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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

382® (RESMETHRIN, TECHNICAL MANUFACTURING USE CT), ID NO. 000432-00487. Evaluation of 2-ation Reproduction Study in Rat and Reevaluation of ollowing Previously Submitted Studies: 3-Generation duction Study in Rat, Six-Month Dog, Rat opmental and Rabbit Developmental Toxicity Studies.

Tox. Chem. No.: 083E
PC No.: 097801
DP Barcode No.: D202920
Submission No.: S464796

a J. Hansen, Ph.D.
on IV, Tox. Branch I
h Effects Division (7509C)

t Brennis, Manager, PM Team 10
d Layne, Reviewer, PM Team 10
istrati.. Division (7505C)

n P. Copley, D.V.M., D.A.B.T., Section Head
on IV, Tox. Branch I
h Effects Division (7509C)

eviewed the two-generation reproduction study in rat SBP-1382®, technical manufacturing use resmethrin ed to this memorandum). The study is acceptable e) for 83-4 and a NOEL for reproductive toxicity was

on, TB-I has reevaluated a previously submitted rat reproduction study, rat and rabbit developmental es and a dog 6-month oral toxicity study (DE: tached) to provide Executive Summaries and additiona: contained in the original reviews. The conclusion: reflect the opinion of the HED RfD/Peer Revie. ting on 10/20/94). Summaries of each study :

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83-4: TWO-GENERATION REPRODUCTION STUDY IN RAT (MRID 431891-01)

EXECUTIVE SUMMARY: In a 2-generation reproduction study, resmethrin (SBP-1382® technical, 86.3% a.i.) was administered continuously in the diet to Crl:CD®BR VAF/Plus® rats (30/sex/dose) at concentrations of 0, 250, 500 or 1000 ppm (0, 17.4, 34.8 or 70.8 mg/kg/day, respectively, based on body weight and food consumption during premating periods). P_1 and F_1 males and females were mated 1:1 for up to 21 days after at least 80 days on test diet before the first mating period, and after a 26 day (P_1) or 17 day (F_1) postweaning rest period.

Parental/reproductive/offspring toxicity: At 1000 ppm, P_1 females showed slightly decreased body weight/weight gain during gestation (5.4% less than controls) and no weight gain during the first 4 days of lactation, due to reduced litter weights. F_{1b} males and females showed decreased body weight, but not gain, (5% to 7% less than controls) early in postweaning, due to reduced weight during nursing. Deaths of 2 F_{1b} males (days 37 and 44 post-weaning) were possible effects of treatment. Significantly decreased viability indices were observed in all generations, with more pronounced decreases in the F_{1a} and F_{2a} generations (33% and 45% less than controls) than the F_{1b} and F_{2b} generations (15% and 9% less than controls). Mean pup birth weight was also significantly decreased in the F_{1a} and F_{2a} generations (8% less than controls), and to a lesser extent in the F_{1b} and F_{2b} generations (5 to 7% less than controls). Pup weight and weight gain were significantly decreased at day 21 of lactation (8% to 15%). A slight increase in stillborn pups was observed in the "a" generations (1.8% and 3.4%, vs. 0.5% - 0.7%, controls). Significantly decreased mating index (30% and 18% less than controls, males and females, respectively) was observed during the F_1 second cohabitation. **The LEL for parental/reproductive/offspring toxicity is 1000 ppm (70.8 mg/kg/day), based on slight decreases in body weight gain in P_1 females during gestation and lactation, decreased body weight in F_{1b} males and females, possible treatment-related mortality in postweaning F_{1b} males, decreased mating index in males and females during the second F_1 mating, decreased viability index and decreased pup weight in all generations at birth and during lactation, and possible slight increase in stillborn pups in the F_{1a} and F_{2a} generations. The NOEL is 500 ppm (34.8 mg/kg/day).**

This study is Core-guideline and satisfies the guideline requirement for a reproduction study (83-4) in the rat.

REEVALUATIONS OF PREVIOUSLY SUBMITTED STUDIES:

83-1b: SIX-MONTH ORAL TOXICITY STUDY IN BEAGLE DOG (MRID 00157961. ORIGINAL REVIEW IN HED DOC. NO. 000741)

EXECUTIVE SUMMARY: In a 180-day oral toxicity study, groups of 6 beagle dogs/dose/sex were administered resmethrin (technical, 48% supplied in filler or 90% a.i.supplied neat) in gelatin capsules admixed with silicate filler as vehicle. Controls received capsules containing 100 mg/kg filler only; doses not adjusted for purity) at 0, 10, 30 or 100/300 mg/kg/day in the diet. The high dose was changed from 100 mg/kg/day to 300 mg/kg/day on Day 57 of the study.

No significant treatment-related effects were observed at any dose tested. Mild liver enlargement occurred in males (+15% of controls at 300 mg/kg/day) and in females (+27%; 16% at 30 mg/kg/day) but no microscopic lesions or changes in liver-related clinical chemistry parameters were observed. The increased liver weight is therefore considered an adaptive metabolic response to administration of the test material. Slightly increased incidence of salivation at 300 mg/kg/day was also not considered of toxicologic significance in the absence of other effects. **The LOEL is >300 mg/kg/day based lack of significant toxicologic effects at the highest dose tested. The NOEL is ≥ 300 mg/kg/day.**

This study is Core-minimum and satisfied the guideline requirements for 83-1b, chronic toxicity study in the dog. Although no treatment-related toxicity was observed in this study, a LOEL for systemic toxicity (430 mg/kg/day) was established in a recently submitted 1-year dog oral toxicity study (MRID 430626-01).

83-3a: DEVELOPMENTAL TOXICITY STUDY IN RAT (MRID 00028453. ORIGINAL REVIEW IN HED DOC. NO. 001915)

EXECUTIVE SUMMARY: In a developmental toxicity study, 25 pregnant Blu (SD) BR strain rats per dose group received 0, 20, 40 or 80 mg SBP 1382/kg/day (technical, 86.5% a.i.; dose not adjusted for purity of test material or increase in maternal body weight during treatment) in corn oil by gavage from gestation Day 6 through 15, inclusive. In addition, a group of 25 rats received 250 mg/kg/day aspirin (salicylic acid) as a positive control for developmental toxicity. Animals were received time-pregnant from the vendor, usually on Day 2 of gestation.

Maternal toxicity occurred at the highest dose tested (80 mg/kg/day) as statistically significant decreases in mean body weight gain at Day 20 of gestation (-33% of vehicle controls) and in food consumption between Days 11-20 of gestation (-26% of vehicle controls). (Positive control group showed no significant maternal toxicity; decreased body weights were due to the sharply reduced litter size). **The maternal toxicity LOEL is 80 mg/kg/day.**

based on reduced body weight and body weight gain, and reduced food consumption. The maternal toxicity NOEL is 40 mg/kg/day.

Developmental toxicity was noted in the high dose groups (80 mg/kg/day) as marginally decreased mean fetal weight (-11% of vehicle controls; not statistically significant) and an increased incidence in delayed ossification of the metacarpals and metatarsals (18% litter incidence vs. 0%, controls) and partial skull (24% litter incidence, vs 13% in controls). A marginal increase in the incidence of distal metacarpals (fetal incidence 19% vs. 7%, controls) and metatarsals (fetal incidence 34% vs. 20%, controls) was also seen. **The developmental toxicity LOEL = 80 mg/kg/day, based on increased incidence of skeletal variations and delayed ossification, and on marginally decreased fetal body weight.**

This study is classified Core-Minimum and satisfies the Guideline requirement (83-3a) for a developmental toxicity (teratology) study in rats, despite several study deficiencies (see DER for details).

83-3b: DEVELOPMENTAL TOXICITY STUDY IN RABBIT (MRID 00029002. ORIGINAL REVIEW IN HED DOC. NO. 001911)

EXECUTIVE SUMMARY: In a developmental toxicity study, 20 pregnant New Zealand White Minnikin rabbits per dose group received 0, 10, 30 or 100 mg SBP 1382/kg/day (technical resmethrin, 90% a.i.; doses not adjusted for purity of test material or for body weight gain during gestation) in corn oil by gavage (1 ml/kg body wt.) from gestation Days 6 through 18, inclusive. In addition, a group of 20 rabbits received 2.5 mg/kg aqueous 2-aminonicotinamide on Day 9 of gestation as a positive control for developmental toxicity.

No maternal toxicity was observed at any dose tested (up to 100 mg/kg/day). **The maternal toxicity LOEL > 100 mg/kg/day. The maternal toxicity NOEL $\geq$ is 100 mg/kg/day.**
Developmental toxicity was noted in the high dose group (100 mg/kg/day) as statistically significantly increased litter incidence of fused sternebrae (38% vs. 0%, controls) and extra sternebrae (38% vs. 15%, controls). **The developmental toxicity LOEL = 100 mg/kg/day, based on increased incidence of skeletal variations, and a possible marginal increase in resorbed litters.**

This study is classified as Core-minimum and satisfies the requirement (83-3b) for a developmental toxicity (teratology) study in rabbits, despite study deficiencies (see DER for details).

83-4: 3-GENERATION REPRODUCTION STUDY IN RAT (MRID NO. 00081276; ORIGINAL REVIEW IN HED DOC. NOS. 001980 and 002266)

EXECUTIVE SUMMARY: In a 3-generation reproduction study, male

and female Wistar rats were administered SBP-1382 (resmethrin, technical, 90% a.i.) in the diet continuously at concentrations of 0, 500, 800 or 1250 ppm (0, 47, 79 or 123 mg/kg/day, average premating values based on actual mean food consumption and body weights). F_0, F_{1a} and F_{2a} males and females were mated 1:1 for up to 1 week after at least 10 weeks (F_0) or 8 weeks (F_{1a} and F_{2a}) of test diet administration before the first mating, and a 2-week rest period between matings.

At 500 ppm (47 mg/kg/day), decreased mean pup weight at Day 21 (5 - 9% less than controls, F_{1a}, F_{1b}, F_{3a} litters; statistically significant) and increased incidence of stillborn pups in the F_{3b} litters (4.3% vs. 1.2%, controls; statistically significant) were observed. In addition, at 800 and 1250 ppm, dose-dependent, statistically significantly decreased viability indices and pup birth weights were observed in some or all generation litters. Parental F_1 and F_2 males and females at 800 and 1250 ppm had decreased mean body weight, but not gain, (10% less than controls during first weeks of premating), resulting from their reduced body weight at weaning. At 1250 ppm, dams had reduced body weight, but not gain, during late F_{2a} and F_{3b} gestation and during lactation (up to 10% less than controls) which were secondary to initially lower body weight and to the reduction in litter size. **The LEL for systemic/reproductive/offspring toxicity is 500 ppm (47 mg/kg/day), based on decreased mean pup weight and increased stillborn pups in the F_{3b} generation litters. The NOEL for systemic/reproductive/offspring toxicity is less than 500 ppm.**

This study is Core-minimum and satisfies the guideline requirement for a reproduction study (83-4) in the rat. Although a NOEL was not determined in this study, a 2-generation reproduction study provided a NOEL of 34.8 mg/kg/day (500 ppm).

ACTION REQUESTED

On March 29, 1994, Roussel UCLAF submitted for review a two-generation reproduction study in rat on SB-1392 (MRID 431891-01). The study was performed to satisfy California EPA's data requirements for resmethrin (the previously submitted rat reproduction study, MRID 00081276, had been designated as unacceptable for regulatory purposes by Cal EPA). US EPA originally required a new study, but later determined that a new study was not necessary (see reviews listed above).

In this submission, TB-I also included reevaluations of the previously submitted 3-generation reproduction study in rat, rat and rabbit developmental toxicity studies and a 6-month dog oral toxicity study. The reevaluations were prepared to provide the RfD/Peer Review Committee with adequate information to assess the studies.

[Resmethrin] Reproduction Study (83-4)

EPA Reviewer: Linnea J. Hansen, Ph.D. Date 10/25/94
Review Section IV, Toxicology Branch I (7509C)
EPA Section Head: Marion P. Copley, D.V.M., D.A.B.T. Date 11/14/94
Review Section IV, Toxicology Branch I (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Multigeneration Reproduction - 2-Generation Study in Rat (83-4)

TOX. CHEM. NO.: 083E

P.C. CODE: 097801

MRID NO.: 431891-01

TEST MATERIAL: SBP-1382®, technical

SYNONYMS: Resmethrin; 5-benzyl-furylmethyl (IRS)-cis,trans-chrysanthemate

STUDY NUMBER: 718-004 (Laboratory Protocol No.); RBT-92-102 (Sponsor ID)

SPONSOR: Roussel Bio Corporation, Lincoln Park, NJ

TESTING FACILITY: Argus Research Laboratories, Inc., Horsham, PA

TITLE OF REPORT: Reproductive Effects of SBP-1382® (Resmethrin) Technical Administered Orally via the Diet to Crl:CD®BR VAF/Plus® Rats for Two Generations with Two Litters per Generation.

AUTHOR: Alan M. Hoberman, Ph.D.. D.A.B.T.

REPORT ISSUED: February 1, 1994

EXECUTIVE SUMMARY: In a 2-generation reproduction study, resmethrin (SBP-1382® technical, 86.3% a.i.) was administered continuously in the diet to Crl:CD®BR VAF/Plus® rats (30/sex/dose) at concentrations of 0, 250, 500 or 1000 ppm (0, 17.4, 34.8 or 70.8 mg/kg/day, respectively, based on body weight and food consumption during premating periods). P_1 and F_1 males and females were mated 1:1 for up to 21 days after at least 80 days on test diet before the first mating period, and after a 26 day (P_1) or 17 day (F_1) postweaning rest period.

At 1000 ppm, P_1 females showed slightly decreased body weight/weight gain during gestation (5.4% less than controls) and no weight gain during the first 4 days of lactation, due to reduced litter weights. F_{1b} males and females showed decreased body weight, but not gain, (5% to 7

less than controls) early in postweaning, due to reduced weight during nursing. Deaths of 2 F_{1b} males (days 37 and 44 post-weaning) were possible effects of treatment. Significantly decreased viability indices were observed in all generations, with more pronounced decreases in the F_{1a} and F_{2a} generations (33% and 45% less than controls) than the F_{1b} and F_{2b} generations (15% and 9% less than controls). Mean pup birth weight was also significantly decreased in the F_{1a} and F_{2a} generations (8% less than controls), and to a lesser extent in the F_{1b} and F_{2b} generations (5 to 7% less than controls). Pup weight and weight gain were significantly decreased at day 21 of lactation (8% to 15%). A slight increase in stillborn pups was observed in the "a" generations (1.8% and 3.4%, vs. 0.5% - 0.7%, controls) Significantly decreased mating index (30% and 18% less than controls, males and females, respectively) was observed during the F_1 second cohabitation. **The LEL for parental/reproductive/offspring toxicity is 1000 ppm (70.8 mg/kg/day), based on slight decreases in body weight gain in P_1 females during gestation and lactation, decreased body weight in F_{1b} males and females, possible treatment-related mortality in postweaning F_{1b} males, decreased mating index in males and females during the second F_1 mating, decreased viability index and decreased pup weight in all generations at birth and during lactation, and possible slight increase in stillborn pups in the F_{1a} and F_{2a} generations. The NOEL is 500 ppm (34.8 mg/kg/day).**

This study is Core-guideline and satisfies the guideline requirement for a reproduction study (83-4) in the rat.

