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[TXR # 0052744]

(Fenvalerate - MRID No. 00085501)

DATE: May 4, 1978

SUBJECT: Three-generation Reproduction Study with Pydrin (SD-43775)
Caswell No. 77A

FROM: William Dykstra, Ph.D.
Toxicology Branch

TO: Charles Mitchell
Product Manager #17

Registrant: Shell Oil Company
One Shell Plaza
P.O. Box 2463
Houston, Texas 77001

Recommendations

1. The three-generation reproduction study in rats with pydrin (SD-43775) is acceptable as core-minimum data. The NOEL for reproductive parameters is considered to be 250 ppm. The NOEL for systemic toxicity in the parents is considered to be 25 ppm based on the reduced mean body weight of the F₂b parents at the high dose level.
2. The determination of SD-43775 in the hamster diet shows that diet preparation was prepared according to specifications.

Review

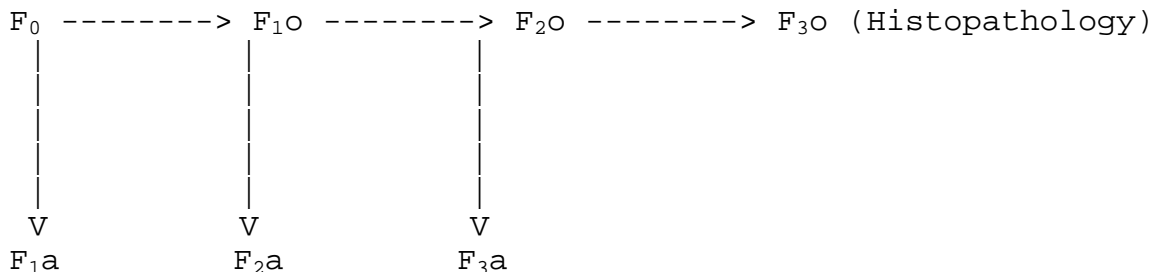
Three-generation Reproduction Study in Rats (LBI Project No. 2540, final report submitted Oct. 24, 1977, revised Feb. 1978)

Test Material: SD-43775 Technical, Code 6-1-0-1; golden brown, highly viscous liquid, (98%)

The test material was incorporated into the diet of weanling rats (Sprague-Dawley origin) for nine weeks prior to selection of the (F₀) parent generation. The experimental design and dose levels are outlined below for the F₀ generation:

<u>Group No.</u>	<u>Number of Rats</u>		<u>Dietary level</u> <u>ppm</u>
	<u>Male</u>	<u>Female</u>	
1 (Vehicle control)	11	22	0
2	11	22	1
3	11	22	5
4	11	22	25
5	11	22	250

Two females and one male from the same treatment group were housed together for mating and a similar arrangement was implemented for succeeding generation as follows:



The following information was collected on each litter: Date of delivery, abnormalities at birth, live and dead pups - Days 1, 5 and 22, Sex ratio-Day 1, 5 and 21, Body Weights by litter - Day 1 and 21, general appearance throughout nursing. At least 10 males and 10 female F₃O weanlings from each treatment group were necropsies. All parent generations were necropsied. From the F₃O weanlings, the brain, heart, liver, and kidneys were weighed. These plus the following tissues were preserved in 10% buffered formalin:

thyroid	prostate
spleen	pancreas
adrenal gland	mesenteric lymph nodes
testes	ovaries
uterus	oviduct
small intestine	stomach
lung	

Tissues from 10 male and 10 female weanlings of each dose group were submitted to A.A. Stein, M.D., Microscopy for biological Research, LTD, Albany, N.Y., for histopathologic evaluation:

Results: Samples of prepared experimental diets were periodically sent to the Sponsor for chemical analysis of the test compound. Results are summarized below:

<u>Desired Dose Level (ppm)</u>	<u>Actual (ppm)</u>	<u>Range (ppm)</u>	<u>Sample size</u>
1	1.2	0.67-2.6	26
5	5.1	4.2-8.5	18
25	25.0	14.0-49.0	19
50	120.0	10-310	19

First generation (Parents F₀ - Offspring F₁a and F₁b)

No remarkable effects noted in F₀ parents at treatment of necropsy.

No effect on reproductive parameters in F₁a and F₁b litters, except an apparent decreased fertility in females at 1 ppm dose level. However, this effect showed no dose response relationship in the higher treatment groups during the F₁ generation.

Second generation (Parents F₁o - Offspring F₂a - F₂b)

The general appearance and behavior of the parent rats of the second generation were judged to reflect no compound - related effect. The necropsy of the F₁b parents demonstrated a frequency of kidney changes (mottled, pale appearance) suggestive of a compound - related response; no effect on reproductive parameters in F₂a and F₂b litters except an apparent decrease in female fertility of the low level (1 ppm) test group. Since a dose - response relationship was not involved, this reduced reproductive capacity was not judged to be compound induced.

Third generation (Parents F₂b - Offspring F₃a and F₃b)

The mean body weights of the parents of the third generation F₂b adults revealed a significant reduction at the high level (250 ppm) when control and treated groups were compared. The necropsy of F₂b parents revealed gross kidney changes similar to changes noted in the F₁b parents. However the distribution with regard to dose was not judged to be consistent with a compound - related change. No effect on reproductive parameters in the F₃a and F₃b litters except an apparent decrease in female fertility of the low level (1 ppm) test group. Since a dose-response relationship was not involved, this reduced reproductive capacity was not judged to be compound induced. Histopathological examination of the F₃b weanling was unremarkable.

Conclusion: The NOEL for reproductive parameters is considered to be the high-dose level (250 ppm). The NOEL for systemic toxicity of the parents is considered, from the evidence of body weight loss of the F₂b parents, to be 25 ppm. The systemic toxicity effect observed in the F₂b parents is evidence that the highest dose level produced a toxic effect.

Classification: Core-Minimum Data

Typists:TH
RD initial G.E.Whitmore 4/26/78
(initial for G.E.W.5/8/78)