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

006414

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

OCT 30 1987

MEMORANDUM

SUBJECT: EPA Reg. No. 4816-72 - Piperonyl Butoxide. Review of a rat multigeneration reproduction study (1986).

TOX CHEM. No.: 670
TOX PROJECT No.: 7-0956
Record No.: 201127

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THRU: Edwin Budd
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10/2/87 10/30/87

The Piperonyl Butoxide Task Force has submitted a multi-generation reproduction study with rats using piperonyl butoxide as the test material in response to an earlier DATA-CALL-IN Notice.

The study was reviewed by Toxicology Branch (TB) and found to be CORE GUIDELINES and satisfies the data requirement for this study type. A copy of the Data Evaluation Record is attached.

Reviewed by: J.D. Doherty 10/2/87
Section II, Tox. Branch (TS-769C)
Secondary reviewer: E.R. Budd 10/2/87
Section II, Tox. Branch (TS-769C)

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DATA EVALUATION REPORT

STUDY TYPE: 83-4: Multi-generation reproduction - rats

TOX. CHEM. NO.: 670

ACCESSION NUMBER: 263635,-6,-7,-8,-9 and -40

MRID NO.: None

TEST MATERIAL: Piperonyl butoxide (FEG-32)

SYNONYMS: PB

STUDY NUMBER(S): 81689

SPONSOR: Piperonyl Butoxide Task Force

TESTING FACILITY: Bio-Research Laboratories, Ltd. (Canada)

TITLE OF REPORT: A-two generation (two-litter) reproduction study of piperonyl butoxide administered in the diet to the rat.

AUTHOR(S): K. Robinson, L. Pinsonneault and B.G. Proctor.

REPORT ISSUED: July 1, 1986

CONCLUSIONS:

NOEL = 1000 ppm

LEL = 5000 ppm (decreases in weight gain and food consumption).

No effects on reproductive performance or development (except weight gain) noted.

Levels tested 0, 300, 1000, and 5000 ppm

Classification: CORE-GUIDELENES

Special Review Criteria (40 CFR 154.7) N/A.

Methods and Protocol

In this study four groups of Sprague-Dawley rats (CD-Crl-COBS CD [SD] BR, 26 males and 26 females per group) were dosed with piperonyl butoxide in their diets at dose levels of 0, 300, 1000 and 5000 ppm in a study designed to assess reproductive performance in adults and developmental toxicity in the offspring. The study consisted of an F_0 generation which was started on the test diet at 42 days of age and which were bred to produce two sets of litters (F_{1a} and F_{1b}). Males and females were selected from the F_{1b} litter, mated and produced F_{2a} and F_{2b} litters.

Mating was accomplished by placing 83-85 day old females with males (one to one) for a maximum of 7 days. The protocol provided that if no evidence of mating occurred, unmated males and females were again paired with individuals they were not already paired with. This procedure was to be repeated three times. If only one pair of rats in any group failed to mate after 7-14 days, no further exchanges were to be made.

After mating the rats were allowed to deliver and when possible parturition was said to be observed. At day 0 post partum, the condition of the dams and pups (including sex and obvious malformations) were noted. On day 4 post partum the litters were culled to 8 pups (4 males and 4 females), the unsaved pups were saved in Bouin's solution for possible future examination.

On day 21 post partum, the pups were weaned, examined and sacrificed except for the case of the F_{1b} generation. F_{1b} generation males and females (at least 26 of each sex) were selected to be the parents for the F_2 generation and 10 of each sex were selected for full gross pathological examination. Adult rats were sacrificed after either mating (males) or weaning (females). The protocol called for saving the tissues for possible future gross and histopathological examination.

Analysis of the reproductive performance consisted of determining the following indices:

Mating index = [Females mated]/[Females placed for mating] x 100

Fertility index = [Pregnant females]/[Females placed for mating] x 100

Conception rate = [Pregnant females]/[Females mated] x 100

Maternal performance was determined as:

Gestation index = [Rats with live pups]/[Pregnant rats] x 100

Litter data were assessed by the following indices:

Viability index = [Live pups on day 4*]/[Live pups on day 0*] x 100

Survival index = [Live pups on day 7*or 14*]/[Live pups on day 4*] x 100

Lactation index = [Live pups on day 21*]/[Live pups on day 4*] x 100

*post partum day.