Special Review Criteria (40 CFR 154.7) None

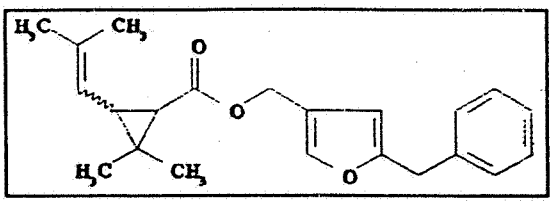
I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: SBP-1382® (resmethrin), technical
   Description: waxy, tan solid
   Lot/Batch #: IN-0198-B3
   Purity: 86.3% (% a.i. not stated in study report; information taken from 1-year dog feeding study, MRID 430626-01)
   Stability of compound: Stable at room temperature when stored in dark (not stated in study report; information taken from 1-year dog feeding study)
   CAS #: 10453-86-8

Structure

Structure



2. Vehicle: None (mixed directly in diet)

3. Test animals: Species: Rat
   Strain: Crl:CD®BR VAF/Plus®
   Age/weight at study initiation: 48 days/60 to 101 g, males and 59 to 97 g, females
   Source: Charles River Laboratories, Portage, MI
   Housing: Mating: one male and one female in male wire-bottom stainless steel cage
   Post-partum: individual dams in nesting boxes no later than day 20 of gestation and for 21 days post-partum
   All other times: individually, wire-bottom stainless steel cage
   Environmental conditions:
   Temperature: 70 - 78°C, except for 7 occasions when the temperature reached up to 81°C for ½ - 8 hrs
   Humidity: 40 - 80%, except for 3 occasions when the humidity was 34 - 38% for ½ hr.
   Air changes: ≥10/hr (filtered air)
   Photoperiod: 12 hr light/12 hr dark
   Acclimation period: about 16 days

4. Diet preparation and analysis: Diet was prepared at least weekly by mixing appropriate amounts of test substance with resmethrin and was stored in the dark at room temperature in airtight containers. Test material was assumed to be 100% for dosage calculations. Homogeneity and stability were tested during the range-finding study at concentrations up to 900 ppm. During the study, samples of treated food were analyzed at study start and at monthly intervals for concentration.

Results -

Homogeneity Analysis: Most preparations of diet with resmethrin were relatively homogeneous, with relative standard deviations of 3% - 6%. The greatest variation was observed in the 600 ppm diet, where the concentration of the top portion was ±2% of target concentration, compared to -7% to -12% in the middle and bottom samples.

Stability Analysis: Resmethrin was demonstrated to be stable for at least 7 days in diet under the conditions of storage used in this study.

Concentration Analysis: Most batches of diet tested were within acceptable range of target concentration (±10%). However, analytical concentrations were lower than expected (-11% to -15%) on several occasions at all dose levels). These variations are noted but are not considered to significantly affect the results of the study.

5. Animals received food (Purina Certified Rodent Chow #5002) and water ad libitum.

B. STUDY DESIGN AND MATING PROCEDURES

1. Animal assignment: P_1 animals were randomly assigned to test groups shown below:

TABLE 1 **Animal Assignment: P1 Generation**

Test groups No.	Designation	Dose (ppm)[1]	Animals per group [2] Males	Females
1	Control	0	30	30
2	Low (LDT)	250	30	30
3	Mid	500	30	30
4	High (HDT)	1000	30	30

1 Diets were administered from the beginning of the study until the animals were sacrificed.
2 The same number of animals were picked from the F_1 litters as parents for the F_2 generation.

2. Mating procedure: One male and one female were placed (random assignment) in the male's cage for a period of up to 21 days. Females were examined daily for evidence of mating and those females with copulatory plugs and/or spermatozoa in vaginal smears were removed to their individual cage. The day on which evidence of mating was observed was designated Day 0 of gestation. Any female showing no evidence of mating after 14 days was placed with another male for up to 7 days.

3. Mating schedule: Matings were conducted with males and females from the P_1 parental generation and from animals culled from the F_{1b} generation. All P_1 and F_{1b} parental females were examined for estrous cycling by vaginal cytology for 7 days prior to the start of the cohabitation periods. For the P_1 generation matings, males and females were cohabited starting after at least 80 days' administration of test diet at the appropriate dietary dose levels. The second mating of P_1 animals was conducted following a 26-day post-weaning rest period and the 7-day estrous cycle examination.

For the F_1 matings, cohabitation was initiated after at least 80 days post-weaning (including estrous cycle examination). The second mating period was initiated after

a post-weaning rest period of 17 days (including the 7-day estrous cycling tests). The same pairs of males and females were cohabited for the second generation matings, whenever possible. All cohabitations were conducted for no more than 21 days. Where no evidence of mating was observed after 14 days, the male was replaced with a proven fertile male for up to 7 days.

4. Culling of litters and selection of F_1 parental animals: All litters larger than 8 pups were culled to 8 on Day 4 postpartum. Whenever possible, equal numbers of males and females were retained in a litter. From the remaining F_{1b} pups, 30 males and 30 females/dose level were randomly selected on Day 21 postpartum and used for the second-generation matings.

5. Dose selection rational: Doses were selected based on results of a one-generation range-finding study, described in Appendix I of the study report. Eight Crl:CD®BR VAF/Plus® rats/sex/dose were administered 125, 250, 500 or 1000 ppm resmethrin in the diet (equivalent to average dose of 0, 5.8, 11.0, 22.7 or 44.2 mg/kg/day, premating males and 0, 7.1, 13.4, 28.9 or 56.7 mg/kg/day, premating females). All animals were administered test diet for 14 days prior to cohabitation and during a 7-day cohabitation. Males were administered test diet after cohabitation for a total of 75 days on test diet; females were administered test diet until scheduled sacrifice on day 21 postpartum (total of 57 - 63 days on test diet) or until day 25 of presumed gestation for females that did not deliver or were not pregnant (40 - 46 days on test diet).

   No mortality or overt clinical signs of toxicity were observed and body weights, weight gain and food consumption were comparable among all groups during premating, gestation and lactation. At 1000 ppm, in utero deaths were increased, and gestation index and viability index were decreased (50% less than controls). In addition, the study author reported difficulties with delivery (perivaginal bleeding often associated with stillbirths or resorptions, pale appearance, delivery of additional pup 2 days post partum) among all treatment groups but not controls: 3/5, 2/4 and 2/4 dams at 250, 500 and 1000 ppm, respectively. The relationship of this to treatment is unclear since there was no dose response and the number of dams/dose group was small.

C. METHODS

1. Observation Schedule

   a. Parental animals: Observations and the schedule for those observations are summarized below in Table 2.

TABLE 2: Observation Schedule

Viability:	2X/day
Clinical signs:	1X/day
Body weight and food consumption	
Premating:	Weekly (parental P_1 and F_{1b} males and females)
Gestation:	Days 0, 6, 10, 15 and 20; body weight only on day 25
Lactation:	Days 1, 4, 7, 10 and 14; body weight only on days 16, 18 and 21

b. Reproductive performance: Parental reproductive performance was assessed from breeding and parturition records of animals in the study. Length of gestation was noted. The following indices were calculated:

$$\text{Male (female) mating index} = \frac{\text{No. males (females) that mated}}{\text{No. males (females) cohabited}} \times 100$$

$$\text{Male fertility index} = \frac{\text{No. females pregnant}}{\text{No. males mated}} \times 100$$

$$\text{Female fertility index} = \frac{\text{No. females presumed pregnant}}{\text{Total no. females mated}} \times 100$$

$$\text{Gestation index} = \frac{\text{No. live litters born}}{\text{No. confirmed pregnancies}} \times 100$$

c. Litter observations: The following litter observations were made (see Table 3).

TABLE 3 F1/F2 Litter Observation Schedule

Number of live pups:	Daily
Pup weight:	Lactation Days 1,4,7,14,21
External alterations:	Daily
Number of dead pups:	Daily
Sex of each pup (m/f):	Lactation Days 1,4,7,14,21

Dead pups were examined grossly for external and internal abnormalities and a possible cause of death was determined for pups born or found dead. Lungs of pups found dead on Day 1 were placed in water to determine if the animal was stillborn (lung

sink) or died postpartum (lungs float). The following F_1 indices were calculated.

$$\text{Live born index} = \frac{\text{No. live pups born}}{\text{No. live + dead pups born}} \times 100$$

$$\text{Viability index} = \frac{\text{No. live pups at day 4}}{\text{No. pups born alive}} \times 100$$

$$\text{Lactation index} = \frac{\text{No. live pups at day 22}}{\text{No. pups born alive}} \times 100$$

d. Necropsy

1) Parental animals: All surviving parental P_1 and F_1 males were sacrificed as soon as possible after the second litters were produced in that generation. Maternal animals were sacrificed on Day 25 postpartum after the last litter of each generation was weaned. Females that did not bear young were sacrificed on Day 25 of presumed gestation. All animals were sacrificed by carbon dioxide asphyxiation. In addition, animals that died during the study were subjected to post mortem examinations as described below.

Necropsy observations: Gross examination consisted of external and internal examination of all body surfaces and the cervical, thoracic and abdominal viscera.

The following tissues (X) from all male and female P_1 and F_{1b} parental animals were prepared in 10% buffered formalin for microscopic examination and weighed (XX):

Reproductive organs:

XX Ovaries	XX Epididymides
XX Uterus	XX Prostate
XX Vagina/cervix	XX Seminal vesicles/coagulating gland
	XX Testes

Other organs/tissues:

XX Brain[1]	XX Pituitary gland
XX Liver[2]	X Gross lesions

1 Weighed but not examined microscopically
2 Weighed but only F_{1b} parental animals examined microscopically

Microscopic examination of the above tissues (except brain and P_1 livers) was conducted on all control and high-dose animals from both parental generations. A

tissues were collected from one control animal and preserved for possible microscopic examination.

2) Offspring: Culled offspring from each litter generation were sacrificed on Day 4 postpartum. The F_1 and F_2 offspring maintained through lactation and not selected as parental animals were sacrificed at 21 days of age. All sacrifices were by carbon dioxide asphyxiation. These animals were necropsied and subjected to complete post mortem gross examinations.

D. STATISTICAL ANALYSIS: Paternal, maternal and pup incidence data were analyzed by the Variance Test for Homogeneity of the Binomial Distribution. Body weight, food consumption, litter averages for pup body weights, percent male pups and percent pup mortality were analyzed by Bartlett's test of homogeneity of variances and ANOVA, followed by Dunnett's test when ANOVA was significant. When Bartlett's test was significant, Kruskal-Wallis test or Fisher's Exact test was used, as appropriate. Dunn's Method of Multiple Comparisons was used to identify significance of individual groups when the Kruskal-Wallis test was significant. The Kruskal-Wallis test was also used to analyze all other natural delivery data. Statistical significance was identified where $P \leq 0.05$.

E. COMPLIANCE Signed and dated GLP and Quality Assurance statements were provided.

II. RESULTS

A. SYSTEMIC (PARENTAL) TOXICITY

1. Mortality and clinical signs:

Mortality - In the P_1 generation, one male at 250 and one at 500 ppm were found dead during the premating period (days 106 and 120, respectively). The deaths did not appear to be treatment-related since a dose-response was not observed. There was no mortality among P_1 females.

In the F_{1b} generation, two males at 1000 ppm were found dead on days 37 and 44 postweaning. Cause of death in these animals was not determined, but they were considered possibly treatment-related since they occurred only at the high dose and since postweaning pup mortality was also increased at that dose. One F_{1b} female died on day 23 of presumed F_{2b} gestation, apparently from complications during delivery. The relationship of this death to treatment is unclear.

Clinical signs - No treatment-related clinical signs were observed among P_1 or F_1 parental males or females. Sporadically effects observed among all treatment [illegible]

control groups included alopecia, chromorhinorrhea and chromodacryorrhea.

2. Body weight:

P_1 males - No treatment-related effects were observed. Sporadic statistically significant decreases in mean body weight observed at 500 ppm during days 8-15 and an increase at 1000 ppm during days 162-165 were not considered effects of treatment.

P_1 females - During the F_{1a} gestation period, females at 1000 ppm showed slight decreases in mean body weight gain during gestation (5.4% less than controls, Days 1 - 20) and lack of weight gain during days 1-4 of lactation (see Appendix 1). Body weight and weight gain were comparable by the end of lactation. The study authors considered the decreases secondary to reduced litter size and weight at this dose.

F_1 males - At 1000 ppm, statistically significantly lower mean body weight (4% to 7% less than controls) for the first 36 days post-weaning was observed. However, this decrease was due to reduced birth/lactation weight, resulting in lower body weight at Day 1 post-weaning. Mean body weight gain (see Appendix 2 of DER) was comparable to controls during this time except during Days 8 - 15 (10% less than controls). Mean body weight was comparable to controls by the end of premating.

F_1 females - At 1000 ppm, significantly decreased mean body weight (6.5% less than controls) was observed on Day 8 postweaning and significantly decreased body weight gain during Days 1 - 8 (7% less than controls). This appeared to be related to reduced pup weight during lactation (Appendix 2). The decrease did not persist throughout premating and body weight gain during premating was comparable to controls. There were no treatment-related effects observed during either F_{2a} or F_{2b} gestation or lactation, except for an initial body weight decrement on Days 1-4 of F_{2a} lactation in the 1000 ppm group (see Appendix 3).

3. Food consumption:

P_1 males - No treatment-related effects on food consumption were observed. A statistically significant increase in the 500 ppm group between days 64 - 71 was not considered toxicologically significant.

P_1 females - No treatment-related effects were observed during premating or gestation. Throughout F_{2a} lactation at 1000 ppm, food consumption was statistically significantly decreased (13 to 17% less than controls; see Appendix 4). During F_{2b} lactation, slight decreases were also observed at 1000 ppm but were not significant (< 10% less than controls; data not shown). Decreases in food consumption during lactation in this

C 14

subsequent litters were probably related to reduced nutritional demands from smaller litter size.

F_{1b} males - No treatment-related effects on food consumption were observed. Slight but statistically significant increases (less than 10%) were observed at 1000 ppm during the first several weeks of post-weaning, which the study authors considered secondary to decreased body weight at the start of premating (data not shown). Small, statistically significant increases were also seen at 500 ppm but were not considered effects of treatment.

F_{1b} females - No treatment-related effects on food consumption were observed during F_{2a} or F_{2b} premating or gestation. A slight but statistically significant increase (7% above controls) between days 8 - 22 of premating at 1000 ppm was not considered of toxicological significance. A slight but statistically significant decrease in food consumption during F_{2a} lactation (< 10%) was observed at 1000 ppm (see Appendix 3) and was probably due to reduced nutritional demands of the smaller litters.

4. Test Substance Intake: Based on food consumption, body weight and dietary analyses results, average doses expressed as mg test substance/kg body weight were calculated by the study author. Average compound intake during the pre-mating period is shown below in Table 4:

TABLE 4: AVERAGE TEST COMPOUND INTAKE (MG/KG/DAY) DURING PREMATINGS

	CONCENTRATION OF RESMETHRIN IN DIET			
Premating period:	0 ppm	250 ppm	500 ppm	1000 ppm
P_1 males Days 1-80	0	16.6	33.5	67.0
Days 106-165	0	11.6	23.5	47.0
P_1 females Days 1-80	0	20.2	40.1	81.1
P_1 Premating Average	0	17.2	34.3	69.1
F_1 males Days 1-99	0	15.6	31.8	64.2
Days 127-176	0	11.4	22.8	46.3
F_1 females Days 1-99	0	21.5	43.3	89.7
P_1 Premating Average	0	17.5	35.3	72.5
P_1/F_1 COMB. TIME-WEIGHTED AVG.	0	17.4	34.8	70.8

1 Data taken from Tables B1, C1, D1, E1 of study report

Mean test compound intake was higher in females than males by about 30% during the premating intervals, and also greater for males in the first premating period compared to the second period (age-related decrease). Test compound intake of females during the interval between first and second matings was not determined.

