

US EPA ARCHIVE DOCUMENT





13544



014928

| | |
|--------------------------|-------------------|
| Chemical: | Dimethoate |
| PC Code: | 035001 |
| HED File Code | 13000 Tox Reviews |
| Memo Date: | 03/03/93 |
| File ID: | TX010065 |
| Accession Number: | 412-02-0004 |

HED Records Reference Center
10/01/2001



CASSELL/FBI



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MAR 3 1993

010065

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

Subject: EPA ID # 035001: Dimethoate - Review of Reproductive Toxicity in Rats

Tox. Chem. Number: 358
Project Number: D177626
Submission Number: S417081
MRID No.: 422515-01
PC Code: 035001

From: Paul Chin, PhD *Paul Chin 12/24/92*
Section 2
Toxicology Branch I
Health Effects Division (H7509C)

To: Don Mackey/Larry Schnaubelt PM 72
Reregistration Branch
Special Review and Reregistration Division (H7508W)

Thru: Melba Morrow, DVM *msm 12/24/92*
Acting Section Head
Section 2, Toxicology Branch I
Health Effects Division (H7509C) *3/1/93*

I. CONCLUSIONS:

The following conclusions have been made regarding the reproductive toxicity of dimethoate:

- 1. Reproductive toxicity study in rat (MRID No.422515-01)

This study satisfies the guideline requirements (83-4) for a reproductive toxicity study in rats.

CLASSIFICATION (Core-Grade): minimum

A reproductive toxicity study was conducted in which Crl:CD BR rats were fed dimethoate in the diet at dosage levels of 0, 1, 15, or 65 ppm (during pre-mating, for males 0.08, 1.20, and 5.46 mg/kg/day and for females 0.09, 1.30, and 6.04 mg/kg/day, respectively).

Parental NOEL = 1 ppm (M/F: 0.08/0.09 mg/kg/day)
Parental LEL = 15 ppm (M/F: 1.2/1.3 mg/kg/day)

based on decreased cholinesterase activity in both sexes and generations.
Based on the findings of the study and DER, the following conclusions were made:

Tentative Reproductive NOEL = 15 ppm
Tentative Reproductive LEL = 65 ppm
based on decreased fertility in the F1b, F2a, and F2b matings;
decreased pup body weight during the lactation period for both sexes and generations;
decreased live births in the F2b litters

However, these findings may not be ~~be~~ indicative of reproductive toxicity as discussed in the attached memorandum from Morrow¹. Therefore, it is recommended that RfD committee provide their opinion.

Test species (strain): rat (Cr1:CD BR)
Route of administration: oral (diet)

II. ACTION REQUESTED:

Review and evaluate the following toxicological study:

1. Reproductive toxicity study in rat

Copy of the DER is provided for your reference.

C:\wp51\dimethoate\repro.mem 2/22/93

¹ M. S. Morrow (dated 1/26/93). Dimethoate--Addendum to the Two Generation Reproduction Study (in Rats)

Reviewer: Melba S. Morrow, DVM *msm 1/26/93*
Toxicology Branch I, Section II

Dimethoate- Addendum to the Two Generation Reproduction Study

Tox. Chem #: 358

MRID #: 422515-01

Study #: DTF 11/91154

Title of Report: The Effect of Dimethoate on Reproductive Function of Two Generations in the Rat

Authors: A.J. Booker, et. al.

Report Issued: 1/10/92

Doses Tested: 0, 1, 15 and 65 ppm

DISCUSSION:

From the data presented in the reproduction study, it was concluded that the reproductive NOEL was 15 ppm and the LOEL was 65 ppm based on subfertility and decreased mean pup weights. The original DER for this study suggested that at 65 ppm, the statistically significant decreases observed for fertility index, number of live pups per litter and mean pup weights were associated with the administration of dimethoate and were all considered to be reproductive effects. It is however, the opinion of this reviewer that the significance of these findings, as they relate to the reproductive toxicity of the compound, are equivocal.

