(15)

7-1-78

(14)

DATE: July -- 1978

SUBJECT: Pydrin TM Insecticide. 2.4 Emulsifiable Concentrate SD#43775 Technical - Lifetime Feeding Study in Rats.
P.P. No. FF2013 E.P.A. File Symbol 201-401 Caswell No. 77A

FROM: Toxicology Branch Jenny Anderson
Registration Division

no Doc.#

MRID 00082244
" 00111888

TO: Charles Mitchell and Chemistry Branch
Product Manager #17

Recommendations

A two-year chronic feeding study of SD-43775 Technical in rats is reviewed herein and has been found adequate to support a systemic N.E.L. of 250 PPM. No remarkable compound-related toxicological or pathological effects are evident. Gross and histo-pathological examinations of all animals used in the study have been reported except as indicated in part A.6.

Review

Lifetime Feeding Study in Rats with SD-43775 Technical (Code 6-1-0-0,98%) (Litton Bionetics, Inc., LBI Project No. 2541, 4'78, submitted by the Shell Chemical Co., /9/78, Acc. Nos. 097075-097082).

A. Procedure

1. Organization of the Study

Twelve hundred rats /Sprague-Dawley , 145 g (males) and 118 g (females) average wts., were randomly assigned to treatment groups after a 9-day acclimatization period as follows;

Dietary Level (PPM)	Number of Rats Males	Females
0 (control)	183	183
1	93	93
5	93	93
25	93	93
250	93	93
0 (Control) *	22	22
500 *	22	22

* Sacrificed at 25 weeks.

The rats were housed in groups of 3 except for 1 group of 4 in each of the 500 PPM and associated control groups; however, each animal was identified by an ear tag.

2. Preparation of Test Compound - Diet Mixtures

Test compound was blended into the diet as a pre-mix of diet and test compound-hexane solution. Hexane was added to diet for the control groups. Volumes of hexane and test compound-hexane solutions added to diet were equal.

Levels of test material in the diet were periodically estimated by chemical analysis throughout the study. Results of the analysis are as follows:

Nominal level (PPM)	Range (PPM)	Average (PPM)
0	0.1 -0.2	0.1
1	0.67-2.6	1.2
5	4.2 -8.5	5.1
25	14-49	25
250	210-310	360
500	450-690	590

3. Observations

Observations of toxic signs and deaths were made daily. Body weights of all animals and food consumption of 20% of all animals/sex/dosage level were recorded weekly during the inital 13 weeks and monthly thereafter. Animals were palpated weekly.

4. Hematology, Clinical Chemistry, Urinalysis

At intervals of 13, 26, 52, and 78 weeks, 10 rats/sex/dosage level (20 rats/sex from controls) were evaluated for hematology, clinical chemistry, and urinalysis. All terminally sacrificed animals were similarly evaluated. Urine was collected while animals were individually housed and fasted overnight. Investigated parameters include the following:

a). Hematology: Hemoglobin, hematocrit (packed cell volume), erythrocyte count, leukocyte count, differential leukocyte count, platelet count, sedimentation rate (excluding animals sacrificed at 2 years), prothrombin time, clotting time.

b). Clinical Chemistry: Calcium, phosphate, creatinine, CPK, uric acid, cholesterol, bilirubin, alkaline phosphatase, LDH, SGOT, glucose, BUN, chloride, potassium, sodium, protein, protein fractions.

c). Urinalysis: Color, specific gravity, pH, sugar, albumin, ketones (acetone), bilirubin, occult blood, microscopic examination of sediment.

5. Gross Pathology

All animals were subjected to necropsy. Weighed organs include brain, heart, liver, Kidneys, testes, adrenal glands, and spleen.

6. Histopathology

Groups of animals examined histopathologically include the following:

	Group (PPM)					
	0	1	5	25	250	500
Month	No. of animals/sex/dosage level					
3	20		10	10	10	10
6	20		12	12	12	12
12	20		10	10		
18	20		10	10		
24	(61M,46F)	(33M, 22F)	(32M,28F)	(32M, 27F)	(34M, 17F)	
Moribund or found dead	(42M,57F)	(18M; 29F)	(19M,23F)	(19M, 24F	17M,31F)	

One hundred sixty eight animals in the 1 and 5 PPM groups which were killed at 13, 26, 52, and 78 weeks were not histopathologically examined. Three rats in the 250 PPM female groups were killed and not histopathologically examined due to a sexing error.

The following tissues and organs were examined microscopically:

Brain	Kidneys
Spinal cord	Bladder
Sciatic nerve	Prostate
Pituitary	Testes
Thyroic	Ovaries
Parathyroid	Uterus
Salivary glands	Fallopian tubes
Heart	Stomach
Lungs	Small intestine (3 levels)
Spleen	Large intestine (3 levels)
Liver	Skeletal muscle (thigh)
Pancreas	Skin (flank)
Adrenal glands	Mammary gland
Mesenteric lymph nodes	All gross lesions
Bone with marrow	

B. Results

1. Mortality

The test material did not significantly affect survival of

the animals during the study. Survival patterns can be realized by comparing the table showing division of animals into treatment groups (part A. 1.) with the table describing groups of animals examined histopathologically (part A. 6.).

2. Toxic Signs

No remarkable test compound- related toxic signs were evident. The predominant lesion was on the ear, presumably due to attachment of the ear tag. Other clinical signs appear to be due to aging or injury, e.g., alopecia, swellings, emaciation, labored breathing, body sores, crusts around nose and eyes.