Average test compound consumption during gestation and lactation is shown below in Table 5:

TABLE 5: AVERAGE COMPOUND CONSUMPTION (MG/KG/DAY). GESTATION AND LACTATION[1]

	CONCENTRATION OF RESMETHRIN IN DIET			
	0 PPM	250 PPM	500 PPM	1000 PPM
Gestation F_{1a} (Days 1-20)	0	18.2	36.2	73.9
F_{1b}	0	15.4	31.4	63.5
F_{2a}	0	15.9	32.0	67.9
F_{2b}	0	15.8	30.2	62.4
COMBINED GESTATION AVG.	0	16.3	32.5	66.9
Lactation F_{1a} (Days 1-14)	0	33.6	66.9	117.1
F_{1b}	0	30.8	58.0	109.4
F_{2a}	0	31.3	61.4	116.5
F_{2b}	0	29.6	53.6	122.9
COMBINED LACTATION AVG.	0	31.3	60.0	116.5

1 Data taken from Tables C2, C3, E2, E3 of study report

Test compound intake was similar among all generations during gestation. During the F_{1a} gestation period, dams at 1000 ppm consumed slightly more test compound (~ 16%) than during the F_{1b} gestation period, particularly during the first several days. At 1000 ppm, F_{1a} gestation compound consumption was slightly greater than F_{2b} gestation, but only by about 8%. Average daily intake was greatest during the lactation periods due to the increased nutritional demands of nursing. Lactation values were also comparable for all generations at 1000 ppm, although the F_{1a} and F_{2b} generations showed overall slight increases (5 to 8%). Average daily intake at each dose was proportional to the increment (2X) in the dietary concentration.

5. Necropsy results

a) Organ weights: No treatment-related effects on organ weights (reproductive organs, brain, pituitary, liver) were reported. The study authors noted a statistically significant increase in mean absolute brain weight of the high-dose P_1 males (mean brain weights, 2.17, 2.23, 2.21 and 2.25 g at 0, 250, 500 and 1000 ppm, respectively). However, TB-I agreed with their conclusion that this was not treatment-related due to the small magnitude of the difference (3.7%), lack of significant relative organ weight increase and absence of this finding in P_1 females or in F_{1b} males or females.

b) Pathology

1) Macroscopic examination: The report noted no observations that were related to the administration of the test substance in any of the parental animal groups.

2) Microscopic examination: The report noted no microscopic observations that were related to the administration of the test substance in the reproductive organs, liver (F_{1b} only examined) or pituitary gland of any of the parental (P_1 or F_{1b}) animal groups. Non-treatment related lesions observed in both control and high dose adult animals of both the P_1 and F_{1b} generations included chronic interstitial prostatitis, testicular atrophy, pigmented macrophage in uterus, cystic endometrial glands, hepatocellular vacuolization or focal necrosis of the liver (F_{1b} males) and vacuolization of pars distalis of the pituitary in F1b males.

B. REPRODUCTIVE AND OFFSPRING TOXICITY

1. Mating and fertility performance of P_1 and F_1 parental animals: Mating and fertility parameters of the F_1 generation parental animals are shown below in Table 6 for both litter groups:

Table 6: P_1 Male and Female Mating and Fertility Indices[1]

Observation	Dose group: Control	Low	Mid	High
P_1 Parents, first cohabitation				
Males				
Number cohabited	30	30	30	30
Precoital interval (days)	3.4	3.0	3.7	3.4
Mating index	100.0	100.0	93.3	96.7
Fertility index	96.7	96.7	100.0	93.1
Females				
Number cohabited	30	30	30	30
Precoital interval (days)	3.4	3.0	3.9	3.5
Mating index	100.0	100.0	100.0	100.0
Fertility index	96.7	96.7	93.3	90.0
P_1 Parents, second cohabitation				
Males				
Number cohabited	30	29[2]	29[2]	30
Precoital interval (days)	3.8	3.6	2.9	4.2
Mating index	90.0	100.0	100.0	86.7
Fertility index	81.5	75.9	75.9	76.9
Females				
Number cohabited	30	30	30	30
Precoital interval (days)	4.0	3.6	3.0	5.0
Mating index	100.0	100.0	100.0	93.3
Fertility index	80.0	76.7	73.3	78.6
F_1 Parents, first cohabitation				
Males				
Number cohabited	30	30	30	28[2]
Precoital interval (days)	6.1	4.0	4.2	4.0
Mating index	86.7	93.3	100.0	89.3
Fertility index	76.9	92.8	76.7	92.0
Females				
Number cohabited	30	30	30	30
Precoital interval (days)	6.1	3.9	4.2	5.4
Mating index	96.7	96.7	100.0	90.0
Fertility index	79.3	93.1	76.7	92.6
F_1 Parents, second cohabitation				
Males				
Number cohabited	30	30	30	28[2]
Precoital interval (days)	3.8	3.1	4.9	6.3
Mating index	93.3	93.3	86.7	64.3**
Fertility index	85.7	85.7	92.3	77.8
Females				
Number cohabited	30	30	30	30
Precoital interval (days)	4.3	3.6	5.3	8.0
Mating index	93.3	93.3	100.0	76.7**
Fertility index	85.7	85.7	86.7	78.3

1 Data from Tables B11, B12, C19, C20, D11, D12, E19 and E20 of study report
2 Excludes animals found dead during premating or postweaning periods
** $p < 0.01$

During the second F_1 cohabitation, both sexes showed slightly increased time to mating and significantly decreased mating index at 1000 ppm. Mating was not affected during any other cohabitation period. Fertility was unaffected by treatment.

2. Gestation observations: Gestation/litter observations are summarized below in Table 7:

TABLE 7 Reproductive Performance: Gestation and Litter Parameters[1]

Observation	Dose group: Control	Low	Mid	High
	F_{1a} Generation			
Gestation length, days	22.8	22.6	22.7	22.7
Gestation index	100.0	100.0	100.0	100.0
Number of litters, Day 1	29	29	28	27
Mean litter size, Day 1	13.8	13.7	14.6	13.1
Liveborn pups/litter	13.7	13.6	14.2	12.7
Total stillborn pups (%)	2 (0.5)	3 (0.8)	9 (2.2)	12 (3.4)
Stillborn pups/litter	0.1	0.1	0.3	0.4
Litters with stillborn pups (%)	2 (6.9)	3 (10.3)	4 (14.3)	5 (18.5)
Total litter losses at birth	0	0	0	0
Total litter losses by Day 21 (%)	0	0	0	2 (7.4)
Total liveborn pups, Day 1	398	394	399	343
Total live pups, Day 4 pre-cull	392	385	386	228
Total live pups, Day 21	230	229	224	168**
Total pup deaths, Day 1	2	3	3	13**
Days 2-4	4	6	10	102**
Days 5-7	0	0	0	0
Days 8-14	0	0	0	1
Days 15-21	1	0	0	1
Days 1-21	7	9	13	116**
Liveborn index	99.5	99.2	97.9	96.6
Viability index	98.5	97.7	96.7	66.5**
Lactation index	99.6	100.0	100.0	99.4
Mean pup weight (g), Day 1	6.1	5.9	5.8	5.6**
Mean pup weight (g), Day 21	43.3	42.0	40.3**	37.3**
Mean wt. gain (g) - Day 1-21[2]	37.2	36.1	34.5	31.7
Male:female ratio	48.6	53.3	54.1	48.6

1 Data taken from Tables C19, C21 and C23 of study report
2 Body weight gain calculated by reviewer; not analyzed statistically
* $p<0.05$. ** $p<0.01$.

TABLE 10 Reproductive Performance: Gestation and Litter Parameters (cont.)

Observation	Dose group Control	Low	Mid	High
	F_{1b} Generation			
Gestation length, days	22.9	22.8	23.0	23.0
Gestation index	100.0	100.0	100.0	100.0
Number of litters, Day 1	24	23	22	22
Mean litter size, Day 1	13.5	14.2	12.2	12.8
Liveborn pups/litter	13.3	14.1	12.0	12.5
Total stillborn pups (%)	4 (1.2)	3 (0.9)	(0.4)	5 (1.8)
Stillborn pups/litter	0.2	0.1	0.0	0.2
Litters with stillborn pups (%)	3 (12.5)	1 (4.3)	1 (4.5)	4 (18.2)
Total litter losses at birth	0	0	0	0
Total litter losses by Day 21 (%)	0	0	1 (4.5)	2 (9.1)
Total liveborn pups, Day 1	320	324	265	275
Total live pups, Day 4 preculling	309	318	260	225
Total live pups, Day 21	186	182	160	144
Total pup deaths, Day 1	4	2	2	13**
Days 2-4	7	4	3	37**
Days 5-7	0	0	0	2
Days 8-14	0	0	0	1
Days 15-21	0	0	0	1
Days 1-21	11	6	5	54**
Liveborn index	98.8	99.1	98.9	97.5
Viability index	96.6	98.1	98.1	81.8**
Lactation index	100.0	100.0	100.0	97.3**
Mean pup weight (g), Day 1	6.1	6.0	6.2	5.7
Mean pup weight (g), Day 21	47.8	49.0	48.0	43.8
Mean wt. gain (g) - Day 1-21[2]	41.7	43.0	41.8	38.1
Percent male pups, Day 1	48.6	53.3	54.1	48.6

1 Data taken from Tables C20, C22 and C24 of study report
2 Body weight gain calculated by reviewer; data not analyzed statistically
* $p<0.05$. ** $p<0.01$.

TABLE 7 Reproductive Performance: Gestation and Litter Parameters (cont.)[1]

Observation	Dose group: Control	Low	Mid	High
	F_2 Generation			
Gestation length, days	22.9	22.8	23.0	22.9
Gestation index	100.0	100.0	100.0	100.0
Number of litters, Day 1	23	27	23	25
Mean litter size, Day 1	12.9	13.4	13.1	13.7
Liveborn pups/litter	12.8	13.2	13.0	13.3
Total stillborn pups (%)	2 (0.7)	5 (1.4)	1 (0.3)	6 (1.8)
Stillborn pups/litter	0.1	0.2	0.0	0.2
Litters with stillborn pups (%)	2 (8.7)	2 (7.4)	1 (4.3)	5 (20.0)
Total litter losses at birth	0	0	0	0
Total litter losses by Day 21 (%)	1 (4.3)	1 (3.7)	0	2 (8.0)
Total liveborn pups, Day 1	294	358	300	333
Total live pups, Day 4 preculling	291	337	286	181**
Total live pups, Day 21	166	200	180	131
Total pup deaths, Day 1	0	9*	4	15**
Days 2-4	3	12	10	137**
Days 5-7	9	5*	0	1**
Days 8-14	0	0	0	2**
Days 15-21	0	1	2	2
Days 1-21	12	27	16	157**
Liveborn index	99.0	98.6	99.3	97.4
Viability index	99.0	94.1	95.3	54.4**
Lactation index	94.8	97.1	98.9	96.3
Mean pup weight (g), Day 1	6.0	6.0	5.8	5.5**
Mean pup weight (g), Day 21	46.0	42.3*	44.0	41.6**
Mean Wt. gain (g) - Day 1-21[2]	40.0	36.3	38.2	36.1
Percent male fetuses, Day 1	48.2	51.8	50.2	47.5

1 Data taken from Tables E19, E21 and E23 of study report
2 Body weight gain calculated by reviewer; data not analyzed statistically
* $p<0.05$ ** $p<0.01$

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TABLE 7 Reproductive Performance: Gestation and Litter Parameters (cont.)[1]

Observation	Dose group: Control	Low	Mid	High
	F_{2b} Generation			
Gestation length, days	23.0	23.0	23.2	23.0
Gestation index	100.0	95.8	100.0	94.4
Number of litters, Day 1	23	27	23	25
Mean litter size, Day 1	14.2	12.7	11.8	13.8
Liveborn pups/litter	14.0	12.5*	11.3*	13.7
Total stillborn pups (%)	3 (0.9)	4 (1.4)	12 (3.9)**	2 (0.8)
Stillborn pups/litter	0.1	0.2	0.5**	0.1
Litters with stillborn pups (%)	1 (4.2)	2 (8.7)	6 (23.1)	2 (11.8)
Total litter losses at birth	0	0	0	0
Total litter losses by Day 21 (%)	2 (8.3)	0	1 (3.8)	0
Total liveborn pups, Day 1	337	287	295**	233
Total live pups, Day 4 preculling	312	284	279	196**
Total live pups, Day 21	174	180	183	135
Total pup deaths, Day 1	1	0	2	5**
Days 2-4	24	3*	14	32**
Days 5-7	0	0	2	1
Days 8-14	[illegible]	0	0	0
Days 15-21	0	0	1	0
Days 1-21	25	3*	19	38**
Liveborn index	99.1	98.0	96.1**	99.1
Viability index	92.6	99.0*	94.6	84.1**
Lactation index	100.0	100.0	98.6	99.3
Mean pup weight (g), Day 1	5.9	6.1	6.2	5.6
Mean pup weight (g), Day 21	49.1	47.9	49.1	44.1**
Wt. gain (g) - Day 1-21[2]	43.2	41.8	42.9	38.5
Percent male pups, Day 1	52.6	52.3	54.4	50.5

1 Data taken from Tables E20, E22 and E24 of study report
2 Body weight gain calculated by reviewer; not analyzed statistically
* $p<0.05$ ** $p<0.01$

Gestation and birth parameters: Gestation index, gestation length and number of litters produced were not affected by resmethrin up to 1000 ppm. The number of stillborn pups and litters containing stillborn pups showed slight, non-statistically signific..

increases at 1000 ppm in the F_{1a} and F_{2a} litter generations, resulting in very slightly decreased liveborn indices TB-I considered this a possible effect of treatment, since the decrease in viability index was pronounced in these generations (including deaths on Day 1 postpartum) and since birth weights were also decreased (decreased live births were also reported in the range-finding study at 1000 ppm). In the F_{2b} generation, a statistically significant increases in the number of stillborn pups was observed at 500 ppm. TB-I agreed with the study author that the increase was probably not related to treatment since no dose response was observed (pup weights were also not affected at that dose).

3. Offspring toxicity

a. Viability and clinical signs:

Viability during lactation was significantly reduced among pups at 1000 ppm for all four offspring groups. Decreased viability was more pronounced in the first (a) litters of both the F_1 and F_2 generations (decreased by 33 - 45% compared to controls) than in the second (b) litters (decreased by 9 - 15%). This effect may have been related to slightly greater compound consumption among the dams during gestation and lactation of the "a" generations. Lactation index was unaffected by treatment.

Clinical signs - No treatment-related clinical signs were observed among offspring of the F_1 and F_2 generations.

b. Body weight: Statistically significant reductions of about 8% in mean pup birth weight were observed in the F_{1a} and F_{1a} offspring groups at 1000 ppm. Smaller, non-significant effects (5 to 7% decrease) were also observed in the "b" offspring groups and were probably a marginal effect of treatment. The decrease may have been greater in "a" offspring because of slightly greater compound intake of the dams during gestation.

Mean body weight and weight gain were also decreased at 1000 ppm on day 21 postpartum (end of lactation) in the F_{1a}, F_{1b}, F_{2a} and F_{2b} offspring by 15%, 8%, 10% and 10%, respectively. Decreases were statistically significant for all but the F_{1b} offspring; body weight gain data were not analyzed statistically.

c. Necropsy results: No treatment-related macroscopic lesions or abnormalities were reported. Skull sections did not show treatment-related incidences of hydrocephalus.