The fertility index (# females delivering/ # sperm positive females) was lower than controls at the highest dose tested in the F1b matings and in both F2 matings. Although these values were not considered statistically significant, the effects were believed to be associated with the administration of the test material. It is believed that the fertility in these animals may have been compromised by the fact that after two successive matings, the animals may have been beyond the period of peak reproductive performance when the second mating was attempted. Additionally, it is possible that the cumulative systemic effects of the compound may be manifested clinically as "dullness" in behavior leading to disinterest in the act of mating, and resulted in what appears to be a real effect on reproduction (fertility).

The amount of time required for half of the paired females to mate in the first mating of the F0 generation was 2.5, 3.0, 3.0 and 3.0 days for the control, low, mid and high dose groups, respectively. By the second mating in this generation, the time required for mating was 3, 3, 2 and 4 days for the control, low, mid and high

dose groups, respectively. During the second mating, three animals in the high dose group were cohabitated for a period that was in excess of two weeks.

Similar findings were present in the F1 second matings, with pre-coital times being 3, 4 and 5 days for the control, low and mid dose groups. Pre-coital times were not calculated for the high dose F1 animals at the second mating because only half of the females in this dose group mated during the 20 day cohabitation period. The pre-coital times tend to support the suggestion that the animals may have been disinterested in mating and the effects on fertility are secondary to the systemic effects of dimethoate.

With regard to the number of live pups/litter, significant differences were reported for the high dose animals in the F1a and F2b generations. The observation made for the F1a generation is not considered to be biologically significant and has no bearing on the reproductive toxicity of the test material. In this generation, the mean number of pups per litter at 65 ppm was 14.2, compared to 16.2 for controls. Both of these numbers are at the high end of the normal range for litter sizes and at 65 ppm, the litter size was approximately equal to or higher than the numbers reported for subsequent control groups. (14.8, 13.9 and 12.1 for F1b, F2a and F2b control groups, respectively).

The biological significance of the 10 pups per litter reported for the F2b high dose animals is questionable. This number may be indicative of a marginal effect on fertility or it may be an anomalous finding.

Mean pup body weights at 65 ppm were statistically lower than controls at day 21 of lactation for F1a, F1b and F2a pups. In the F1b and F2a pups, significantly lower body weights were reported for high dose pups at day 8 of lactation. The day 21 pup weights are believed to be compound related but may be indicative of systemic toxicity based on the fact that at this age, pups were probably consuming feed containing the test material. Furthermore, since the effects on body weight were not reported at day 0, the observed effects may be more developmental in nature (retarded growth) rather than reproductive.

All of these factors should be considered when assessing the reproductive toxicity of the compound. Most of the observed effects could be associated with the systemic toxicity of the compound.

FINAL

DATA EVALUATION REPORT

DIMETHOATE

Study Type: Reproductive Toxicity

Prepared for:

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031

| | | | |
|----------------------|----------------------|------|----------------|
| Principal Reviewer | <u>Pia Lindström</u> | Date | <u>12/8/92</u> |
| | Pia Lindström, DPH | | |
| Independent Reviewer | <u>Sanju Diwan</u> | Date | <u>12/8/92</u> |
| | Sanju Diwan, Ph.D. | | |
| QA/QC Manager | <u>Sharon Segal</u> | Date | <u>12/8/92</u> |
| | Sharon Segal, Ph.D. | | |

Contract Number: 68D10075
Work Assignment Number: 1-124
Clement Number: 93-114
Project Officer: James Scott

Guideline Series 83-4: Reproductive Toxicity

EPA Reviewer: Paul Chin, Ph.D.
Review Section II, Toxicology Branch I/HED

Signature: Paul Chin
Date: 12/15/92

Acting EPA Section Head: Melba Morrow, D.V.M.
Review Section II, Toxicology Branch I/HED

Signature: M Morrow
Date: 12/17/92

010065

DATA EVALUATION REPORT

STUDY TYPE: Reproductive toxicity; Guideline No: 83-4

EPA IDENTIFICATION NUMBERS

TOX CHEM. NUMBER.: 358
PC code: 035001
MRID NUMBER.: 422515-01

DP Barcode: D177626

TEST MATERIAL: O,O-dimethyl-S-(N-methylcarbamoylmethyl) phosphorodithioate

SYNONYMS: Dimethoate; Fosfamid; AC 12880; Cekuthoate; Daphene; De-Fend; Devigon; Dimet; Dimethogen; Trimethion