In addition several other parameters were investigated such as body weight gain, food consumption, and behavioral responses.

Statistical procedures used included mainly the Kruskal-Wallis test and the Mann-Whitney 'U' test for assessing significance of the viability, survival and lactating indices. One-way analysis of variance and Student's "t" test were used for analysis of body weight data.

Results

1. Sample analyses and stability. (Refer to appendix 85 of the study report).

Analytical data were provided to show that the test samples were usually close to 100% of the targeted dietary levels of 300, 1000, and 5000 ppm and that piperonyl butoxide was stable in the food preparation for up to 60 weeks. The sample mixtures were also shown to be homogeneous with respect to distrbution of piperonyl butoxide.

The test diets were assessed some 25 times over a 60 week period. The results indicated that sometimes the content was as low as 67% and as high as 127% of the expected value. Most of the low values resulted during week 24, but multiple runs eventually showed that the sample was near 100% and subsequent runs at later weeks were also close to 100% of the expected value.

2. Mortality and behavioral reactions.

No evidence of increased mortality or increases in behavioral responses or chemical signs related to the test chemical were reported for either adults or the pups.

3. Body weight gain.

The study report maintains that only the high dose group (5000 ppm) was affected and showed decreases in weight gain in both adults and the pups.

Inspection of the data tables indicates that there are occasional statistically significant weight decreases in the mid dose group but not of the consistency or magnitude to set the mid dose level as a firm effect level.

Both the F_0 and F_1 parental groups for both the male and females displayed growth curves that showed that the high dose group was consistently lower in weight (F_0 males 6 to 12%, F_0 females about 9% and F_1 males about 12% and F_1 females about 9%). Data were also presented which showed that the females in the high dose group did not gain weight during the different stages of pregnancy and lactation as did the controls and low and mid dose groups.

Decreased pup weight in the high dose group became evident at post partum day 4. The weights of the pups in the high dose group were equivalent to the control and lower dose groups at birth. The pup weight differences (in percent decrease) in the high dose groups relative to the controls at day 4 and day 21 are shown in the following table.

	Day 4	Day 21	Page
F_1A	-8^{*} /-8^{*}	-18^{***}/-18^{***}	B35.B36
F_1B	-9^{ns}/-5^{ns}	-15^{***}/-12^{***}	B43,B44
F_2A	-6^{ns}/-13^{ns}	-10^{ns}/-13^{**}	B83,B84
F_2B	-12^{ns}/-12^{*}	-18^{***}/-19^{***}	B91,B92

males/females

* $p < .05$, ** $p < .01$, *** $p < .001$

There was also noted a corresponding decrease in food consumption.

TB concurs that the NOEL for effects on pup weight gain is 1000 ppm.

4. Compound intake. [Calculated based on body weight and food Consumption.]

There were wide variations in the compound intake which was determined for the F_0 and F_{1b} parental groups. For example, survey of the data from both the F_0 and F_{1b} indicated that the low dose males ingested 14-43, females 17-47; mid dose males 47-151, females 36-158; and high dose males 251-856, females 316 to 878 mg/kg/day. The wide variation probably reflects changes in the growth of the rats.

5. Reproductive performance.

There was no evidence presented to indicate that PB affected the reproductive performance as determined by the indices listed above.

6. Pup development.

There was no evidence presented to indicate the the viability, survival and lactation indices for the treated groups were different from the controls.

7. Gross pathology.

No dose related increased incidences of grossly observable pathological findings were evident.

CONCLUSION: This study is CORE GUIDELINES. The following one-liner applies:

NOEL = 1000 ppm

LEL = 5000 ppm (decreases in weight gain and food consumption).

No effects on reproductive performance or development (except weight gain) noted.

Levels tested: 0, 300, 1000, 5000 ppm.