III. DISCUSSION

A. MATERNAL TOXICITY: In general, TB-I agreed with the conclusions of the stud

author. The results of this study suggest that nursing and young rats may be more sensitive to resmethrin than mature adult rats. The effects on body weight appeared to be either the result of toxicity to young (nursing) animals or, in gestating/lactating dams, secondary to effects on litter size/weight, and therefore was not direct toxicity to the dams. A separate NOEL/LEL for maternal toxicity was therefore not indicated. No toxicity was observed among P_1 males or females during either premating interval, and the small decreases in maternal body weight at 1000 ppm during late gestation and Days 1 - 4 of gestation were probably related to the reduced size of the litters at that dose. In the F_{1b} rats used for mating, the reduction in body weight during the first week(s) postweaning was primarily related to the reduced body weights at birth and during lactation. The two males that died during the study also died shortly after weaning (Days 37 and 44). The slight decreases in maternal food consumption relative to controls during several of the lactation periods were probably due to reduced milk production burden from reduced litter size. The minimal toxicity observed in adult rats at the doses tested in this study is consistent with results of other studies on rats which tested at similar dose levels (developmental, chronic).

B. REPRODUCTIVE AND LITTER TOXICITY: Resmethrin at 1000 ppm in the diet caused a pronounced decrease in pup survival (decreased viability index) and pup body weight in all litter generations, and possibly a slight increase in stillborn pups in the first litters of each generation. Toxicity was slightly greater in the first (a) litter of each generation, possibly due to slightly increased compound intake by the dams during the first gestation periods. The toxicity observed in pups from the 1000 ppm group suggests that the offspring may be affected both in utero, as evidenced by reduced birth weight and possible increases in stillbirths, as well during lactation, suggested by the decreased body weights of surviving pups on Day 21 postpartum. TB-I notes that a metabolite of resmethrin is found in the milk of goats given resmethrin. The mating index, but not fertility or gestation indices, of F_{1b} rats was reduced during the second cohabitation period. The results are consistent with those of a previously conducted rat 3-generation reproduction study (MRID 00081276).

C. STUDY DEFICIENCIES: No significant deficiencies were identified.

D. CORE CLASSIFICATION: Core-Guideline

Maternal/Reproduction/Offspring Toxicity NOEL = 500 ppm (34.8 mg/kg/day).
Maternal/Reproduction/Offspring Toxicity LOEL = 1000 ppm (70.8 mg/kg/day), based on marginal decreases in body weight or weight gain of P_1 females during gestation and lactation and of F_{1b} males and females during early postweaning, and possible mortality of postweaning F_{1b} males (maternal/paternal effects secondary to effects on offspring), decreased viability index and pup weight in all generations, decreased mating index during the F_{2b} cohabitation and possible increase in stillborn pups in the F_{1a} and P_{1a} offspring.

APPENDIX 1

TABLE C10 (PAGE 1)1 MATERNAL BODY WEIGHT DATA - FIRST GESTATION PERIOD - SUMMARY - F1 GENERATION FEMALE RATS

GROUP (PPM)	I 0(VEHICLE)	II 250	III 500	IV 1000
RATS TESTED	30	30	30	30
PREGNANT	29	29	28	27
INCLUDED IN ANALYSES a	28	25	28	27
MATERNAL BODY WEIGHT (G)				
DAY 0 MEAN±S.D.	270.6 ± 21.3	274.2 ± 21.0	271.3 ± 25.2	270.8 ± 21.7
DAY 6 MEAN±S.D.	300.4 ± 22.5	304.5 ± 22.8	297.3 ± 26.1	298.3 ± 21.3
DAY 10 MEAN±S.D.	313.4 ± 24.0	316.9 ± 23.3	310.8 ± 25.2	311.1 ± 21.9
DAY 15 MEAN±S.D.	335.9 ± 23.9	338.0 ± 23.1	333.5 ± 28.2	332.1 ± 22.4
DAY 20 MEAN±S.D.	388.3 ± 26.1	389.0 ± 27.8	389.2 ± 27.3	379.4 ± 25.7

DAY = DAY OF GESTATION

a. Excludes values for dams without a confirmed mating date.

TABLE C11 (PAGE 2): MATERNAL BODY WEIGHT DATA - FIRST LACTATION PERIOD - SUMMARY - F1 GENERATION FEMALE RATS

GROUP (PPM)		I 0(VEHICLE)	II 250	III 500	IV 1000
RATS TESTED	N	30	30	30	30
PREGNANT	N	29	29	28	27
DELIVERED LITTERS	N	29	29	28	27
MATERNAL BODY WEIGHT CHANGE (G)					
DAYS 1 - 4	MEAN±S.D.	+6.7 ± 12.8	+6.8 ± 10.3	+6.2 ± 12.5 [27]a	0.1 ± 13.0 [25]b,c
DAYS 4 - 7	MEAN±S.D.	+7.3 ± 9.8	+6.5 ± 9.6	+6.8 ± 12.0	+7.4 ± 12.2 [25]b,c
DAYS 7 - 10	MEAN±S.D.	+13.9 ± 8.3	+13.8 ± 8.7	+15.2 ± 9.7	+17.2 ± 8.6 [24]b,c,d
DAYS 10 - 14	MEAN±S.D.	+3.8 ± 10.6	+3.5 ± 10.3	+8.7 ± 10.2	+5.1 ± 16.5 [24]b,c,d
DAYS 14 - 16	MEAN±S.D.	+6.4 ± 9.8	+6.3 ± 11.0	+4.3 ± 10.2	+3.2 ± 16.9 [25]b,c
DAYS 16 - 18	MEAN±S.D.	+0.6 ± 9.6	-2.3 ± 11.9	+2.7 ± 6.9	+0.1 ± 12.8 [25]b,c
DAYS 18 - 21	MEAN±S.D.	-8.8 ± 11.5	-7.9 ± 14.4	-9.2 ± 11.4	-0.5 ± 10.8* [25]b,c
DAYS 1 - 21	MEAN±S.D.	+27.8 ± 15.6	+26.7 ± 20.8	+34.8 ± 14.4 [27]a	+32.8 ± 14.7 [24]b,c,d

DAYS = DAYS OF LACTATION
[ ] = NUMBER OF VALUES AVERAGED
a. Excludes values for dam 3029, which delivered two additional pups after completion of weighing on day 1 of lactation.
b. Excludes values for dam 3063, which had no pups surviving on day 1 postpartum.
c. Excludes values for dam 3068, which had no pups surviving after day 1 postpartum.
d. Excludes values for dams that had interrrupted water access.
* Significantly different from the vehicle control group value (P≤0.05).

APPENDIX 2

PROTOCOL 718-004: REPRODUCTIVE EFFECTS OF SBP-1382® (RESMETHRIN) TECHNICAL ADMINISTERED ORALLY VIA THE DIET TO Crl:CD®BR VAF/Plus® RATS FOR TWO GENERATIONS WITH TWO LITTERS PER GENERATION (SPONSOR'S STUDY NUMBER: RBT-92-102)

TABLE D8 (PAGE 1): BODY WEIGHT CHANGES - SUMMARY - F1B GENERATION MALE RATS

GROUP (PPM)		I 0(VEHICLE)	II 250	III 500	IV 1000
RATS TESTED		30	30	30	30
BODY WEIGHT CHANGE (G)					
DAYS 1 - 8	MEAN±S.D.	+42.9 ± 4.4	+43.7 ± 3.9	+42.4 ± 5.8	+40.9 ± 4.8
DAYS 8 - 15	MEAN±S.D.	+59.1 ± 5.8	+58.1 ± 5.4	+58.1 ± 6.5	+55.7 ± 6.3
DAYS 15 - 22	MEAN±S.D.	+63.2 ± 4.7	+62.3 ± 4.5	+63.7 ± 5.8	+60.4 ± 5.1
DAYS 22 - 29	MEAN±S.D.	+59.7 ± 7.4	+60.1 ± 5.8	+57.9 ± 5.0	+57.8 ± 6.9
DAYS 29 - 36	MEAN±S.D.	+52.6 ± 7.6	+53.1 ± 6.6	+56.7 ± 8.1	+52.6 ± 6.8
DAYS 36 - 43	MEAN±S.D.	+41.3 ± 10.5	+44.5 ± 6.3	+43.5 ± 7.1	+45.4 ± 7.2 [29]a
DAYS 43 - 50	MEAN±S.D.	+38.3 ± 6.1	+37.7 ± 7.4	+40.9 ± 7.3	+39.9 ± 9.6 [28]a
DAYS 50 - 57	MEAN±S.D.	+30.7 ± 9.1	+31.4 ± 14.8	+32.5 ± 8.0	+33.4 ± 5.4 [28]a
DAYS 57 - 64	MEAN±S.D.	+25.4 ± 9.0	+23.7 ± 9.5	+26.6 ± 4.9	+28.1 ± 5.9 [28]a

DAYS = DAYS POSTWEANING
[ ] = NUMBER OF VALUES AVERAGED
a. Excludes values for rats that were found dead.

PROTOCOL 718-004: REPRODUCTIVE EFFECTS OF SBP-1382® (RESMETHRIN) TECHNICAL ADMINISTERED ORALLY VIA THE DIET TO Crl:CD®BR VAF/Plus® RATS FOR TWO GENERATIONS WITH TWO LITTERS PER GENERATION (SPONSOR'S STUDY NUMBER: RBT-92-102)

TABLE D8 (PAGE 2): BODY WEIGHT CHANGES - SUMMARY - F1B GENERATION MALE RATS

GROUP (PPM)		I 0(VEHICLE)	II 250	III 500	IV 1000
RATS TESTED		30	30	30	30
BODY WEIGHT CHANGE (G)					
DAYS 64 - 71	MEAN±S.D.	+22.5 ± 5.7	+23.0 ± 5.7	+19.7 ± 5.7	+20.2 - [-]a
DAYS 71 - 78	MEAN±S.D.	+16.9 ± 7.1	+20.9 ± 5.6	+16.7 ± 9.8	+18.5 - [-]a
DAYS 78 - 85	MEAN±S.D.	+15.2 ± 7.0	+15.8 ± 5.3	+18.5 ± 7.8	+16.4 - [-]a
DAYS 85 - 92	MEAN±S.D.	+16.1 ± 6.4 [28]b	+15.0 ± 6.8	+16.7 ± 5.9	+16.8 - [-]a
DAYS 92 - 99	MEAN±S.D.	+13.5 ± 9.5 [28]b	+12.4 ± 7.2 [28]c,d	+14.5 ± 5.2 [26]c,d	+13.6 - [-]a
DAYS 1 - PRECOHABITATION (F2A LITTERS) d	MEAN±S.D.	+505.2 ± 62.4	+511.6 ± 33.8	+517.3 ± 56.2	+501.7 -

DAYS = DAYS POSTWEANING
[ ] = NUMBER OF VALUES AVERAGED
a. Excludes values for rats that were found dead.
b. Because body weight values were recorded at weekly intervals, based on each rat's day postweaning, day 85 post... was the last day on which the youngest rats (in this group) had a body weight value recorded.
c. Because body weight values were recorded at weekly intervals, based on each rat's day postweaning, day 92 post... was the last day on which the youngest rats (in this group) had a body weight value recorded.
d. Excludes values for rats that had interrupted water access.
e. Precohabitation body weights were recorded on the day that cohabitation began for the F1B generation rats; at ... these rats were 105 to 126 days of age.

TABLE E9 (PAGE 3): BODY WEIGHT DATA - PREMATING PERIOD - SUMMARY - F1B GENERATION FEMALE RATS

GROUP (PPM)		I 0(VEHICLE)	II 250	III 500	IV 1000
RATS TESTED	N	30	30	30	30
BODY WEIGHT CHANGE (G)					
DAYS 1 - 8	MEAN±S.D.	+37.9 ± 3.8	+39.5 ± 5.3	+35.7 ± 4.7	+35.3 ± 4.6*
DAYS 8 - 15	MEAN±S.D.	+37.7 ± 5.3	+41.0 ± 5.0*	+37.7 ± 5.2	+39.5 ± 5.6
DAYS 15 - 22	MEAN±S.D.	+31.5 ± 6.2	+31.4 ± 5.2	+31.7 ± 3.9	+33.4 ± 5.4
DAYS 22 - 29	MEAN±S.D.	+22.8 ± 5.9	+24.3 ± 5.0	+24.1 ± 4.7	+23.4 ± 5.5
DAYS 29 - 36	MEAN±S.D.	+22.3 ± 6.4	+21.8 ± 5.4	+19.4 ± 5.5	+19.8 ± 5.7
DAYS 36 - 43	MEAN±S.D.	+16.5 ± 7.4	+17.5 ± 5.7	+18.2 ± 5.2	+18.1 ± 5.5
DAYS 43 - 50	MEAN±S.D.	+18.4 ± 7.1	+16.6 ± 5.2	+17.8 ± 6.2	+17.1 ± 4.7
DAYS 50 - 57	MEAN±S.D.	+13.9 ± 7.2	+10.8 ± 5.9	+13.1 ± 5.3	+13.0 ± 6.4
DAYS 57 - 64	MEAN±S.D.	+8.6 ± 7.9	+10.9 ± 5.7	+10.7 ± 7.2	+11.4 ± 5.1

DAYS - DAYS POSTMATING
* - Significantly different from the vehicle control group value (P≤0.05).

APPENDIX 3

TABLE E11 (PAGE 2): MATERNAL BODY WEIGHT DATA - FIRST LACTATION PERIOD - SUMMARY - F1B GENERATION FEMALE RATS

GROUP (PPM)	I 0(VEHICLE)	II 250	III 500	IV 1000
RATS TESTED	30	30	30	30
PREGNANT	23	27	23	25
DELIVERED LITTERS	23	27	23	25
MATERNAL BODY WEIGHT CHANGE (G)				
DAYS 1 - 4	MEAN±S.D. +2.4 ± 10.6	+4.3 ± 10.9 [26]a	+2.5 ± 8.7	-0.6 ± 13.6 [23]b
DAYS 4 - 7	MEAN±S.D. +4.6 ± 9.1 [21]c,d	+6.2 ± 8.6 [26]a	+7.9 ± 8.0	+7.3 ± 8.5 [23]b
DAYS 7 - 10	MEAN±S.D. +9.8 ± 8.5 [20]c,d	+8.5 ± 11.1 [26]b	+7.8 ± 10.0	+10.4 ± 9.2 [21]b,e,f
DAYS 10 - 14	MEAN±S.D. +6.5 ± 8.6 [21]c,d	+2.3 ± 12.0 [26]a	+6.6 ± 11.9	+12.9 ± 9.8 [21]b,e,f
DAYS 14 - 16	MEAN±S.D. +4.9 ± 15.4 [22]a	+6.4 ± 10.0 [26]a	+8.0 ± 9.3	+3.7 ± 11.5 [21]b,e,f
DAYS 16 - 18	MEAN±S.D. -0.8 ± 11.7 [20]c,d	-1.2 ± 8.7 [25]c,d	-1.0 ± 7.9 [22]d	-0.2 ± 11.1 [21]b,e,f
DAYS 18 - 21	MEAN±S.D. -3.2 ± 9.0 [20]c,d	-6.5 ± 17.6 [23]c,d	-0.3 ± 11.0 [22]d	-4.4 ± 11.1 [20]b,d,e,f
DAYS 1 - 21	MEAN±S.D. +21.5 ± 18.9 [22]c	+21.2 ± 15.4 [24]c,d	+22.7 ± 21.8	+29.9 ± 13.6 [20]b,d,e,f

DAYS = DAYS OF LACTATION
[ ] = NUMBER OF VALUES AVERAGED

a. Excludes values for dam 40, which had no pups surviving after day 3 postpartum.
b. Excludes values for dams 91 and 113, which had no pups surviving after day 1 postpartum.
c. Excludes values for dam 27, which had no pups surviving after day 4 postpartum.
d. Excludes values for dams that had interrupted water access.
e. Excludes values for dam 100, which had no pups surviving after day 8 postpartum.
f. Excludes values for dam 99, which had no pups surviving after day 9 postpartum.