SPONSOR: The Dimethoate Task Force (address not reported)

STUDY NUMBER: DTF 11/91154

TESTING FACILITY: Huntingdon Research Centre, Ltd., Cambridgeshire, England

TITLE OF REPORT: The Effect of Dimethoate on Reproductive Function of Two-Generations in the Rat

AUTHORS: A.J. Brooker, B.A. Homan, C.A. Parker, J.M. Offer, A. Anderson, and I.S. Dawe

REPORT ISSUED: January 10, 1992

CONCLUSIONS: In a two-generation reproduction study, Crl:CD®BR rats were fed dimethoate in the diet at dosage levels of 0, 1, 15, or 65 ppm (during pre-mating, for males 0.08, 1.20, and 5.46 mg/kg/day and for females 0.09, 1.30, and 6.04 mg/kg/day, respectively). Compound-related systemic toxicity was observed at 15 and 65 ppm as evidenced by decreased cholinesterase activity in both sexes and generations. In addition, female body weight gain at 15 and 65 ppm was decreased in both generations during the gestation periods. Based on these results, the NOEL and LOEL for parental toxicity were 1 and 15 ppm, respectively.

Compound-related reproductive toxicity was observed at 65 ppm. Effects were manifested as decreased fertility in the F_{1B}, F_{2A}, and F_{2B} matings; decreased pup body weight during the lactation period for both sexes and generations; and decreased live born litter sizes in F_{1A} and F_{2B} litters. Based on these

Guideline Series 83-4: Reproductive Toxicity

results, the NOEL and LOEL for reproductive toxicity were 15 and 65 ppm, respectively.

CLASSIFICATION: CORE Minimum Data. This study meets the minimum requirements set forth under Guideline Series 83-4 for a two-generation reproductive toxicity study in rats. The following study deficiencies were observed:

Body weight gain data for parental animals were not provided.
Insufficient historical control data were submitted.
Clinical signs were recorded only once a week.
Food consumption data were of limited use since the animals were not individually housed (except for pregnant females).
Standard deviations were not reported for several parameters.
Summary data of body weight during lactation were incorrect.

A. MATERIALS

Test Compound

Purity: 96.44%
Description: White crystalline solid
Stability: Stable at 4°C for 2 years
Batch number: 611A
Date Received: February 7, 1989 and January 16, 1990
Contaminants: Not reported

Vehicle: Ethanol (the test material was dissolved in ethanol before mixing with the diet)

Test Animals

Species: Rat
Strain: Crl:CD® (SD) BR VAF/PLUS
Source: Charles River France, Limited, St. Aubin les Elbeuf, France
Age: F₀ males--7 weeks at start of study
F₀ females--7 weeks at start of study
Weight: F₀ males--224-322 g at start of study
F₀ females--169-234 g at start of study

B. STUDY DESIGN

This study was designed to assess the potential of dimethoate to cause reproductive toxicity when administered continuously in the diet for two successive generations.

Mating: After 20 days of acclimatization followed by 70 days of dietary treatment, the F₀ females were mated with males from the same group in a ratio of 1:1 until evidence of mating (presence of sperm in a vaginal smear) was obtained or for a maximum of 20 days. The day on which mating was confirmed was designated day 0 of gestation. The F₀ females were allowed a rest period of 10 days before the second mating. The F₁ animals were mated twice in a similar fashion following at least 84 days on the test diet. In addition, a third mating was carried out with the

F₁ males and females that had previously been unsuccessful in the two earlier matings. Sibling matings were avoided.

Environmental Conditions: Females were housed four/cage during pre-mating and individually following the mating period. Males were housed four/cage throughout the study with the exception of the mating period. A 12/12-hour light/dark cycle was maintained. The temperature was 21°C; the humidity was 55%.

