 5.34, 63.1 mg/kg/day in females: decreased body weight gains, decreased RBC, HGB, HCT in females; at 45.7 mg/kg/day, decreased body weights in males (97.5% a.i.; minimum)
1-year dog	0.76	3.64	0.68, 3.41, 42.9 mg/kg/day (♂); 0.76, 3.64, 44.9 mg/kg/day (♀): decreased body weight gain, decreased RBC, HGB, HCT (♀); at 42.9 mg/kg/day, decreased body weight gain and decreased (reversible) RBC, HCT (♂) (97.5% a.i.; minimum)
13-week rat	< 10	10	20, 100, 200 mg/kg/day: ↓ RBC (♂+♀), ↓ leucocytes (♀), ↑ cholesterol, inorganic phosphate (♂+♀), renal calculi in 3/20 (♂+♀). Seriously affected nutrition of treated rats (97.5% a.i., supplementary)
13-week dog	5	50	5, 50, 100 mg/kg/day: ↓ albumin and ↑ globulin levels (♂), ↑ urinary specific gravity (♂) and ketone levels. Seriously affected nutrition of treated dogs (97.5% a.i., minimum)
Propazine			
2-year rat	5	50	0.15, 5, 50 mg/kg/day: decrease in body weight (Tech., minimum)
3-month dog	5	25	1.25, 5, 25 mg/kg/day: body weight loss (Propazine 80W, no Core Grade, 1 paragraph DER, hematology, plasma biochemistry, liver function tests, urinalysis, gross and microscopic examinations and organ weights measured. No other details).

Structure-Activity Comparison of Chlorinated s-Triazines for Rat and Dog Studies			
Study	NOEL	LEL	Effects (Core Grade)
3-month rat	10	50	2.5, 10, 50 mg/kg/day: decrease in body weight gain, hyperirritability to handling during 8th and 11th weeks, 1 female death (Propazine 80W, no Core Grade, 1 paragraph DER, hematology, plasma biochemistry, liver function tests, urinalysis, gross and microscopic examinations and organ weights measured. No other details).

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Chemical:	**Propazine (ANSI)**
PC Code:	**080808**
HED File Code	***11000 Greybeard Reviews***
Memo Date:	**02/09/95**
File ID:	**DPD206649**
Accession Number:	**412-02-0005**

HED Records Reference Center
10/25/2001