GS-123
TR-2621

3/22/83

Oxyfluorfen
Caswell No. 188AAA
Accession No. 248728

TOXICOLOGY BRANCH
DATA REVIEW

002621

3-Months Dietary Toxicity Study in Mice Rohm & Hass Co.
Report No. 82R 12, 10-28-82.

Test Material: Oxyfluorfen, Goal, Technical (RH-2915) 72.5% a.i.

Test Animals: Charles River CD-1 mice.

Purpose: This study was requested to estimate the maximum tolerated dosage level (MTD), which was needed for evaluating the adequacy of the highest dosage level used in the 20-months oncogenicity mouse study previously submitted.

Experimental Design

Group	Dose (ppm) in diet)[a]	No. of Mice M	F	Laboratory Studies Week 13[b]		Post Mortem. Exam
1	0	15	15	10M,	10F	All
2	200	15	15	10M,	10F	All
3	800	15(1)c	15	10M,	10F	All
4	3200	15(9)c	15(2)	10M,	10F	All

a Concentration of active ingredient.
b Urinalysis performed during week 11 and 13.
c Deaths are shown in parenthesis. The death at 800 and not considered to be treatment related.

Mortality

	Males	Females
At 800 ppm	7%	0%
At 3200	67%	13%

Test material toxicity was shown at all dose levels. Deaths were related to treatment only at the highest dosage, 3200 ppm.

Neither the 200 or 800 ppm level was demonstrated to shorten life span.

Body weight loss: Decreases in body weight gain after 3-months was not found at any dosage level.

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Hematology:

Hematological effects at 13 weeks, from Goal, were seen at all dose levels, 200, 800, and 3200 ppm. These were dose related decreases in hemoglobin, hematocrit, red blood cell count and lymphatic count, also dose related increases in platelet count and segmented neutrophils. Some examples follow:

Platelet Increases Relative to Controls

Group ppm	Males %	Females %
200	9.5	23.4
800	28.9	45.6
3200	102.0	94.9

Hemoglobin Decreases Relative to Controls

Group ppm	Males %	Females %
200	10.4	3.3
800	13.6	8.9
3200	30.0	24.8

The white blood cell count was little changed for the females at the 200 and 800 ppm levels, but increased to 153% relative to controls at 3200 ppm. No monocytes were detected at the 3200 ppm level for males or females. Abnormal red blood cells were found at the 3200 ppm level in males and at th. 800 and 3200 ppm level in females.

Clinical Chemistry:

Changes in clinical chemistry values were seen at all dose levels, 200, 800, and 3200 ppm. Enzyme increases appeared to be those which might be related to tissue repair.

See following tabulation.

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Clinical Chemistry Values form Rohm & Hass

	0		200 ppm		800 ppm		3200 ppm	
	M	F	M	F	M	F	M	F
SGPT	47.44	17.30	36.70	68.30	215.00	127.60	606.00	270.60
Alk	40.38	52.00	38.70	49.30	112.70	108.50	748.40	566.70
BUN	51.70	38.83	60.46	37.80	47.49	49.93	46.00	56.16
GLU	143.00	101.40	143.10	104.60	124.20	94.40	81.20	84.20
T Prot	5.15	4.84	5.49	5.01	5.54	5.29	7.02	6.64
Alb	2.86	3.03	2.88	3.02	2.99	2.98	3.54	3.66
Glob	2.29	1.81	2.61	1.99	2.55	2.31	3.48	2.98
A/G	1.26	1.86	1.13	1.54	1.23	1.30	1.02	1.23
Chol	92.25	55.70	101.20	86.50	162.40	136.50	352.40	324.70
G-GT	00	00	00	00	.40	.44	59.60	12.10
Creat	.47	.44	.49	.44	.48	.51	.58	.52

Key to Clinical Chemistry Parameters

SGPT - Serum Glutamic Pyruvic Transaminase (international units per liter)

Alk - Alkaline Phosphatase (international units per liter)

BUN - Blood Urea Nitrogen (mg per deciliter)

GLU - Glucose (mg per deciliter)

T Prot - Total Protein - (g per deciliter)

Alb - Albumin (g per deciliter)

Glob - Globulin (g per deciliter)

A/G - Albimin/Globulin ratio

Chol - Cholesterol (mg per deciliter)

G-GT - Gamma Glutamyl Transpeptidase (units per liter)

Creat - Creatinine (mg per deciliter)

Urinalysis:

Ketonuria was found in females at all dose levels. Urine was dark in color. Darkening was dose related.

