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

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JAN 22 1987
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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of SC-0224 Two-Generation Reproduction Study in Rats, Addendum I: Response to EPA Comments Submitted by Stauffer Chemical Company.
EPA Reg. No.: 476-2225/476-2226
TOX Chemical No. 893C

TO: Robert Taylor, PM 25
Herbicide/Fungicide Branch
Registration Division (TS-767)

FROM: Brian Dementi, Ph.D. Brian Dementi 1/21/87
Review Section #1
Toxicology Branch/HED (TS-769)

THRU: Robert B. Jaeger, Section Head 1/21/87
Review Section #1
Toxicology Branch/HED (TS-769)

Applicant: Stauffer Chemical Company
1200 S. 47th Street
Richmond, CA

Stauffer Chemical Co. has provided a company response to questions raised in our 5/30/86 review (Dementi) regarding the 2-generation reproduction study. TOX Branch concluded in that review that no NOEL had been established, on the basis of finding reduced relative spleen weight in F2B weanling males at the lowest dose level of 150 ppm. A NOEL for increased platelet count in F2B adults (M,F) was estimated at the lowest level administered (150 ppm). Additionally, TOX Branch noted a statistically significant reduction in thymus weight (absolute and relative) for F2B adult males at 2000 ppm. In view of these effects, TOX Branch expressed concern that SC-0224 may be exerting an adverse effect on the reticuloendothelial system.

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In the present submission, Stauffer provides results of additional study and suggests that these data support their previous conclusion that a NOEL of 150 ppm was established.

The following responses are provided for each concern raised in our 5/30/86 review:

I. Reduction in Relative Spleen Weight

Stauffer claims that statistically significant decreases in relative spleen weight which were evident at 150, 800 and 2000 ppm in F2B weanling males is attributed to atypically elevated mean absolute spleen weight and low mean body weight for the control animals. Stauffer compared spleen weights of F1B and F2B weanling males and females to help illustrate this point.

Absolute Spleen Weight, Grams

Group	F1B		F2B	
	M	F	M	F
Control	.329	.315	.474	.354

Spleen weights of F2B males are numerically greater than F1B males, and except for F2B males the other control values are comparable to absolute spleen weights of the Low Dose group.

Furthermore, Stauffer argues that body weights of control F2B weanlings (M,F) were relatively low, perhaps due to increased litter size of this group:

Body Weight, grams

Group	M	F
Control F1B Weanlings	78.9	79.3
" F2B "	70.2	66.6

In addition to these data purporting to explain the reduced relative spleen weights in the various dose groups, Stauffer provided additional data on body weights and spleen weights of control animals. In 50 weanling male rats having a mean body weight of 81.3 grams (a figure comparable to F1B weanling mean weight of 78.9 grams), the mean spleen weight was 0.339 grams. This figure does support Stauffer's position that a mean spleen weight of 0.474 grams in rats of comparable size is unusually high. Consequently, a relative spleen weight of 0.418 as derived

from the supplemental spleen and body weight data appears to be a more reliable control value than that reported for weanling F2B male controls (0.676) in the original study.

TOX Branch is satisfied that Stauffer has adequately addressed this concern and that SC-0224, at doses evaluated in the previous study, did not exert an adverse effect on spleen weight at 150 ppm.

II. Thymus

In our previous review we noted that for F2B male adults, absolute and relative thymus weights were reduced, being statistically significant at the high dose.

The Registrant has tabulated thymus weight changes for the different generations at the various dose levels. Statistically significant absolute thymus weight decreases are noted for P1 (M,F) at 800 and 2000 ppm and for P0 (M), F1B weanlings (F) and F2B (M) adults at 2000 ppm. When expressed on a relative weight basis, the only significant decreases were for groups P0 (M), P1 (F) and F2B adult (M) at the 2000 ppm dose level.

TOX Branch agrees with the Registrant that a NOEL = 150 ppm has been demonstrated for thymus weight changes in this study.

III. Platelet Counts

In our review of the original 2-generation study, TOX Branch identified significant increases in platelet count at 800 and 2000 ppm in both sexes of F2B adults. (Appendices 103, 114)

ppm Level	Males	N	Females	N
0	855 ± 169	5	863 ± 87	5
150	888 ± 65	5	899 ± 178	5
800	1017 ± 69	5	1042 ± 49	5
2000	1092 ± 68	4	1107 ± 162	5

In Addendum I, Stauffer provided historical platelet count control data for male and female rats in the age groups 1-3 months and 4-14 months, and notes that all of the platelet values for animals in the 800 and 2000 ppm dose groups fall within the reference range for the laboratory. Furthermore, Stauffer emphasizes that one of the male reference ranges used has a skewed distribution. The petitioner also points out

that the study controls appear to be atypical and that this particular group of controls is derived from the same group of animals in which the atypical spleen weights were observed. For these reasons Stauffer would have the Agency accept that an apparent dose related increase in platelet count in both sexes has no biological significance.

Tox Branch adheres to the conclusion reached in our original review that the increases in platelet count observed in both sexes at 800 and 2000 ppm are significant. Therefore NOEL=150 ppm for this biological effect. Since platelet count was altered at the higher doses and there is uncertainty as to what dose represents the LOEL, any additional studies which include assessments of this and/or related parameters should be carefully evaluated.

NOEL = 150 ppm, LOEL = 800 ppm

TOX Branch conclusions: NOEL < 150 ppm [reduced feed intake and body weight in both parents and pups; reduced absolute thymus weight, P1 (M,F); platelet count increase, F2B adults (M,F)]

CORE: UPGRADE FROM Supplementary to Guideline

Brian Dement
1/30/87