3. Body Weight Data

The test material changed body weight according to the data presented below:

Dosage level (PPM)	Initial	13wks.	25 wks.	53wks.	77 wks	101 wks.
0 (male)	147.4	446.1	540.2	595.6	712.0	727.8
1	139.3*	453.1	560.0*	606.5	744.2*	767+
5	146.0	441.7	526.0*	565.6*	704.3	715.4
25	145.6	430.0*	519.9*	562.4	674.4*	684.1*
250	147.6	434.1*	510.6*	581.1	703.1	682.4*
D	136.5	439.0	561.3	-----	-----	------
500	136.3	422.9	563.0	-----	-----	------
0 (female)	116.3	257.0	291.6	346.3	429.5	457.5
1	110.3*	259.4	293.7	343.3	401.3*	449.5
5	119.2	254.1	290.5	345.1	425.9	489.0
25	123.4*	260.9	295.9	352.0	419.3	453.3
250	118.0	262.3	290.1	347.8	422.3	443.0
0	116.9	260.4	293.0	-----	-----	-----
500	121.2	235.4*	280.5	-----	-----	-----

* Significantly different from control ($p < 0.05$).

Significant differences are sporadic and appear to be marginal. A definite dose-related compound effect is not apparent.

4. Food Consumption: Unremarkable.

5. Urinalysis: Unremarkable

6. Hematology: Unremarkable

7. Clinical Chemistry: Unremarkable. However, decreased levels of α-2 serum proteins were found at 26 weeks in males and females fed 500 PPM.

8. Organ Weights, Organs/Body/Weight Ratios: Generally unremarkable. Sporadic significant differences were calculated, but a dose-related

compound effect was not indicated.

9. Histopathology

a). Results at 3 Months

Changes attributable to the test compound were not evident. Pathological manifestations were confined mainly to the lungs and mesenteric lymph nodes. Examination of mammary glands was not indicated.

b). Results at 26 Weeks

No test material-related effects were indicated. Outstanding pathological changes include chronic respiratory disease, focal myocarditis or myocardial fibrosis, nematodiasis, and malignant lymphomas. Microscopic examination of mammary glands was not indicated for all animals in each dosage group.

c). Results at 52 Weeks

No test-compound related effects were found. Parenchymal changes in liver did not usually reflect a fatty change. Lymphoid hyperplasia present in several organs did not elicit functional impairment. Splenic hemosicerosis was present in many animals.

d). Results at 18 Months

No effects attributable to the test compound were observed. Neoplastic, hyperplastic, and inflammatory lesions were found in all dosage groups. The most common neoplasm were pituitary chromophobes. Adrenal cortical changes and mammary gland secretory activity were associated with the chromophobes. Splenic hemosiderosis was common in all dosage groups, especially females.

e). Results at Terminal Sacrifice

i). Lesions of the nervous system were primarily radiculoneuropathy and degenerative myelopathy and were found in all dosage groups. Degenerative neurological changes were attributed to aging and were not considered to be due to an effect of the test material.

ii). Proliferative and neoplastic lesions generally occurred with either similar incidences or a random distribution throughout all groups of animals examined as terminal sacrifices and intercurrent deaths. Pituitary tumors were frequently observed in all groups. The incidence of mammary tumors in female rats is shown in the following table:

	GROUP 1			GROUP 2			GROUP 3			GROUP 4			GROUP 5		
	Term. KILL	Int. DEATH	TOTAL	Term. KILL	Int. DEATH	TOTAL	Term. KILL	Int. DEATH	TOTAL	Term. KILL	Int. DEATH	TOTAL	Term. KILL	Int. DEATH	TOTAL
MORS	CONTROL			1PPM			5PPM			25PPM			250PPM		
BENIGN	15/46	10/56	25/102	7/21	9/28	16/49	8/28	10/23*	18/51	13/27	8/24	21/51	8/17	12/31*	20/48*
Percentages	33%	18%	25%	33%	32%	33%	29%	43%	35%	48%	33%	41%	47%	39%	42%
MALIGNANT	5/46	13/56	18/102	5/21	4/28	9/49	8/28	3/23	11/51	6/27	3/24	9/51	3/17	8/31	11/48
Percentages	11%	23%	18%	24%	14%	18%	29%	13%	22%	22%	13%	18%	18%	26%	23%
TOTAL	20/46	23/56	43/102	12/21	13/28	25/49	16/28	13/23	29/51	19/27*	11/24	30/51	11/17	20/31	31/48*
Percentages	43%	41%	42%	57%	46%	51%	57%	57%	57%	70%	46%	59%	65%	65%	65%

* Statistically significant from controls ($p < 0.05$).

iii). Non-neoplastic lesions were either similarly or randomly distributed throughout all dosage groups. Most commonly observed lesions include chronic kidney disease, myocardial degeneration, adrenal cortical degeneration in females, splenic hemosiderosis and/or hematopoiesis, and minimal to mild pulmonary disease. No lesion was attributed to the test material.

C. Conclusions

a). Classification: Core Guidelines

b). No outstanding toxicity due to administration of the test compound was reported; therefore, the systemic N.E.L. is concluded to be 250 PPM. In a concurrent 26 week study, a 500 PPM level of the test material did not induce remarkable toxicological signs. Formation of mammary gland tumors appears to be spontaneous as a result of aging and not as a result of a test compound effect.

RD inital R.E.:7/14/78:lf

7/27/78

7-1-78

DER #1

Fenvalerate: 2-Year Feeding Study in Rats
Shell Chemical Company. 1978. MRID No. 00082244, 00111888.
HED Doc. No. ?.