Gross Necropsy:

No compound related gross abnormalities were reported.

Relative Organ Weights:

Relative weights of those organs which were much different from controls are shown in the tabulation below. Only the relative weight changes for the livers were large for dosages less than 3200 ppm. The relative weight changes for livers compared to controls were + 62.0% for the 800 ppm dosage group and 242% for the 3200 ppm group.

3-Month Mouse Feeding Study

Relative Organ Weights and Percent Differences from Controls

	Control Rel. Wt.	200 ppm Rel. Wt.	%	800 ppm Rel. Wt.	%	3200 ppm Rel. Wt.	%
Males:							
Adrenals	1.339	1.535	+14.6	1.464	+ 9.3	1.611	+29.0
Gonads	75.3	73.2	- 2.8	70.7	- 6.1	64.0	-15.0
Liver	455	558	+22.6	743	+63.3	1704	+274
Spleen	24.20	41.94	+73.3	26.66	+10.2	35.74	+47.7
Females:							
Adrenals	4.357	4.671	+ 7.2	4.298	- 1.4	3.092	-29.0
Gonads	14.90	14.62	- 1.9	13.94	- 6.4	10.00	-99.3
Liver	469	510	+ 8.7	761	+62.0	1608	+242
Spleen	31.79	32.27	+ 1.5	31.84	+ 0.2	48.72	+53.2

Histopathology:

In the table below are presented data showing changes which may be treatment related. Some lesions appear only in the highest dosage group (3200 ppm), these include vacuolationof adrenal cortex in males, atrophy and congestion of bone marrow in females, atrophy and focal necrosis in spleen, and atrophy in thymus. Other lesions appear to be dose related but much more severe in the highest dosage group. Still others appear to be treatment related but not dose related, as diffuse hepatocytic hypertrophy, single cell necrosis, hypersiderosis, and centrilobular vacuolation, all in the liver.

Rohm and Hass 3-Month Mouse Feeding Study
Incidence of Histomorphologic Observations
(Values Excepted from Rohm and Hass Report)

ose Group (ppm)	0	200	800	3200	0	200	800	3200
ex:	M	M	M	M	F	F	F	F
drenal Glands:								
vacuolation, cortex	0	0	0	2	0	0	1	12
one Marrow:								
hyperplasia	3	11	10	9	0	0	6	12
atrophy	0	0	0	0	0	0	0	2
congestion	0	0	0	0	0	0	0	1
iver:								
diffuse hepatocytic hypertrophy	0	7	15	15	0	13	15	12
single-cell necrosis	0	0	10	8	0	6	6	11
focal necrosis	0	2	5	7	3	1	3	2
hemosiderosis	0	4	14	5	0	13	23	13
bile ductule proliferation	0	0	0	5	0	0	0	13
centrilobular hepatocytic vaculation	0	1	3	0	0	2	10	1
pleen:								
atrophy	0	0	0	5	0	0	0	2
focal necrosis	0	0	0	0	0	0	0	1
red pulp hyperplasia	0	5	5	6	1	0	1	9
hymus:								
atrophy	0	0	0	7	0	0	0	3
rinary Bladder:								
mucosal hyperplasia	0	0	3	12	0	1	1	13

Conclusion:

Treatment effects were demonstrated at all dosage levels.

Conclusions on maximum tolerated-dose (as related to acceptability of dose levels for oncogenicity testing) is deferred to William Dykstra who requested this study.

Core Classification: Minimum.

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3-22-83

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Oxyfluorfen
Caswell No. 188AAA
Accession No. 248728

TOXICOLOGY BRANCH
DATA REVIEW

3-Months Dietary Toxicity Study in Rats Rohm & Haas Co.
Report No. 82R-62, 10-26-82.