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APPENDIX 4

TABLE C16 (PAGE 2)1 MATERNAL FEED CONSUMPTION DATA - FIRST LACTATION PERIOD - SUMMARY - F1 GENERATION FEMALE RATS

GROUP (PPM)	I 0(VEHICLE)	II 250	III 500	IV 1000
DATE TESTED	30	30	30	30
PREGNANT	29	29	28	27
DELIVERED LITTERS	29	29	28	27
INCLUDED IN ANALYSES	29	29	28	25a,b
MATERNAL RELATIVE FEED CONSUMPTION (G/KG/DAY)				
DAYS 1 - 4	MEAN±S.D. 90.5 ± 18.6	89.0 ± 20.2	93.1 ± 20.3 [27]c	75.0 ± 20.0**
DAYS 4 - 7	MEAN±S.D. 124.6 ± 24.2	122.0 ± 22.6	119.9 ± 19.8	105.5 ± 22.4**
DAYS 7 - 10	MEAN±S.D. 140.1 ± 19.2	142.9 ± 18.9 [28]d	145.2 ± 17.3	128.5 ± 24.5** [24]e
DAYS 10 - 14f	MEAN±S.D. 164.6 ± 18.9	165.6 ± 18.2	160.7 ± 18.7	143.6 ± 30.2* [24]e
DAYS 1 - 14f	MEAN±S.D. 135.8 ± 16.6	136.3 ± 16.6	133.8 ± 14.9 [27]c	117.1 ± 23.5** [24]e

DAYS = DAYS OF LACTATION
[ ] = NUMBER OF VALUES AVERAGED

a: Excludes values for dam 3065, which had no pups surviving on day 1 postpartum.
b: Excludes values for dam 3066, which had no pups surviving after day 1 postpartum.
c: Excludes values for dam 3029, which delivered two additional pups after completion of weighing on day 1 of lactation.
d: Excludes values that were associated with spilled feed.
e: Excludes values for dams that had interrupted water access.
f: Because it is presumed that the pups begin to consume maternal feed after day 14 of lactation, maternal feed consumption values are not tabulated for days 14 to 21 of lactation.
* Significantly different from the vehicle control group value ($P \leq 0.05$).
** Significantly different from the vehicle control group value ($P \leq 0.01$).

TABLE 116 (PAGE 2) MATERNAL FEED CONSUMPTION DATA - FIRST LACTATION PERIOD - SUMMARY - F1B CONTINUOUS FEMALE RATS

GROUP (PPM)	I 0	II 250	III 500	IV 1000
RATS TESTED	30	30	30	30
PREGNANT	23	27	23	25
DELIVERED LITTERS	23	27	23	25
MATERNAL RELATIVE FEED CONSUMPTION (G/KG/DAY)				
DAYS 1 - 4	MEAN±S.D. 80.1 ± 19.9 [23]b	87.7 ± 27.8 [26]b	78.9 ± 20.7	76.3 ± 40.1 [23]c
DAYS 4 - 7	MEAN±S.D. 112.8 ± 23.0 [21]d,e	114.4 ± 31.2 [26]b	109.9 ± 18.8 [22]e	100.8 ± 35.2 [23]c
DAYS 7 - 10	MEAN±S.D. 129.8 ± 24.3 [20]d,e	131.2 ± 23.0 [26]b	133.5 ± 23.1	126.6 ± 31.1 [21]c,f,g
DAYS 10 - 14b	MEAN±S.D. 155.6 ± 21.7 [21]d,e	154.2 ± 26.3 [26]b	154.8 ± 20.4	142.9 ± 31.6 [21]c,f,g
DAYS 1 - 14b	MEAN±S.D. 123.5 ± 20.9 [22]d	125.3 ± 22.1 [26]b	122.9 ± 17.3	116.5 ± 31.3 [21]c,f,g

DAYS = DAYS OF LACTATION
[ ] = NUMBER OF VALUES AVERAGED

a: Includes values that were associated with spilled or soiled feed.
b: Includes values for dam 40, which had no pups surviving after day 3 postpartum.
c: Includes values for dams 91 and 113, which had no pups surviving after day 1 postpartum.
d: Includes values for dam 27, which had no pups surviving after day 4 postpartum.
e: Includes values for dams that had interrupted water access.
f: Includes values for dam 186, which had no pups surviving after day 0 postpartum.
g: Includes values for dam 99, which had no pups surviving after day 9 postpartum.
h: Because it is presumed that the pups begin to consume maternal feed after day 14 of lactation, maternal feed consumption values are not tabulated for days 14 to 21 of lactation.

[RESMETHRIN]

Chronic Oral Study 83-1

EPA Reviewer: Linnea J. Hansen
Review Section IV, Toxicology Branch I (7509C)
EPA Section Head: Marion P. Copley
Review Section IV, Toxicology Branch I (7509C)

Linnea P. Hansen, Date 1/2/94
Marion Copley, Date 6/10/94

DATA EVALUATION REPORT
(Supplemental DER to Original Review, HED Doc. No. 000791)

STUDY TYPE: Chronic Oral - Dog (83-1b)

TOX. CHEM. NO: 083E

P.C.CODE.: 097801

MRID NO.: 00157961

TEST MATERIAL: SBP-1382

SYNONYMS: Resmethrin; 5-benzyl-3-furylmethyl (IRS)-cis,trans-chrysanthemate

STUDY NUMBER: 6289

SPONSOR: At time of study, S.B. Penick Corporation, Lyndhurst, NJ.
Registrant is now Roussel Bio Corporation, Lincoln Park, New Jersey

TESTING FACILITY: Food and Drug Research Lab, Waverly, NJ

TITLE OF REPORT: 180-Day Subchronic Oral Dosing Study with Resmethrin (SBP-1382) in Beagle Dogs

AUTHOR: L. Gephart, M.P.H., W. Johnson, Ph.D., Becci, Ph.D. and R. Parent, Ph.D.

REPORT ISSUED: December 18, 1980

EXECUTIVE SUMMARY: In a 180-day oral toxicity study, groups of 6 beagle dogs/dose/sex were administered resmethrin (technical,) in gelatin capsules admixed with silicate filler as vehicle. Controls received capsules containing 100 mg/kg filler only; doses not adjusted for purity) at 0, 10, 30 or 100/300 mg/kg/day in the diet. The high dose was changed from 100 mg/kg/day to 300 mg/kg/day on Day 57 of the study.

No significant treatment-related effects were observed at any dose tested. Mild liver enlargement occurred in males (+15% of controls at 300 mg/kg/day) and in females

(+27%; 16% at 30 mg/kg/day) but no microscopic lesions or changes in liver-related clinical chemistry parameters were observed. The increased liver weight is therefore considered an adaptive metabolic response to administration of the test material. Slightly increased incidence of salivation at 300 mg/kg/day was also not considered of toxicologic significance in the absence of other effects. The LOEL is >300 mg/kg/day based lack of significant toxicologic effects at the highest dose tested. The NOEL is ≥ 300 mg/kg/day.

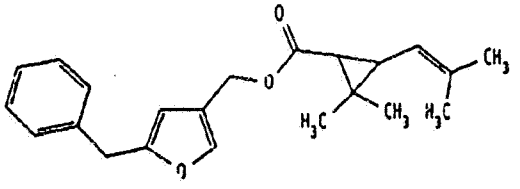
This study is Core-minimum and satisfied the guideline requirements for 83-1b, chronic toxicity study in the dog. Although no treatment-related toxicity was observed in this study, a LOEL for systemic toxicity (430 mg/kg/day) was established in a more recent 1-year dog oral toxicity study submitted (MRID 430626-01).

Special Review Criteria (40 CFR 154.7) None

Note: This DER supplement is intended to provide an Executive Summary and details of the study that were not included in the original DER. The conclusions of this supplemental DER supercede those of the original DER, where different.

A. MATERIALS:

1. Test Material: Resmethrin, technical
   Description: Light tan powder
   Lot/Batch #: 8147-LCO-1/FDRL ID No. 79-1149; 8176-RT/FDRL ID No. 80-0265; 8147-LCO-1/FDRL ID No. 80-0386
   Purity: For the 8147 lots, reported at 48.89% ai; analytical value (supplied in silicate filler)
   For the 8176 lot, 90% a.i. (technical grade, supplied neat for admixture with silicate filler).
   Stability of compound: Stable at room temperature when stored in dark
   CAS #: 10453-86-8
   Structure



2. Vehicle: Gelatin Capsules with Microcel E silicate filler (Lot no. 9199-RB, FDRL II

no. 79-1170).

3. Test animals: Species: Dog
Strain: Beagle
Age and weight at study initiation: 5-6 mos; males weighed between 6.6 - 13.1 kg; females weighed between 6.4 - 10.2 kg.
Source: Laboratory Research Enterprises, Kalamazoo, MI
Housing: Individual pens (cage type not described)
Environmental conditions: It was stated in the study report that animals were housed in a controlled environment; however, actual conditions were not reported. A 12 hr on/off photoperiod was used.
Acclimation period: not indicated

B. STUDY DESIGN:

1. Animal assignment: See original DER. Assignment to test groups was random.

Dose selection rationale: None provided. The study authors also did not indicate the rationale for using capsules instead of admixture in diet.

2. Test material dosing preparation and analysis

Test material was administered orally in gelatin capsules as a 50% w/w mixture of test material in Microcel E silicate filler, 7 days a week, for 26 weeks. Frequency of capsule administration varied with dose group: 3-5 capsules/day, controls; 1, 10 mg/kg/day; 2-3, 30 mg/kg/day; 5-10, 100 mg/kg/day or 14-34, 300 mg/kg/day. It was stated in the study protocol that dosage would be determined based on the most recent body weight measurement for each animal. Dosages were not adjusted for purity of the active ingredient (100% purity assumed).

Test material was stored frozen (reported <0°C). Concentration of test material in silicate filler was verified analytically as 48.89% a.i. Homogeneity of bulk test material (SBP-1382 in silicate filler), stability and concentration analyses of the prepared capsules were determined periodically throughout the study.

Results - Homogeneity: Measurements of the concentration of test material in Microcel E silicate filler (50% w/w) taken from top, middle and bottom layers of the material were homogeneous within 1% of each other.

Stability: Test material in silicate filler was stable for at least 7 days (only interval tested). Measurements at 7 days were within 7% of original analytical concentration.

Concentration: Samples of dosing preparations at each dose level were taken for analysis at week 1, 2, 3, 5, 8, 9, 17 and 26. Average dietary concentration was within 5% of target concentration. Occasional variations outside acceptable range (±15%) of target concentration at mid-dose at week 1, low dose at week 5 and high dose at week 26 were not considered to have significantly affected the course of the study.

3. Animals received food (Purina Certified Canine Diet #5007) and water ad libitum.

4. Statistics - Statistical analyses of body weight, food consumption, clinical chemistries and organ weight data were analyzed using one-way analysis of variance (ANOVA). Differences among groups were identified using the Least Significant Difference test. Differences were judged to be statistically significant where $p<0.05$.

5. A signed and dated quality assurance statement and GLP statement were present; however, this study was conducted prior to EPA GLP guidelines, and was conducted under FDA GLP guidelines. A Quality Insurance Unit inspected the study on several occasions.

C. METHODS AND RESULTS:

1. Observations:

Animals were inspected daily for signs of toxicity and mortality. A thorough clinical examination was performed once each week.

Results - See original DER. There was no mortality during the study. Incidence of tremors is shown below in Table 1:

TABLE 1: CLINICAL OBSERVATIONS[1]

	0 mg/kg/day	10 mg/kg/day	30 mg/kg/day	300 mg/kg
Males:				
Tremors	1 (1)[2]	0	2 (1,14)	5 (1,1,1..
Avg. time to occurrence	17	-	91	131
Salivation	2 (1,2)	1 (1)	3 (2,3,3)	6 (1,1,1,1..
Avg. time to occurrence (days)	80	71	107	88
Females:				
Tremors	0	0	1 (1)	1 (1)
Avg. time to occurrence (days)	-	-	95	142
Salivation	1 (2)	1 (2)	0	4 (5,7,..
Avg. time to occurrence (days)	59	48	-	62

1 Data taken from Table 1 and Appendix III of study report
2 Number of dogs affected (total number of days effect was observed in each an.. affected)

Although the number of males with tremors (classified as slight to mild) at 300 mg/kg/day was increased compared to controls (5 vs. 1), TB-I agrees with the original DER that this was not a treatment-related effect since frequency of observation was low (total 1-2 days/animal) at high dose. Similarly, salivation showed increased incidence and frequency among some animals at 300 mg/kg/day but with one exception (50 days for one female), frequency was low and probably not of toxicologic significance in the absence of other effects. Excess salivation may have been related to the large number of capsules administered daily to the high dose animals. Lacrimation was observed frequently among animals in all four groups.

2. Body weight

Animals were weighed prior to initiation of treatment and weekly throughout the study.

Results - Mean body weight gain for males and females at selected intervals is shown below in Table 2:

TABLE 2: MEAN BODY WEIGHT GAIN (KG) AT 13-WEEK INTERVALS[1]

DOSE, MG/KG/DAY:	0	10	30	300
MALES: Weeks 1-5	0.7	1.1	0.9	0.9
5-10	0.2	0.5	0.7	0.6
10-15	0.4	0.7	0.1	0.0
15-20	0.4	0.2	0.7	0.4
20-23	0.3	0.4	0.3	0.4
23-25	0.0	0.3	0.1	-0.1
25-26	0.0	-0.2	0.0	0.0
1-26	1.7	2.8	2.5	2.0
FEMALES: Weeks 1-5	0.5	0.5	0.6	0.7
5-10	0.3	0.4	0.4	0.2
10-15	0.1	0.0	0.0	0.0
15-20	0.5	0.5	0.5	0.2
20-23	0.4	0.2	0.4	0.4
23-25	0.3	0.0	0.0	0.2
25-26	-0.1	0.1	0.0	-0.4
1-26	2.0	1.7	1.9	1.3

1 Data taken from Table 2B of study report

Results - No treatment-related effects on body weight or body weight gain were observed. Sporadic, statistically significant differences in the mean body weight, both increases and decreases, were observed among all treated groups compared to the controls. At termination, mean body weights at 0, 10, 30 or 300 mg/kg/day were 11.6, 13.3, 12.7 or 12.1 for males and 9.8, 9.8, 9.9 or 9.3 for females, respectively. In general, the variable body weights appeared to correlate with variations in food

consumption that occurred in all groups. The decrease in mean body weight observed at 26 weeks in high dose females was not considered treatment-related since it was only observed during the last weeks of the study and was not statistically significant.

3. Food consumption

Food consumption for each animal was recorded weekly. Food efficiency was not calculated.

Results - Representative mean weekly food consumption is shown in Table 3:

TABLE 3: SELECTED MEAN DAILY FOOD CONSUMPTION (G/ANIMAL/DAY)[1]

SEX/WEEK	0 MG/KG/DAY	10 MG/KG/DAY	30 MG/KG/DAY	300 MG/KG/DAY[2]
MALES/ 1	398.3	352.5	378.3	425.0
5	525.0	512.5	437.5	582.5
10	505.8	432.8	495.8	522.2
15	473.7	618.5	469.7	563.5
20	448.0	384.2	559.2	518.3
23	539.2	452.3	550.0	549.2
26	522.7	572.2	511.8	537.3
FEMALES/1	263.3	415.7*	395.8*	365*
5	329.8	361.2	443.3	376.2
10	398.2	390.2	474.8	485.8
15	381.2	496.0	508.2	498.3
20	448.0	467.2*	288.2	273.7
23	456.7	465.0	418.3	419.2
26	397.0	496.5	368.0	257.3*

1 Data taken from Table 3 of study report
* $p < 0.05$

No treatment-related decreases in mean food consumption were seen during the study. Variable food consumption was observed among all groups. Sporadic statistically significant increases and decreases in food consumption were observed in treated animals compared to controls.

