BB-125
TXR-707

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

000707

JUL 15 1981

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: July 10, 1981

SUBJECT: EPA Reg.#707-145; Goal 2E Herbicide; Response to Proposed Testing Requirements presented in Position Document 1/2/3
CASWELL#188AAA Accession#245398

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

WJD for LDC 7/10/81 CFC 7/15/81

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

Jolene Chinchilli
Special Pesticides Review Division (TS-791)

Amy Rispin, Ph.D
Hazard Evaluation Division (TS-769)

Recommendations:

1. The review of the final report of the 2-year dog feeding study indicates that the low-dose of 100 ppm can be considered the NOEL for the study.

2. Toxicology Branch defers comment on the data submitted with regard to the mouse and rat oncogenicity studies requested in the Oxyfluorfen PD 1/2/3 to Dr. Bernard Haberman of the Cancer Assessment Group (RD-689). Following the comments of CAG, Toxicology Branch will further address these issues.

3. Toxicology Branch defers comment on the protocols submitted with regard to mutagenicity studies requested in the Oxyfluorfen PD 1/2/3 to Dr. Vicci Dellarco of the Reproductive Effects Assessment Group (RD-689).

175

Review:

Item #2: Goal Teratogenic Toxicity: The submitted protocol of the rabbit teratology study is acceptable.

Item #3: Goal Mutagenic Toxicity: Deferral to Reproductive Effects Assessment Group (RD-689).

Item #4: Goal Oncogenicity Toxicity: Deferral to Cancer Assessment Group (RD-689).

Item #5: Goal Chronic Dog Toxicity Study:

a) 104-Week Toxicity Study in Dogs with RH 2915 (Final Report, Hazelton Project No. 417-367, April 9, 1981.

Draft report reviewed in memo of 10/30/80 from William Dykstra to Richard Mountfort.

Materials and Methods: Same as draft report.

Results:

Evaluation of the final report revealed that exposure of dogs to RH 2915 resulted in significant decreased hemoglobin, hematocrit and

RBC values in dogs fed RH 2915 at the highest dietary level. Total protein values were also significantly decreased at this level. Elevation of absolute organ weights and organ to body weight ratios showed that the absolute liver weights and liver to body weight ratio were significantly increased in dogs fed Rh 2915 at the mid- and high-dose levels. Alkaline phosphate was also significantly elevated in the mid- and high-dose groups.

Microscopic evaluation of the tissues of dogs sacrificed after fifty-two weeks of treatment were unremarkable. After 104-weeks, histopathological examination revealed renal tubular epithelial vacuolization which was increased in the high-dose males in comparison to controls.

Lymphocytic thyroiditis, frequently with follicular atrophy and/or C-cell hyperplasia was present in control and treated dogs at similar degrees. Minimal to moderate bile pigmented hepatocytes were observed in animals at the mid- and high-dose at significant degrees in comparison to controls. A comparision of the incidence of bile-pigmented hepatocytes, other histological findings and clinical parameters indicate that at the low-dose level no effects were observed which could clearly be related to treatment.

2

Conclusion:

These data show that feeding RH-2915 to dogs produced definite effects at the mid- and high-dose levels. These data also indicate that the NOEL for the study can be considered to be 100 ppm (low-dose).

Classification: Core-Minimum Data

TABLE I
Bile Pigmented Hepatocytes - 104-Weeks

Dosage	MALES No. Affected/No. Dogs (grades of lesion)	FEMALES No. Affected/No. Dogs (grades of lesion)
Control	2/8 (1, 3)	1/8 (1)
100 ppm	3/4 (1, 1, 1)	1/4 (1)
600 ppm	4/4 (1, 1, 2, 2)	4/4 (1, 1, 2, 2)
2000 ppm	4/4 (1, 2, 2, 3)	4/4 (3, 3, 3, 3)

TS-769:th:TOX/HED:WDykstra:7-10-81:card 3

Test for Significance of Differences Between Proportions 7/10/81

Liver [illegible] *Male Dogs* 000707

	[illegible]	Total	% +/-2(S.E.)	One Tail P Statistic Yuan's
[illegible]	[illegible]	[illegible]	25.00+/-([illegible])	
[illegible]	[illegible]	[illegible]	75.00+/-([illegible])	0.152
[illegible]	[illegible]	[illegible]	100.00+/-(12.50)	0.050
[illegible]	[illegible]	[illegible]	100.00+/-(12.50)	0.050

[illegible] Linear Trend in Proportions P = 0.023

BEST AVAILABLE COPY

4

Test for Significance of Differences Between Proportions

Female Dogs

000707

[illegible]	# Resp	Total	% +/-2(S.D.)	One Tail P Statistic Fisher's
[illegible]	1	[illegible]	[illegible]+/-(29.17)	
100.[illegible]	1	[illegible]	[illegible]5.00+/-(54.94)	0.576
[illegible]	[illegible]	[illegible]	[illegible]+/-(12.50)	0.01[illegible]
[illegible]	[illegible]	[illegible]	[illegible]+/-([illegible])	0.01[illegible]

Test for [illegible] in Proportions P = 0.00[illegible]

BEST AVAILABLE COPY

5