Test Material: Oxyfluorfen, Goal, Technical (RH-2915) 72.5% a.i.

Test Animals: Long Evans Rats

Purpose: This study was requested to estimate the maximum tolerated dosage level (MTD), which was needed for evaluating the adequacy of the highest dosage level used in the 20-months oncogenicity rat study previously submitted.

Experimental Design

Group	RH-2915 (Goal - tech.) ppm[a] Weeks 1-2	Weeks 3-4	Weeks 5-13	Number of Rats M	F	Laboratory Studies[b] Weeks 4 and 13	Post Mortem Examination
1	0	0	0	15	15	10 M, 10 F	All
2	400	560	800	15	15	10 M, 10 F	All
3	800	1,120	1,600	15(1)[c]	15	10 M, 10 F	All
4	1,600	2,240	3,200	15(2)[c]	15	10 M, 10 F	All

[a]Concentration of active ingredients.
[b]Urinalysis performed during week 11 only.
[c]Deaths are shown in parenthesis.

Body Weight and Food Consumption:

Body Weight Loss

	Males	Females
At 800 ppm	6%	0%
At 1600 ppm	13%	3%
At 3200 ppm	21%	7%

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Body weights and food consumption decreased in males at all dose levels. Food consumption did not decrease in females and female decrease in body weight was slight (significant only at the highest dosage).

Hematology

Several hematological parameters decreased in a dose related manner. The decrease was more pronounced at the 1600 and 3200 ppm dosage levels, as shown in the following tabulation. The platelet count increased at the 800 ppm level (+ 11.5%) then decreased at higher levels.

Percentage Decreases of some Hematological Values

Dosage	HBG		HCT		RBC		Platelet Count	
(ppm)	M	F	M	F	M	F	M	F
1600	9.1	5.1	11.9	3.9	7.0	-	11.7	12.0
3200	19.3	11.5	21.3	8.7	11.7	-	15.8	10.8

Clinical Chemistry:

Several clinical parameters changed with treatment as shown in the following tabulation. Values are percentage differences from controls.

Treatment Effects on Clinical Chemistry Values
Percentage Differences from Controls

Dosage	SGPT		ALK	BUN	GLU	CHOL	
(ppm)	M	F	M	M	M	M	F
800	17.1	-3.3	9.5	21.4	- 1.8	-2.3	10.8
1600	27.4	-6.0	21.8	27.1	- 6.5	11.1	26.5
3200	31.1	6.1	32.3	20.8	-12.1	33.4	39.1

Also it was noted that gama glutamyl transpeptidase increased from 0.00 to 0.50 for males and 0.00 to 0.98 for females at the 3200 ppm level.

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Urinalysis:

Urinary specific gravity was decreased in females at all dosages and in males at 1600 and 3200 ppm.

Gross Pathology:

No compound related gross abnormalities were reported.

Organ Weights:

Dosage related increases were found. Note changes in relative organ weights as percent of controls for liver, kidney and adrenals. A copy of the table of mean absolute and relative organ weights as per cent of controls follows.

Histopathology:

Liver: Treatment related microscopic changes were seen in males at all treatment levels, but in females only at the highest dosage level (3200 ppm). Lesions observed were predominantly diffuse hepatocellular hypertrophy. Centrilobular hepatic necrosis was observed in three high dosage males. Vacuolization was seen in one of these.

Adrenals: Hypertrophy of cells in the zona glomerulosa of the cortex was seen in all treated rats. Severity was dose related.

Kidneys: Focal areas of basophilic cortical tubules of renal cortex were found in eight high dose males. Pilation of collecting tubules was seen in 4 males and one female of the highest dosage group. Focal papilites and focal interstitial edema were also seen in high dosage rats.

Spleen: Hyperplasia was seen in spleens of males (1600 and 3200 ppm).

Bone Marrow: Hyperplasia of bone marrow was seen in 1600 and 3200 ppm males and in 3200 females.