4. Ophthalmoscopic examination

Eyes were examined by indirect ophthalmoscopy following administration of a mydriatic agent prior to initiation of treatment and during Week 25.

Results - No treatment-related ocular effects were observed.

5. Blood was collected at Weeks 4, 8, 12, 16, 20 and 26 for hematology and clinical

analysis from all animals (fasted 14 - 16 hrs). The CHECKED (X) parameters were examined.

a. Hematology

X		X	
| X |	Hematocrit (HCT)*	| X |	Leukocyte differential count*
| X |	Hemoglobin (HGB)*	| |	Mean corpuscular HGB (MCH)
| X |	Leukocyte count (WBC)*	| |	Mean corpusc. HGB conc.(MCHC)
| X |	Erythrocyte count (RBC)*	| |	Mean corpusc. volume (MCV)
| X |	Platelet count*	| |	Reticulocyte count
| |	Blood clotting measurements		
| |	(Thromboplastin time)		
| |	(Clotting time)		
| |	(Prothrombin time)		

* Required for subchronic and chronic studies

Results - No treatment-related effects on blood cell parameters were observed.

b. Clinical Chemistry

X		X	
	Electrolytes:		Other:
| X |	Calcium*	| X |	Albumin*
| X |	Chloride*	| |	Blood creatinine*
| |	Magnesium	| X |	Blood urea nitrogen*
| X |	Phosphorus*	| X |	Cholesterol*
| |	Potassium*	| X |	Globulins
| X |	Sodium*	| X |	Glucose*
	Enzymes	| X |	Total bilirubin
| X |	Alkaline phosphatase (ALK)	| X |	Total serum protein (TP)*
| |	Cholinesterase (ChE)	| |	Triglycerides
| |	Creatinine phosphokinase	| |	Serum protein electrophores.
| X |	Lactic acid dehydrogenase (LDH)		
| X |	Serum alanine aminotransferase (also SGPT)*		
| X |	Serum aspartate aminotransferase (also SGOT)*		
| |	Gamma glutamyl transferase (GGT)		
| |	Glutamate dehydrogenase		

* Required for subchronic and chronic studies

Results - No biologically significant differences were observed among treated animals when compared to controls.

6. Urinalysis

Urine was collected fr[illegible]sted animals at Weeks 4, 8, 12, 16, 20 and 26. The

CHECKED (X) parameters were examined.

X		X	
X	Appearance*	X	Glucose*
	Volume*	X	Ketones*
X	Specific gravity*	X	Bilirubin*
X	pH		Blood*
X	Sediment (microscopic)*		Nitrate
X	Protein*	X	Urobilinogen

* Required for chronic studies

Results - No treatment-related effects were observed on the urinalysis parameters examined.

7. Sacrifice and Pathology

All animals were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs, in addition, were weighed.

X		X		X	
	Digestive system		Cardiovasc./Hemat.		Neurologic
	Tongue	X	Aorta*	XX	Brain*,
X	Salivary glands*	XX	Heart*	X	Periph. nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	XX	Pituitary*
X	Duodenum*	XX	Spleen	X	Eyes (optic n.)*
X	Jejunum*	X	Thymus*		Glandular
X	Ileum*		Urogenital	XX	Adrenal gland*
X	Cecum*	XX	Kidneys* +		Lacrimal gland
X	Colon*	X	Urinary bladder*	X	Mammary gland*
X	Rectum*	XX	Testes*'	XX	Parathyroids*''
XX	Liver *'	XX	Epididymides	XX	Thyroids*''
X	Gall bladder*	X	Prostate		Other
X	Pancreas*		Seminal vesicle	X	Bone*
	Respiratory	XX	Ovaries*'	X	Skeletal muscle*
X	Trachea*	XX	Uterus*	X	Skin*
X	Lung*				All gross lesions and masses*
	Nose				
	Pharynx				
	Larynx				

* Required for subchronic and chronic studies.
' Organ weight required in subchronic and chronic studies.
'' Organ weight required for non-rodent studies.

Results -

a. Organ weight - See original DER. In contrast to the original review, TB-I does n

consider the increased liver weights sufficient for establishing a NOEL in the absence of microscopic lesions or altered clinical chemistry profiles.

b. Gross pathology - No treatment-related gross lesions were observed.

c. Microscopic pathology - No treatment-related microscopic lesions were observed.

E. DISCUSSION: TB-I does not currently agree with the conclusions of original DER that a NOEL of 10 mg/kg/day and LOEL of 30 mg/kg/day were observed, based only on liver enlargement (+17% in males). This effect is considered, as noted by the study author, a result of increased hepatic metabolism of the test compound. TB-I agrees that the reported increase in salivation and mild tremors at 300 mg/kg/day were not of toxicologic significance. They were also not seen in the 1-year dog study at doses up to about 1400 mg/kg/day.

NOEL: $\geq$300 mg/kg/day
LOEL: >300 mg/kg/day

STUDY DEFICIENCIES are as follows:

- LOEL not achieved,
- Some clinical chemistry parameters not examined,
- Some details on study methods and results not included in report,
- Study conducted for 6 months; at time of conduct this was accepted by Agency
- Study not conducted under EPA GLP

Core-classification: Minimum. This study is considered acceptable for regulatory purposes, despite the deficiencies listed above, which are not expected to significantly alter the conclusions of the study. In addition, a second study in dogs (1 yr exposure) determined a similar LOEL. Although the study report did not include the % a.i. in the technical resmethrin that was not 50% in silicate filler, the information was obtained from another study (MRID 00029002) conducted by FDRL. Furthermore, based on the analytical report, the concentrations of a.i. in the dosing preparations were adequate and indicated that in general the appropriate amount of test material was administered.

[RESMETHRIN, TECH.]

Developmental Study (83-3)

EPA Reviewer: Linnea J. Hansen, Ph.D. Date 6/5/94
Review Section 4, Toxicology Branch I (7509C)
EPA Section Head: Marion P. Copley, D.V.M., D.A.B.T. , Date 6/10/94
Review Section 4, Toxicology Branch I (7509C)

DATA EVALUATION RECORD
(Supplement to Original Review, HED Doc. no. 001915)

STUDY TYPE: Developmental Study - Rat (83-3a)

TOX. CHEM. NO.: 083E

P.C. CODE: 097801

MRID No.: 00028453

TEST MATERIAL: SBP-1382, technical

SYNONYMS: Resmethrin; 5-benzyl-3-furylmethyl (IRS)-cis,trans chrysanthemate

STUDY NUMBER: 2054-066

SPONSOR: (at time of study) S.B. Penick Co., Orange Research Laboratory, Orange, NJ. Registrant is now Roussel Uclaf Corporation, Montvale, NJ

TESTING FACILITY: Booz, Allen and Hamilton, Inc., Foster D. Snell Division, Florham Park, NJ

TITLE OF REPORT: Teratologic Evaluation of SBP-1382 Technical in the Albino Rat

AUTHORS: Richard A. Machi, B.S., Claudine Kam, M.S., Michael A. Gallo, Ph.D. and Kent R. Stevens, Ph.D.

REPORT ISSUED: November 26, 1979

EXECUTIVE SUMMARY: In a developmental toxicity study, 25 pregnant Blu (SD) BR strain rats per dose group received 0, 20, 40 or 80 mg SBP 1382/kg/day (technical, 86.5% a.i.; dose not adjusted for purity of test material or increase in maternal body weight during treatment) in corn oil by gavage from gestation Day 6 through 15, inclusive. In addition, a group of 25 rats received 250 mg/kg/day aspirin (salicylic acid) as a positive control for developmental toxicity. Animals were received time-pregnant from the vendor, usually on Day 2 of gestation.

Maternal toxicity occurred at the highest dose tested (80 mg/kg/day) as statistically significant

decreases in mean body weight at Day 20 of gestation (-15% of vehicle controls) and in food consumption between Days 11-20 of gestation (-26% of vehicle controls). The decreased body weight correlated with decreased food consumption. (Positive control group showed no significant maternal toxicity; decreased body weights were due to the sharply reduced litter size). **The maternal toxicity LOEL is 80 mg/kg/day, based on reduced body weight and body weight gain, and reduced food consumption. The maternal toxicity NOEL is 40 mg/kg/day.**

Developmental toxicity was noted in the high dose groups (80 mg/kg/day) as marginally decreased mean fetal weight (-11% of vehicle controls; not statistically significant) and an increased incidence in delayed ossification of the metacarpals and metatarsals (18% litter incidence vs. 0%, controls) and partial skull (24% litter incidence, vs 13% in controls). A marginal increase in the incidence of distal metacarpals (fetal incidence 19% vs. 7%, controls) and metatarsals (fetal incidence 34% vs. 20%, controls) was also seen. **The developmental toxicity LOEL = 80 mg/kg/day, based on increased incidence of skeletal variations and delayed ossification, and on marginally decreased fetal body weight. The developmental toxicity NOEL is 40 mg/kg/day.**

This study is classified Core-Minimum and satisfies the Guideline requirement (83-3a) for a developmental toxicity (teratology) study in rats, despite several study deficiencies (see Discussion, below).

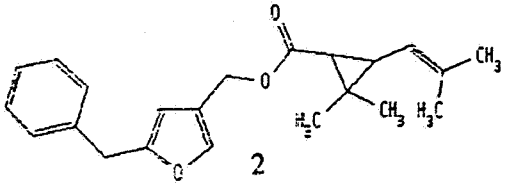
Special Review Criteria (40 CFR 154.7) None

Note: This DER supplement is intended to provide an Executive Summary and details of the study that were not included in the original DER. The conclusions of this supplemental DER supersede those of the original DER, where different.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: SBP-1382 (resmethrin)
   Description: not provided in study report
   Lot/Batch #: 9037-RB/LS#4549 (all LS lot #s assigned by laboratory)
   Purity: 85.6% a.i.
   Stability of compound: stable under storage conditions
   CAS #: 10453-86-6
   Structure



2

2. Vehicle and/or positive control: Corn Oil, Lot #LS4551, Supplier: Mazola. Positive control - salicylic acid, Lot #LS 4552 (supplier not indicated in study report).

3. Test animals: Species: Rat
Strain: BLU: (SD) BR
Age and weight at study initiation: about 13 weeks/197-300 g (females)
Source: Blue Spruce Farms, Altamont, NY
Housing: individually in suspended wire-mesh bottom cages
Environmental conditions: Temperature: 70±3°F
No other information provided

Acclimation period: none (matings were done at the supplier in 3 stages and pregnant dams were supplied 2-3 days after mating; total of 125 pregnant dams supplied).

B. PROCEDURES AND STUDY DESIGN:

1. Mating: Mating was conducted at the supplier's facility in 3 groups that were each mated 2 days apart. Females were mated 3:1 with fertile male albino rats of the same strain. Day 0 of gestation was designated as the day on which a vaginal sperm plug was observed. The number of male rats used for the matings was not indicated. About 40 pregnant females were produced in each mating group.

2. Animal Assignment and dose selection are described in the original DER. Assignment was random. Animals from each mating group were included in all the dose groups.

3. Dose selection rationale: No rationale was provided in the study report

4. Dosing: Test material and positive control were administered in corn oil in a volume of 10 ml/kg body weight/day prepared daily during the dosing period. The test material was kept in a 60°C incubator in an amber bottle during the treatment period to keep it in a molten state for dosing. The dosing solutions were not reported to have been analyzed for concentration. Solutions were prepared by adding 0.20, 0.40 or 0.80 g of molten test substance and diluted to 100 ml with corn oil to obtain the 3 dosing concentrations. Dosing was based on individual animal body weight on gestation day 6. Negative controls received corn oil only.

C. OBSERVATIONS:

1. Maternal Observations and Evaluations - The animals were checked daily for mortality or clinical signs. Dams were sacrificed by CO_2 asphyxiation on day 20 of gestation. Examinations at sacrifice consisted of examination of body and organ surfaces for grossly visible abnormalities and detailed examination of the urogenital tract. Uteri

were removed, weighed and cesarean section performed. The contents of each uterus were examined to determine number of corpora lutea, implantation sites, early/late resorptions, live/dead fetuses, sex of fetuses and body weight of all live fetuses. The above information was also collected from dams that died or were sacrificed moribund during the study, but these dams were excluded from statistical evaluation of the data.

2. Fetal Evaluations - The fetuses were examined in the following manner: All fetuses were examined grossly for visible external abnormalities. One-third of the fetuses per litter were randomly selected (and any fetus showing external abnormality) for examination of viscera, and were preserved in Bouin's fluid. Visceral examinations were conducted using the Wilson free-hand slicing technique. The remaining fetuses were fixed overnight in 70% isopropyl alcohol, macerated in 2% KOH, washed, stained with Alizarine red S dye, cleared and examined under low power magnification for variations and malformations of the skeleton.

3. Historical control data were not provided to allow comparison with concurrent controls.

D. STATISTICAL ANALYSIS: The study protocol included in the study report stated that control and test groups would be analyzed statistically using 95% confidence intervals for all percentages and proportions. Where appropriate, analysis by ANOVA using an 0.05 level of significance was employed. No further details were provided.

E. COMPLIANCE: Signed and dated GLP and Quality Assurance statements were not provided. The study was conducted prior to initiation of EPA Good Laboratory Practices. The report stated that the study was conducted according to the Booz, Allen and Hamilton Good Laboratory Procedures guidelines and that the Quality Assurance Unit reviewed the protocol and final reports.

II. RESULTS

A. MATERNAL TOXICITY: (Daily examinations conducted as described above under methods).

1. Mortality - The 18 deaths during the study described in the original DER occurred as 0, 9, 3, 2 and 4 among the vehicle control, positive control, low, mid- and high dose groups, respectively. Examination at necropsy indicated that at least 14 of these deaths were due to gavage error as indicated by fluid in lungs/thoracic cavity or red/distended stomach. No relationship of mortality to treatment with the test material was observed

2. Clinical Observations - No treatment-related clinical observations were reported. Incidence of rales and red nasal discharge were reported among all dose groups.

3. Body Weight - Mean body weights during treatment and non-treatment portions of gestation are given in the attached table taken from the study report. Mean body weight gain data is presented below in Table 1:

TABLE 1 Body Weight Gain (grams)[a]

Group:	Prior to Dosing Period	Dosing Period	Post Dosing Period	Entire Gestation Period	Corrected Body Weight Gains Dosing P.[1]	Entire[2]
Control	25.03	30.75	68.48	124.26	-1.25	54.53
Aspirin	25.44	-19.83	33.99	39.60	-32.10	27.33
LDT	22.23	16.83	85.93	124.99	49.34	58.82
MDT	26.41	35.14	63.72	110.99	-29.44	46.41
HDT	24.58	15.43	85.93	83.55	-45.88	22.24

a = Data calculated from body weight data in Table 3 of study report. Body weight gain data not analyzed statistically

[1] Corrected body weight gain for dosing period = body weight gain for dosing period minus gravid uterus weight.

[2] Corrected body weight gain for entire gestation period = body weight gain for entire gestation period minus gravid uterus weight.