FH-2315 (GUM TECH) 3 MONTH DIETARY TOXICITY STUDY IN RATS
PROTOCOL NO. 318-306
REPORT NO. 326-62

TABLE 12 MEAN ABSOLUTE ORGAN WT. AS % OF CONTROL MEAN

GROUP	DOSE PPM	BODY WEIGHT	ADRENALS	BRAIN	GONAD	HEART	KIDNEYS	LIVER	SPLEEN	THYMUS
MALE										
2	800	93.9	83.4	96.6	96.3	92.1	96.2	117.1	92.0	88.8
3	1,600	86.3	79.3	100.2	101.2	86.5	97.7	120.3	93.7	91.2
4	3,200	73.2	83.1	99.4	97.1	82.0	93.3	121.8	90.8	88.5
FEMALE										
2	800	101.8	106.3	100.1	100.5	93.1	102.4	103.2	106.6	95.7
3	1,600	97.1	104.3	99.1	102.0	91.5	97.9	111.0	95.4	99.9
4	3,200	91.9	107.9	99.3	93.7	91.5	109.6	124.5	105.4	96.3

MEAN RELATIVE ORGAN WT. AS % OF CONTROL MEAN
RELATIVE = ORGAN WEIGHT X 10,000 / BODY WEIGHT

GROUP	DOSE PPM	ADRENALS	BRAIN	GONAD	HEART	KIDNEYS	LIVER	SPLEEN	THYMUS
MALE									
2	800	88.3	102.9	102.8	98.1	102.3	124.7	97.6	93.2
3	1,600	93.1	117.1	113.1	100.9	113.7	139.6	104.4	101.6
4	3,200	105.7	123.9	124.4	105.1	119.3	156.0	115.8	97.8
FEMALE									
2	800	105.1	97.9	99.1	95.7	100.6	106.4	104.1	85.0
3	1,600	103.4	101.6	105.0	94.0	101.0	112.7	97.	103.0
4	3,200	116.7	107.5	102.2	99.2	118.3	135.7	114.9	106.2

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Conclusion:

Treatment effects were demonstrated at all dosage levels.

Conclusions on maximum-tolerated-dose (as related to acceptability of dose levels for oncogenicity testing) is deferred to William Dykstra who requested this study.

Core Classification: Minimum

W Thomas Edwards

Unsatisfactory 3-22-83

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Oxyfluorfen
Caswell No. 188AAA
Accession No. 248728

TOXICOLOGY BRANCH
DATA REVIEW

13-Weeks Dietary Toxicity Study in Rats Normura Research Instutite, 1981 with review and abstract by S. S. Burke of Rohn and Hass, 1982.

Test Material: Oxyfluorfen, Technical Grade (Lot 2-3985, Rohm and Hass) 72%.

Test Animals: Rats from Japan Charles River Co., CRJ-CDF strain.

Purpose: This study was furnished by Rohm and Hass as supplementary support for estimating a MTD.

Experimental Design

Compound	Dose (ppm)	Sacrifice after 90 day-administration
Control	0	male, female rats 10 each
Oxyfluorfen	200	male, female rats 10 of each
	1000	male, female rats 10 of each
	5000	male, female rats 10 of each

Mortality: It was stated that no mortality was observed.

Body Weight Decreases

	Males	Females
At 200 ppm	6%	4
At 800 ppm	6%	11%
At 3200	25%	17%

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Hematology

Decreases were found in the red blood cell counts, hematocrits, and hemoglobin in males and females as compared to controls. These were greater in the 5000 ppm group but also occurred to a lesser extent at the 1000 ppm level. A large decrease in segmented neutrophils was found in females of the 5000 ppm level.

Increases compared to controls were seen in the numbers of oversized red blood cells. Also an increase of reticutocytes was found in males at the 5000 ppm level. Percentage changes as compared to controls are tabulated below.

Percentage Differences Compared to Controls

	1000 ppm		5000 ppm	
	Males	Females	Males	Females
RBC		-7.4%	-19.2%	-17.0%
Ht	-1.6%	-4.1	-10.2	- 8.7
Hb		-3.1	-11.0	- 9.1
MCH			+ 8.7	
MCV			+11.2	+ 9.0
Lympho				+ 9.9
Seg.				-41.7
Reticulo.			+31.1	

Clinical Chemistry

Several values appear treatment related. Dose dependence is less obvious. Tabulated values on the following pages were copied from the Rohm and Haas report.

Urinalysis

No meaningful differences between groups were reported.

Necropsy

Dark brown coloration of livers and/or kidneys were seen in several animals as indicated by the following tabulation.

	1000 ppm		5000 ppm	
	Males	Females	Males	Females
Liver	3/10	1/10	10/10	3/10
Kidney	2/10	8/10	10/10	10/10

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SERUM BIOCHEMICAL FINDINGS IN MALE RATS FED OXYFLUORFEN FOR 3 MONTHS.

COMPOUND:	OXYFLUORFEN			
DOSE (PPM)	0	200	1000	5000
NO. OF ANIMALS	10	10	10	10
GOT (IU/L)	155. ± 42.	111. ± 16. +	125. ± 25.	116. ± 14. +
GPT (IU/L)	83. ± 19.	45. ± 4.**	54. ± 14.**	67. ± 14. *
ALP (IU/L)	221. ± 21.	223. ± 36.	215. ± 41.	260. ± 35.**
LDH (IU/L)	1535. ± 434.	1571. ± 235.	1764. ± 347.	1600. ± 419.
CHE (U/L)	884. ± 108.	903. ± 107.	960. ± 170.	870. ± 122.
CHO (MG/DL)	57.3 ± 3.4	53.3 ± 5.4	50.4 ± 4.5**	55.4 ± 4.2
TG (MG/DL)	135. ± 32.	141. ± 49.	114. ± 27.	82. ± 20.**
GLU (MG/DL)	209. ± 22.	178. ± 25.**	182. ± 22. *	195. ± 31.
T.P. (G/DL)	7.23 ± 0.15	7.30 ± 0.10	7.50 ± 0.22**	7.42 ± 0.29
ALB (G/DL)	4.35 ± 0.14	4.36 ± 0.11	4.46 ± 0.13	4.48 ± 0.19
A/G	1.51 ± 0.09	1.46 ± 0.08	1.48 ± 0.11	1.52 ± 0.11
BIL (MG/DL)	0.23 ± 0.01	0.23 ± 0.03	0.30 ± 0.22	0.20 ± 0.02**
UREA-N (MG/DL)	21.2 ± 1.2	19.0 ± 1.1**	21.3 ± 2.6	25.0 ± 1.9**
NA (MEQ/L)	142. ± 2.	142. ± 1.	143. ± 1.	144. ± 1.**
K (MEQ/L)	3.9 ± 0.3	4.2 ± 0.4	4.1 ± 0.3	4.0 ± 0.5
CL (MEQ/L)	100. ± 2.	101. ± 1.	101. ± 2.	101. ± 2.

THE VALUES WERE EXPRESSED AS MEAN ± S.D.

* P<0.05, ** P<0.01 SIGNIFICANT DIFFERENCE FROM CONTR (STUDENT'S T-TEST)
+ P<0.05, ++ P<0.01 SIGNIFICANT DIFFERENCE FROM CONTR (ASPIN-WELCH'S T-TEST)

SERUM BIOCHEMICAL FINDINGS IN FEMALE RATS FED OXYFLUORFEN FOR 3 MONTHS.