Mean maternal body weight gain was decreased at 80 mg/kg/day (-33% of controls; statistically significant). The decrease was partially due to slight reduction in mean pup weight and to decreased food consumption during the latter half of gestation. However, corrected body weight gain at 80 mg/kg/day was less than half the vehicle control, low or mid-dose gain, suggesting that the decrease was also related to toxicity of resmethrin.

Positive controls: Corrected body weight gain was also significantly reduced in the aspirin-treated dams and is considered a treatment-related effect.

4. Food Consumption

The summary table of mean food consumption during gestation from the study report is attached to this DER.

Results - Treatment-related effects on food consumption were observed at 80 mg/kg/day and, to a lesser extent, at 40 mg/kg/day. Mean food consumption between Day of receipt (approximately Day 2 of gestation) and Day 20 for dams treated w

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resmethrin at 20, 40 and 80 mg/kg were 9%, 17% and 24% less, respectively, than vehicle controls. At 80 mg/kg/day, consumption was statistically significantly lower during gestation Days 6 - 21. Food efficiency calculations [using (total food consumption + uncorrected total gestational body weight gain)x100] indicate that there was a slight decrease among the high dose group (41% vs. 47%, controls and 50%, 20 and 40 mg/kg/day). In the absence of other signs of maternal toxicity, TB-I does not consider the decreases in food consumption at low and mid dose to be of toxicologic significance.

Positive controls: Food consumption was 19% lower than vehicle controls.

5. Gross Pathology - No treatment-related gross pathology was observed at necropsy.

6. Cesarean Section Data - The summary table from the study report is attached. TB-I considers the slight decrease in mean fetal body weight (-11% of controls; not statistically significant) at 80 mg/kg/day to represent a marginal treatment-related effect, possibly secondary to decreased food consumption and body weight in females at this dose.

Positive controls: Fetuses in the aspirin-treated group showed sharply reduced number of live fetuses/dam, increased resorptions/dam and decreased average fetal weight. Mean gravid uterine weight was also markedly decreased due to increased fetal death.

B. DEVELOPMENTAL TOXICITY:

1. External Examination - No treatment-related effects were observed (see original DER and attached table from study report).

2. Visceral Examination - No treatment-related effects were observed (table from study report attached; also see original DER).

Positive controls: an increased incidence of auricle engorged with blood clot and enlarged liver blood vessel were observed; however, the small number of animals (9) available for evaluation makes interpretation of variations difficult.

3. Skeletal Examination - Skeletal effects are described in the original DER; table from study report is also attached. TB-I agrees with the conclusions of the original DER. Incidence of partial skull and incompletely ossified metacarpals and metarsals showed increased litter incidence (skull, 24% vs. 13% controls; metacarpals/tarsals, 18% vs 0%, controls) the incidence of metacarpals and metatarsals showed increased fetal incidence only (19% vs. 7%, controls and 34% vs. 20%, controls, respectively), since it was already observed frequently on a liter basis in controls. TB-I notes th...

the distal metacarpal/metatarsal variation was not adequately described, since this is not a commonly observed variation.

Positive controls: An increased incidence of partial skull or skull with wide cranial suture, partially ossified ilium, ischium and pubis, partially ossified leg bones, distal metacarpals and metatarsals was observed.

III. DISCUSSION

A. MATERNAL TOXICITY: Maternal toxicity was observed at the highest dose tested (80 mg/kg/day) based on a statistically significant decrease in mean body weight on Day 20 and decreased body weight gain during gestation, corrected and total, compared to the vehicle control group. The decrease was only partially accounted for by decreased gravid uterus weight (due to slight reduction in mean fetal weight) or to decreased food consumption, which was statistically significantly lower than vehicle controls between Days 11 - 20 of gestation.

B. DEVELOPMENTAL TOXICITY:

1. Deaths/Resorptions: No treatment-related effects on fetal death or resorptions were observed at any dose level of resmethrin tested.

2. Altered Growth: A marginal decrease in mean fetal weight (-11% compared to vehicle controls) was observed at 80 mg/kg/day. Although this decrease was not statistically significant, TB-I considers it to be a marginal treatment-related effect, probably related to the decreased food consumption and body weights in dams at this dose.

3. Developmental Variations: Slightly increased incidence of skeletal variations were observed in fetuses from the 80 mg/kg/day group. These included distal metatarsals, partial skull and delayed ossification of metacarpals and metacarpals. The effects are consistent with slight delays in development and were probably secondary to maternal toxicity observed at the high dose.

4. Malformations: No treatment-related malformations were observed in this study at any dose level tested.

C. STUDY DEFICIENCIES:

- analyses of dosing solutions not conducted,
- methods used for statistical analysis not indicated,
- relatively high incidence of gavage error mortality,
- not conducted under EPA GLP (old study)

D. CORE CLASSIFICATION: Core-minimum. Although there were several deficiencies in this study, TB-I considers the study to have been adequate for assessing the developmental toxicity of resmethrin in rats. The study was conducted prior to FIFRA 1988 GLP guidelines, or development of Guidelines for 83-3.

TB-I is concerned about the high incidence of gavage errors in this study, but adequate numbers of surviving dams and litters were available for examination. Although there was no analysis of the dosing solutions themselves, the method of dose preparation was adequately described and the concentration analysis of the test material provided information on concentration and stability under the conditions of storage during this study. Actual dose concentration of resmethrin is lower than nominal, based on the purity (86.5%) and lack of correction during the dosing period for maternal body weight gain.

Maternal NOEL = 40 mg/kg/day
Maternal LOEL = 80 mg/kg/day, based on decreased maternal body weight/body weight gain and food consumption.
Developmental Toxicity NOEL = 40 mg/kg/day
Developmental Toxicity LOEL = 80 mg/kg/day, based on increased incidence of skeletal variations and marginally decreased fetal body weight.

Page _____ is not included in this copy.

Pages 49 through 55 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

✓ FIFRA registration data.

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_____ The document is not responsive to the request.

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[RESMETHRIN, TECH.]

Developmental Study (83-3)

EPA Reviewer: Linnea J. Hansen, Ph.D.
Review Section 4, Toxicology Branch I (7509C)
EPA Section Head: Marion P. Copley, D.V.M., D.A.B.T.
Review Section 4, Toxicology Branch I (7509C)

Linnea J. Hansen, Date 6/2/94

Marion Copley, Date 6/4/94

DATA EVALUATION RECORD
(Supplement to Original Review, HED Doc. no. 001911)

STUDY TYPE: Developmental Study - Rabbit (83-3b)

TOX. CHEM. NO.: 083E

P.C. CODE: 097801

MRID No.: 00029002

TEST MATERIAL: SBP-1382, technical

SYNONYMS: Resmethrin; 5-benzyl-3-furylmethyl (IRS)-cis,trans chrysanthemate

STUDY NUMBER: 6288

SPONSOR: (at time of study) S.B. Penick Co., Orange Research Laboratory, Orange, NJ. Registrant is now Roussel Uclaf Corporation, Montvale, NJ

TESTING FACILITY: Food and Drug Research Laboratories, Inc., Waverly, NY

TITLE OF REPORT: Teratologic Evaluation of SBP-1382 Technical in Albino Rabbits

AUTHORS: M. Knickerbocker, P. Becci, Ph.D. and R. Parent, Ph.D.

REPORT ISSUED: October 31, 1979

EXECUTIVE SUMMARY: In a developmental toxicity study, 20 pregnant New Zealand White Minnikin rabbits per dose group received 0, 10, 30 or 100 mg SBP 1382/kg/day (technical resmethrin, 90% a.i.; doses not adjusted for purity of test material or for body weight gain during gestation) in corn oil by gavage (1 ml/kg body wt.) from gestation Days 6 through 18, inclusive. In addition, a group of 20 rabbits received 2.5 mg/kg aqueous 2-aminonicotinamide on Day 9 of gestation as a positive control for developmental toxicity.

No maternal toxicity was observed at any dose tested (up to 100 mg/kg/day). **The maternal toxicity LOEL > 100 mg/kg/day. The maternal toxicity NOEL ≥ is 100 mg/kg/day.**

Developmental toxicity was noted in the high dose group (100 mg/kg/day) as statistically significantly increased litter incidence of fused sternebrae (38% vs. 0%, controls) and extra sternebrae (38% vs. 15%, controls). The developmental toxicity LOEL = 100 mg/kg/day, based on increased incidence of skeletal variations, and a possible marginal increase in totally resorbed litters.

This study is classified as Core-minimum and satisfies the requirement (83-3b) for a developmental toxicity (teratology) study in rabbits, despite study deficiencies (see Discussion, below).

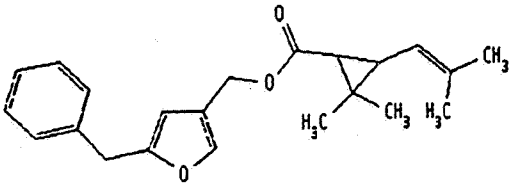
Special Review Criteria (40 CFR 154.7) None

Note: This DER supplement is intended to provide an Executive Summary and details of the study that were not included in the original DER. The conclusions of this supplemental DER supercede those of the original DER, where different.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: SBP-1382 (resmethrin)
   Description: tan crystalline solid
   Lot/Batch #: 8176-RT
   Purity: 90% a.i.
   Stability of compound: not indicated in study report
   CAS #: 10453-86-6
   Structure



2. Vehicle and/or positive control: Corn Oil, Lot and supplier not indicated.
   Positive control - 6-aminonicotinamide, Lot and supplier not indicated.

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3. Test animals: Species: Rabbit
Strain: New Zealand White Minnikin
Age and weight at study initiation: about 5 months/1.45-2.52 kg (females)
Source: Dutchland Laboratory Animals, Denver, PA
Housing: individually in wire-mesh bottom cages
Environmental conditions: It was stated that the animals were housed in temperature controlled quarters; however, data on actual conditions during the study were not provided. Animals were administered Charles River Rodent Chow (Agway) and tap water ad libitum.

Acclimation period: not indicated

B. PROCEDURES AND STUDY DESIGN:

1. Mating: Female rabbits were injected with 200 IU human chorionic gonadotropin (marginal ear vein), then placed in the male's cages to mate. Copulation was taken as positive evidence of pregnancy. It was stated in the study report that mating was performed according to the laboratory standard operating procedure, but details were not provided. No further details were provided.

2. Animal Assignment and dose selection were described in the original DER. Assignment was random. Enough females were mated (20/dose group) to allow extra females in each dose group so that in the event of excessive mortality or reduced fertility there would still be at least 12 pregnant females.

3. Dose selection rationale: No rationale was provided in the study report

4. Dosing: Test material and positive control were administered in corn oil in a volume of 1 ml/kg body weight/day prepared daily during the dosing period. The dosing solutions were not reported to have been analyzed for concentration, homogeneity and stability. Dosing was based on individual animal body weight on gestation day 6. Negative controls received corn oil only.

Positive control animals were administered 2.5 mg/kg aminonicotanimide in a total volume of 2 ml water/kg on Day 9 of gestation only.

C. OBSERVATIONS:

1. Maternal Observations and Evaluations - The animals were checked daily for mortality or clinical signs. Maternal body weights were determined on Days 0, 6, 12, 18, 1[illegible] and 29. Dams were sacrificed by intracardiac injection of a lethal dose of sodium pentobarbital on day 29 of gestation. The report did not state whether females w[illegible]

examined sacrifice for grossly visible abnormalities. Uteri were removed, weighed and cesarean section performed. The contents of each uterus were examined to determine number of corpora lutea, implantation sites, early/late resorptions, live/dead fetuses, sex of fetuses and body weight of all live fetuses. The above information was also collected from dams that died or were sacrificed moribund during the study, but these dams were excluded from statistical evaluation of the data.

2. Fetal Evaluations - The fetuses were examined in the following manner: All fetuses were examined grossly for visible external abnormalities. Fetuses were then placed in an incubator (exact temperature illegible in copy of study report) for 24 hrs to determine neonatal viability. Survivors were sacrificed by exposure chloroform vapor. All fetuses were then examined for visceral/soft tissue abnormalities. Eviscerated and skinned fetuses were processed for skeletal examination by fixation in 70% isopropyl alcohol, maceration in 3% KOH, washing, staining with Alizarin-red S dye and clearing with glycerine. Skeletons were examined under low power magnification for variations and malformations.

3. Historical control data were provided for a limited number of parameters from Dutch belted but not New Zealand Minnikin rabbits for comparison with concurrent controls (attached).

D. STATISTICAL ANALYSIS: Control and test groups were compared using 95% confidence intervals for proportions or by computation of exact probabilities. Continueous data were analyzed by one-way completely ramdon classification ANOVA for fixed effects. Statistical significance was assumed where $p < 0.05$. The least significant difference test was employed to determine which test groups differed from the control. All comparisons used the dam or litter as unit of observation.

E. COMPLIANCE: Signed and dated GLP and Quality Assurance statements were not provided. The study was conducted prior to initiation of EPA Good Laboratory Practices. The report stated that the study was conducted according to FDA Good Laboratory Procedures guidelines and that a Quality Assurance Unit reviewed the protocol and final reports.

II. RESULTS

A. MATERNAL TOXICITY: (Daily examinations conducted as described above under methods).

1. Mortality - No treatment-related mortality was observed. At 0, 10, 30 or 100 mg/kg/day, 1, 3, 0, 2 and 0 does died or were sacrificed. Three does died in the positive control group (2.5 mg/kg aminonicotinamide). The study report did :

indicate whether mortality resulted from gavage error or other cause; no gross examination was performed at necropsy to determine cause of death.

2. Clinical Observations - No treatment-related clinical observations were reported.

3. Body Weight - There were no treatment-related effects on mean maternal body weight or body weight gain. Corrected mean body weights were also similar among all groups (data not shown).

4. Food Consumption - Not measured in this study.

5. Gross Pathology - Not indicated in report if gross examinations were conducted at sacrifice.

6. Cesarean Section Data - The summary table from the study report is attached. A non-statistically significant increase in completely resorbed litters was observed at high dose: 3/16 litters (19%), vs 0% in vehicle controls and low- and mid-dose. Statistically significant increases in the number of dams with one or more resorption was increased at all dose levels but since there was no dose-related increase, TB-I considers it to be sporadic and not a treatment-related effect.

   Also attached to this DER are additional calculations of cesarean parameters on fetal survival from a letter (Dr. Ralph Fogleman to Dr. Maarten deVries, 1-14-80) that were included with the study report. No significant treatment-related effects were observed following treatment with resmethrin.

   Positive controls showed pronounced reduction of the number of fetuses/dam, average fetal weight, viability and total litter resorption (60%).

B. DEVELOPMENTAL TOXICITY:

1. External Examination - No treatment-related effects were observed (see attached table from study report).

   Positive controls showed statistically significant increases in the incidence of clubbed feet, crossed hindlegs, underdeveloped eyes, harelip, short tail and small size.

2. Visceral Examination - No treatment-related effects were observed (table from study report attached). TB-I does not currently agree with the original DER that the occurrence of "dark liver" at all dose levels in treated fetuses only was related to treatment since the incidence did not show a dose-response.

3. Skeletal Examination - Skeletal effects are described in the original DER; table from study report is attached. TB-I agrees with the conclusions of the original DER that the sternebral effects (fused and extra) were treatment-related effects.

Positive controls showed statistically significant increases in the incidence of fused and extra sternebrae, scrambled vertebrae, tail defects and scoliosis. Incomplete ossification of the sternebrae (not statistically significant) was also observed in 5/6 litters.