COMPOUND	OXYFLUORFEN			
DOSE (PPM)	C	200	1000	5000
NO. OF ANIMALS	10	10	10	10
GOT (IU/L)	95. ± 12.	93. ± 15.	90. ± 13.	93. ± 18.
GPT (IU/L)	42. ± 7.	35. ± 6. *	34. ± 3. *	32. ± 3.**
ALP (IU/L)	218. ± 34.	199. ± 38.	211. ± 26.	208. ± 26.
LDH (IU/L)	725. ± 209.	665. ± 123.	671. ± 350.	856. ± 436.
CHE (U/L)	4610. ± 539.	4346. ± 524.	4394. ± 569.	2809. ± 304.**
CHO (MG/DL)	73.5 ± 4.6	69.5 ± 5.1	71.5 ± 4.9	80.4 ± 7.0 *
TG (MG/DL)	84. ± 19.	73. ± 15.	71. ± 10.	69. ± 8.
GLU (MG/DL)	195. ± 8.	191. ± 11.	195. ± 10.	180. ± 9.**
T.P. (G/DL)	6.79 ± 0.28	6.86 ± 0.33	6.89 ± 0.30	7.13 ± 0.19**
ALB (G/DL)	4.19 ± 0.16	4.13 ± 0.16	4.14 ± 0.14	4.31 ± 0.12
A/G	1.61 ± 0.07	1.52 ± 0.07**	1.52 ± 0.09 *	1.53 ± 0.05**
BIL (MG/DL)	0.16 ± 0.02	0.20 ± 0.08	0.15 ± 0.02	0.18 ± 0.02
UREA-N (MG/DL)	19.5 ± 1.1	20.3 ± 2.1	19.5 ± 1.8	22.9 ± 2.6**
NA (MEQ/L)	140. ± 1.	141. ± 1.	140. ± 3.	141. ± 1.
K (MEQ/L)	3.6 ± 0.2	3.9 ± 0.3 *	3.7 ± 0.5	3.5 ± 0.1
CL (MEQ/L)	104. ± 1.	104. ± 1.	105. ± 1. *	103. ± 1.

THE VALUES WERE EXPRESSED AS MEAN ± S.D.

* P<0.05, ** P<0.01 SIGNIFICANT DIFFERENCE FROM CONTROL (STUDENT'S T-TEST)
* P<0.05, ** P<0.01 SIGNIFICANT DIFFERENCE FROM CONTROL (ASPIN-WELCH'S T-TEST)

Irregular reddish local hexatic lesions were seen in three males. One at the 1000 ppm level and two at the 5000 ppm level.

No other remarkable differences were found.

Organ Weights

The percentages compared to controls of several, statistically significant, relative weights of organs are tabulated below:

	1000 ppm		5000 ppm	
	Males	Females	Males	Females
Thyroid	+18.0%		+24.0	
Thymus	- 9.9		-18.2	
Liver	+10.8		+33.7	+31.7
Adrenals			+ 8.8	+20.7

Increases in relative weights of liver, adrenals and thyroid were dosage dependent. Decreases in relative weight of thymus was dosage dependent.

As expected the largest increases were in liver weights.

The author postulated that thymus changes were adrenal hormone dependent.

Histopathology

Dosage related lesions were found in livers and kidneys. Histopathological changes in the adrenals were seen only in the highest dosage male group.

See tabulation, excepted from Rohm and Haas, shown on next page.