III. DISCUSSION

A. MATERNAL TOXICITY: There was no evidence of maternal toxicity observed in this study.

B. DEVELOPMENTAL TOXICITY:

1. Deaths/Resorptions: A slight increase in totally resorbed litters was observed at 100 mg/kg/day; 3 litters (19%) were affected compared to 0 at all doses (except for the positive control, which had 60% litters affected. This increase was not statistically significant, and litter resorption is not uncommon among rabbits. TB-I considers the increase a possible marginal effect of treatment. Statistically significant increases at low and mid dose in the number of does with one or more resorption were considered a sporadic occurence.

2. Altered Growth: No treatment-related effects on fetal growth were observed.

3. Developmental Variations: Statistically significant increases in the incidence of skeletal variations (fused sternebrae and extra sternebrae) were observed in fetuses at 100 mg/kg/day. Historical control data was not available for comparison. TB-I considers this to be a treatment-related effect. Although incidence of dark livers were reported in all treatment groups (liver incidence about 25%), it is not considered a clear treatment-related effect since neither fetal nor litter incidence showed a dose-response.

4. Malformations: No treatment-related malformations were observed in this study at any dose level tested.

C. STUDY DEFICIENCIES:

- analyses of dosing solutions not included (stated to have been summarized in Volume V, not in the study report available to the reviewer,
- method used for statistical analysis not indicated,
- not conducted under EPA GLP (old study),
- incubation of fetuses for 24 hrs after cesarean section, which would interfere with

detection of delayed ossification,
- numerous details of the study procedure (eg mating procedure, enviromental conditions) were omitted from the study report,
- pre- and postimplantation loss not determined,
- complete gross examinations of dams at sacrifice not performed.

D. CORE CLASSIFICATION: Core-Minimum. The study is considered adequate for regulatory purposes despite the above deficiencies, since adequate numbers of litters were available for analysis and a NOEL/LOEL for developmental toxicity was established. Although the ability to detect delayed ossification may have been compromised by the study design, there was no maternal toxicity and no effect on fetal growth which might have caused increased incidence of this effect. The study was conducted under FDA GLP guidelines and with quality assurance, and for the most part was conducted according to standard procedures for developmental toxicity studies.

Maternal NOEL $\geq$ 100 mg/kg/day
Maternal LOEL > 100 mg/kg/day.
Developmental Toxicity NOEL = 30 mg/kg/day
Developmental Toxicity LOEL = 100 mg/kg/day, based on increased incidence of skeletal variations and possibly slightly increased total litter resorption.

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Pages 63 through 69 are not included in this copy.

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EPA Reviewer: Linnea J. Hansen, Ph.D. Linnea T. Hansen, Date 10/26/94
Review Section IV, Toxicology Branch I (7509C)
EPA Section Head: Marion P. Copley, D.V.M., D.A.B.T. Marion Copley, Date 11/4/94
Review Section IV, Toxicology Branch I (7509C)

DATA EVALUATION RECORD
Supplemental to Original DERs, HED Doc. Nos. 001908 and 002266)

STUDY TYPE: Multigeneration Reproduction - 3-Generation Study in Rat (83-4)

TOX. CHEM. NO.: 083E

P.C. CODE: 097801

MRID NO.: 00081276

TEST MATERIAL: SBP-1382®, technical

SYNONYMS: Resmethrin; 5-benzyl-furylmethyl (IRS)-cis,trans-chrysanthemate

STUDY NUMBER: 5739

SPONSOR: Roussel Bio Corporation, Lincoln Park, NJ (at time of submission, S.B. Penick, Lyndhurst, NJ)

TESTING FACILITY: Food and Drug Research Laboratories, Inc.

TITLE OF REPORT: The Evaluation of the Effects of SBP-1382® Following Dietary Administration Through Three Generations in Sprague-Dawley Rats.

AUTHOR: Charles S. Schwartz, B.S., Larry Gephart, M.P.H., Peter J. Becci, Ph.D. and Richard A. Parent, Ph.D.

REPORT ISSUED: July 13, 1979

EXECUTIVE SUMMARY: In a 3-generation reproduction study, male and female Wistar rats were administered SBP-1382 (resmethrin, technical, 90% a.i.) in the diet continuously at concentrations of 0, 500, 800 or 1250 ppm (0, 47, 79 or 123 mg/kg/day, average premating values based on actual mean food consumption and body weights). F_0, F_{1a} and F_{2a} males and females were mated 1:1 for up to 1 week after at least 10 weeks (F_0) or 8 weeks (F_{1a} and F_{2a}) of test diet administration before the first mating, and a 2-week rest period between matings.

At 500 ppm (47 mg/kg/day), decreased mean pup weight at Day 21 (5 - 9% less than control; F_{1a}, F_{1b}, F_{3a} litters; statistically significant) and increased incidence of stillborn pups in the F_{1b} litters (4.3% vs. 1.2%, controls; statistically significant) were observed. In addition, at 800 and

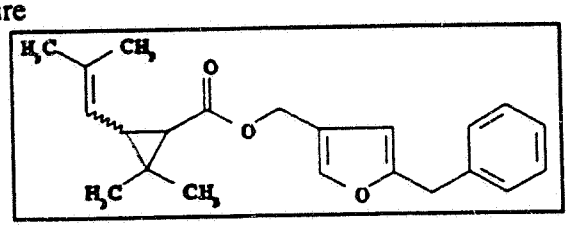
1250 ppm, dose-dependent, statistically significantly decreased viability indices and pup birth weights were observed in some or all generation litters. Parental F_1 and F_2 males and females at 800 and 1250 ppm had decreased mean body weight, but not gain, (10% less than controls during first weeks of premating), resulting from their reduced body weight at weaning. At 1250 ppm, dams had reduced body weight, but not gain, during late F_{2a} and F_{3b} gestation and during lactation (up to 10% less than controls) which were secondary to initially lower body weight and to the reduction in litter size. **The LEL for systemic/reproductive/offspring toxicity is 500 ppm (47 mg/kg/day), based on decreased mean pup weight and increased stillborn pups in the F_{3b} generation litters. The NOEL for systemic/reproductive/offspring toxicity is less than 500 ppm.**

This study is Core-minimum and satisfies the guideline requirement for a reproduction study (83-4) in the rat. Although a NOEL was not determined in this study, a 2-generation reproduction study provided a NOEL of 34.8 mg/kg/day (500 ppm).

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: SBP-1382® (resmethrin), technical
   Description: brown crystalline solid
   Lot/Batch #: 8176-RT
   * Purity: 90%
   Stability of compound: Stable at room temperature when stored in dark (information taken from 1-year dog feeding study)
   CAS #: 10453-86-8
   Structure



2. Vehicle: Mazola® corn oil

3. Test animals: Species: Rat
   Strain: Sprague-Dawley BLU (SD)
   Age/wt. at receipt: Weanling/approx. 50 g
   Source: Blue Spruce Farms Inc., Altamont, NY
   Housing and environmental conditions: Housed individually (exce during mating) according to standard FDRL procedures and NI laboratory animal guidance (NIH-78-23); no further det provided.

Acclimation period: about 8 days

4. Diet preparation and analysis: Diet was prepared weekly by melting the test substance at 100°C, mixing with Mazola® corn oil and combining appropriate amounts of test substance with diet to give a 10% premix, which was used to prepare the three test dietary concentrations. Treated diets were stored at room temperature in plastic bags.

Test compound concentration in the diet was analyzed in samples taken at 3-month intervals. Stability of the test compound in diet under environmental conditions was tested at each concentration by removing samples of a test diet preparation from feeders daily for 1 week. Duplicate samples were analyzed using gas chromatography methods.

Results - Homogeneity Analysis: Not conducted.

Stability Analysis: After 1 week, slight decreases in the concentration of test compound in diet were observed at 500, 800 and 1250 ppm ($\leq 10\%$).

Concentration Analysis: When adjusted for recovery, analytically determined dietary concentrations were within 10% of target concentration except for the initial sampling of the 500 and 800 ppm diets, where concentrations were 78% and 86%.

5. Animals received food (Agway Charles River RMH Commercial Laboratory Chow) and water ad libitum.

B. STUDY DESIGN AND MATING PROCEDURES

1. Animal assignment: P_1 animals were randomly assigned to test groups shown below:

TABLE 1 Animal Assignment: P1 Generation

Test groups No.	Designation	Dose (ppm)[1]	Animals per group[2] Males	Females
1	Control	0	20	20
2	Low (LDT)	500	20	20
3	Mid	800	20	20
4	High (HDT)	1250	20	20

1 Diets were administered from the beginning of the study until the animals were sacrificed.
2 The same number of animals were picked from the F_{1a} litters as parents for the F_2 generation.

2. Mating procedure: One male and one female were placed (random assignment) in the male's cage for up to 7 days. Females were examined daily for evidence of mating and those females with copulatory plugs were

removed to their individual cage. The day on which evidence of mating was observed was designated Day 0 of gestation. Any female showing no evidence of mating after 7 days was placed with another male for up to 7 days. Females that did not mate after cohabitation with 3 males were not included in the study. Dams with vaginal plugs that did not show large weight gain indicative of pregnancy on Day 8 of presumed gestation were remated and recording of gestation weights continued according to both mating dates until determination of actual successful mating date was made (eg. second vaginal plug, body weight gain).

3. Mating schedule: Matings were conducted with males and females from the F_0 parental generation and with animals culled from the F_{1a} and F_{2a} generations (at least 1/sex/litter), avoiding sibling matings. For the F_0 generation matings, males and females were cohabited after 10 weeks' administration of test diet at the appropriate dietary dose levels. The second mating of F_0 animals was conducted following a 2-week rest period after weaning of F_{1a} pups.

   For the F_{1a} and F_{2a} parental animals, cohabitation was initiated after 8 weeks post-weaning. The second mating period was initiated after a rest period of 2 weeks after weaning of the F_{2a} or F_{3a} generation pups.

4. Culling of litters and selection of F_1 parental animals: All litters larger than 8 pups were culled to 8 on Day 4 postpartum. Whenever possible, equal numbers of males and females were retained in a litter. From the remaining F_{1a} and F_{2a} pups, 20 males and 20 females/dose level were randomly selected on Day 21 postpartum and used for the second- and third-generation matings.

5. Dose selection rational: No information provided.

C. METHODS

1. Observation Schedule

   a. Parental animals: Observations and the schedule for those observations are summarized below in Table 2.

TABLE 2: Observation Schedule

Viability and clinical signs:	1X/day
Body weight and food consumption	
F_0 Premating:	Weekly, first 10 weeks of study
F_0 Mating Interval:	Weekly, 2 week interval between F_{1a} weaning and second mating
F_{1a} and F_{2a} Premating:	Weekly, 8 week interval between weaning and mating
F_{1a} and F_{2a} Mating Interval:	Weekly, 2 week interval between F_{2a}/F_{2b} weanings and second matings
Mating:	not recorded
Gestation:	Days 0, 8, 15 and 19; body weight only on day 25
Lactation:	Days 28, 35 and 42 after presumed Day 0 of gestation

b. Reproductive performance: Parental reproductive performance was assessed from breeding and parturition records of animals in the study. The following indices were calculated:

$$\text{Male fertility index} = \frac{\text{No. females pregnant}}{\text{No. males mated}} \times 100$$

$$\text{Female fertility index} = \frac{\text{No. females presumed pregnant}}{\text{Total no. females mated}} \times 100$$

$$\text{Gestation index} = \frac{\text{No. live litters born}}{\text{No. confirmed pregnancies}} \times 100$$

c. Litter observations: The following litter observations were made:

TABLE 3 F1/F2 Litter Observation Schedule

Number of live pups:	At Birth and Lactation Days 1,4,21
Pup weight:	At Birth and Lactation Days 1,4,21
External alterations:	At Birth and Lactation Days 1,4,21
Number of dead pups:	At Birth and Lactation Days 1,4,21
Sex of each pup (m/f):	At Birth and Lactation Days 1,4,21

The following litter indices were calculated:

$$\text{Stillborn index} = \frac{\text{No. stillborn pups}}{\text{No. live + dead pups born}} \times 100$$

$$\text{Viability index} = \frac{\text{No. live pups at day 4}}{\text{No. pups born alive}} \times 100$$

$$\text{Lactation index} = \frac{\text{No. live pups at day 21}}{\text{No. pups born alive}} \times 100$$

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d. Necropsy

1) Parental animals: All surviving parental P_1 and F_1 males were sacrificed as soon as possible after the second litters were produced in that generation. Maternal animals were sacrificed on Day 21 postpartum after the last litter of each generation was weaned. Females that did not bear young were sacrificed on Day 21 of presumed gestation. All animals were sacrificed by chloroform anesthesia.

Necropsy observations: The only animals given post-mortem gross or microscopic examinations were the F_{2a} males and females. Gross examinations were performed. The following tissues (X) were preserved in 10% buffered formalin (but not examined microscopically):

Reproductive organs:

X Ovaries	X Epididymides
X Uterus	X Prostate
X Vagina/cervix	X Seminal vesicles/coagulating gland
	X Testes

Other organs/tissues:

X Brain	X Eyes
X Liver	X Pituitary gland
X Stomach	X Spleen
X Pancreas	X Thyroid
X Large intestine	X Parathyroids
X Small intestine	X Adrenals
X Heart	X Gross lesions
X Kidneys	X Lungs
X Urinary bladder	

2) Offspring: Culled offspring from each litter generation were sacrificed on Day 4 postpartum. The offspring maintained through lactation and not selected as parental animals were sacrificed at 21 days of age. All sacrifices were by chloroform anesthesia. All pups were discarded after sacrifice.

D. STATISTICAL ANALYSIS: Body weight, food consumption and continuous reproductive data were evaluated by ANOVA (one-way). Discrete data were evaluated by binomial expansion methods. When dose responses were evident, they were evaluated by partitioning the treatment variance to yield variance due to linear regression as described by Remington and Schork. Significance was identified where $p \leq 0.05$.

II. RESULTS See original DER

Attached tables The following tables taken from the study report provide information not included in the original DER:

- Selected mean parental body weights, pre- or intermating (statistically significant decreases);
- Dam mean body weight, F_{2a} and F_{3b} gestations (statistically significant decreases);
- Dam mean body weight gain, all generations;
- Litter observations, all generations;
- Pups cast dead, all generations;
- Viability index, all generations

III. DISCUSSION

TB-I agreed with the conclusions of the original DER that a NOEL was not established in this study for reproductive effects based on decreased Day 21 body weights at all dose levels tested in several litter generations, and on increased stillborn pups in the F_{3b} generation at all dose levels tested. At 800 and 1250 ppm, viability index and pup birth weight were also affected in some or all litters.

The reduced body weights of the parental animals at 800 and/or 1250 ppm are not considered direct systemic toxicity effects, but rather appear to be secondary to reproductive effects. Body weights, but not body weight gain, of F_{1a} and F_{2a} premating parental animals were lower because birth and/or Day 21 weights were lower. Gain in these animals was comparable to controls. (Statistically significant reductions in mean body weight in F_0 males and females at week 2 were related to a transient decrease in food consumption and did not persist thereafter). Reduced gestation/lactation body weight in F_{2a} andF_{3b} dams was related to smaller weights on Day 0 of gestation, as well as smaller litter size. Total body weight gain was comparable to controls. A separate NOEL/LEL for parental systemic toxicity was therefore not determined.

A NOEL for reproductive toxicity was not determined in this study, but a NOEL of 34.8 mg/kg/day (500 ppm; actual daily intake was lower in that study because animals were larger) was identified in a later study (MRID 431891-01). The effects observed in both studies were consistent. Both studies indicate that effects on growth of pups during lactation and on very young animals are observed at dietary concentrations of resmethrin that do not cause toxicity in mature animals.

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Pages 77 through 90 are not included in this copy.

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