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HISTOPATHOLOGICAL FINDINGS IN RATS FED OXYFLUORFEN FOR 3 MONTHS

COMPOUND		OXYFLUORFEN															
DOSE (PPM)		0				200				1000				5000			
NO. OF ANIMALS		10				10				10				10			
FINDINGS	GRADE*	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3
Males																	
LIVER																	
CONGESTION		10	0	0	0	10	0	0	0	9	0	1	0	8	0	2	0
SWELLING OF HEPATIC CELLS		10	0	0	0	10	0	0	0	6	4	0	0	0	5	5	0
FAT DEPOSITION		10	0	0	0	10	0	0	0	6	4	0	0	0	10	0	0
YELLOW OR BROWN PIGMENTS DEPOSITION		10	0	0	0	10	0	0	0	10	0	0	0	4	6	0	0
KIDNEY																	
CALCIUM DEPOSITION		10	0	0	0	10	0	0	0	0	2	0	0	2	4	4	0
VACUOLAR DEGENERATION OF DISTAL TUBULI		10	0	0	0	10	0	0	0	10	0	0	0	7	3	0	0
HYPERTRO. & HYPERPLA. OF TRANSITIONAL EPITHEL.		10	0	0	0	10	0	0	0	5	5	0	0	0	8	2	0
YELLOW PIGMENT IN TUBULAR EPITHERIA & LUMENS		10	0	0	0	8	2	0	0	2	6	2	0	0	4	6	0
ADRENAL																	
FINE VACUOLATION		10	0	0	0	10	0	0	0	10	0	0	0	6	4	0	0
Females																	
LIVER																	
CONGESTION		10	0	0	0	10	0	0	0	10	0	0	0	10	0	0	0
SWELLING OF HEPATIC CELLS		10	0	0	0	10	0	0	0	10	0	0	0	8	2	0	0
FAT DEPOSITION		6	4	0	0	4	6	0	0	6	4	0	0	6	4	0	0
YELLOW OR BROWN PIGMENTS DEPOSITION		10	0	0	0	10	0	0	0	10	0	0	0	10	0	0	0
KIDNEY																	
CALCIUM DEPOSITION		10	0	0	0	10	0	0	0	2	7	1	0	2	6	2	0
VACUOLAR DEGENERATION OF DISTAL TUBULI		10	0	0	0	7	3	0	0	4	6	0	0	1	2	7	0
HYPERTRO. & HYPERPLA. OF TRANSITIONAL EPITHEL.		10	0	0	0	10	0	0	0	2	8	0	0	0	8	2	0
YELLOW PIGMENT IN TUBULAR EPITHERIA & LUMENS		10	0	0	0	7	3	0	0	4	5	1	0	0	5	5	0
ADRENAL																	
FINE VACUOLATION		10	0	0	0	10	0	0	0	10	0	0	0	10	0	0	0

* DEGREE OF HISTOLOGICAL CHANGES : (0) NO LESION, (1) SLIGHT, (2) MODERATE AND (3) MARKED.
NO REMARKABLE FINDINGS IN CEREBRUM, CEREBELLUM, HEART, SPLEEN, OVARY, UTERUS STOMACH, DUODENUM, COLON, PANCREAS, LYMPH NODE, BONE MARROW, MAMMARY GLAND, SUBMAXILLARY GLAND AND SKIN.

Conclusion:

Treatment effects were demonstrated at all dosage levels.

Conclusions on maximum-tolerated-dose (as related to acceptability of dose levels for oncogenicity testing) is deferred to William Dykstra, in response to whose concern this study was submitted.

Core Classification: Supplementary

W Thomas Edwards

3-12-83

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TELEPHONE (215) 592-3000

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ROHM AND HAAS COMPANY

November 3, 1982

Mr. Richard F. Mountfort
Product Manager (23)
Fungicide-Herbicide Branch
Registration Division (TS-767)
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Dear Mr. Mountfort:

Subject: GOAL(R) 2E Herbicide (707-145)
Subchronic Toxicology Studies
Avian Reproduction Studies
Your Letter of September 14, 1982

The attached data binders contain the results of toxicology studies that we agreed to conduct as conditions for the continued registration of GOAL herbicide. These studies were requested in your letter of September 14, 1981. The binders (3 copies of each) include the following items:

1. a. 3-Month Dietary Toxicity Study in Rats
   b. 3-Month Dietary Toxicity Study in Mice
   c. 13-Week Dietary Toxicity Study in Rats - Nomura Research Institute

2. a. One Generation Reproduction Study in Mallard Ducks
   b. One Generation Reproduction Study in Bobwhite Quail

These studies specifically addressed several questions raised in your September 14 letter. The subchronic rat and mouse studies confirm that the dose levels used in previously submitted chronic studies were near the maximum tolerated dose. The avian studies are repeat studies which answer concerns raised by the Agency during their review of previously submitted reproduction studies.

These reports complete the list of toxicology studies required under the conditional registration for GOAL herbicide. We believe that the data we have presented to the Agency is sufficient to support the conclusion that no additional toxicology studies of GOAL are warranted.

Sincerely,

Thomas D. Rogerson

Thomas D. Rogerson
Product Registration Manager-Herbicides
Product Integrity

TDR/cap
Attachment
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