Group Arrangement: Parental animals were distributed amongst four groups using a computer-generated randomization based on the body weight five days after arrival as follows:

| Test Group | Dietary Level (ppm) | Number Assigned per Group | | | |
|------------|---------------------|---------------------------|---------|----------------|---------|
| | | F ₀ | | F ₁ | |
| | | Males | Females | Males | Females |
| Control | 0 | 28 | 28 | 24 | 24 |
| Low-dose | 1 | 28 | 28 | 24 | 24 |
| Mid-dose | 15 | 28 | 28 | 24 | 24 |
| High-dose | 65 | 28 | 28 | 24 | 24 |

Dosage Administered: The test material was administered continuously in the diet (Labsure Laboratory Diet No. 2) for two consecutive generations. The test diets were adjusted for purity. Diets were prepared weekly and stored frozen until used. A premix was prepared by dissolving the test material in ethanol and then mixing it with the diet and placing it in a rotary evaporator at room temperature to allow the ethanol to evaporate. The proper concentrations and homogeneity were achieved by diluting this premix with the rodent chow and either manually shaking the diets in plastic bags for three minutes or, for larger quantities, by using a rotary double cone blender for seven minutes. The control diets were also treated with ethanol. All diets were stored frozen until used. Stability, concentration, and homogeneity of the test material in the diet were analyzed prior to start of the study. In addition, concentration analyses were conducted on samples from all dosage levels for each generation at the start of pre-mating and mating periods and at the end of pregnancy/start of lactation.

Dosage Rationale: Dosages were selected based upon a preliminary study (No. DTF 10/891204A); at 75 and 100 ppm, "...obvious signs of toxicity to females and offspring..." were elicited. (No further details were given.)

Observations: Observations for mortality and moribundity were conducted once a day. Clinical signs were recorded daily for the first two weeks for the F₀ animals and for the first week for the F₁ animals. Thereafter, clinical signs were only recorded weekly. Food consumption was recorded at one- or two-day intervals for the first pre-mating periods for each generation, but not for the gestation and lactation periods, and

was reported on a weekly basis. Water consumption was recorded daily for the first and last two weeks during the first pre-mating periods for each generation. Body weight was recorded weekly; for females during gestation, it was recorded on days 0, 7, 14, 17, and 20; and for females during lactation, it was recorded on days 0, 4, 7, 14, and 21. Erythrocyte and plasma cholinesterase activities were determined two weeks prior to each mating in the F₀ generation; four weeks postweaning, two weeks prior to the first mating and in the week preceding the second mating in the F₁ generation; and prior to terminal sacrifice for both generations. Blood was drawn from the orbital sinus for these determinations.

The following data were recorded for each litter with the exception of the F_{2C} litters:

- Number of live and dead pups, pup weight, sex, and external abnormalities at birth
- Dead and/or abnormal pups daily
- Pup weight on days 4, 8, 12, 16, and 21
- Surface righting reflex from day 1; startle reflex from day 11; gripping reflex once on day 13 or 16; air righting reflex from day 14; and pupil reflex once on day 20
- Onset of vaginal opening for all females from day 28 and occurrence of cleavage of the balanopreputial skinfold for all males from day 35

The following data were recorded for the F_{2C} litters:

- Number of live and dead pups, pup weight, sex, and external abnormalities at birth and on day 4

On lactational day 4, pups were randomly culled to 4/sex/litter whenever possible; culled pups and pups found dead were necropsied. Pups with anomalies were preserved in fixative for future evaluation. The brain from one male and one female culled pup/litter was weighed and frozen for later evaluation of cholinesterase activity. Twenty-four male and twenty-four female F₁ pups were randomly selected as F₁ parental animals. The remaining pups were sacrificed and necropsied.

Parental animals found dead or sacrificed moribund and females that did not deliver were necropsied. Pregnancy status was confirmed by Salewski's method. Parental F₀ and F₁ animals were sacrificed and subjected to a gross pathological examination (F₀ males and females after 119-120 and 117-132 days of feeding, respectively; F₁ males and females after 158-167 and 151-177 days of feeding, respectively). The following tissues were collected and examined histologically at the control and high-dosage levels:

- | | | |
|---------------------|----------------|-----------|
| - Coagulating gland | - Pituitary | - Ovaries |
| - Seminal vesicles | - Testes | - Uterus |
| - Prostate | - Epididymides | - Vagina |

The following organ weight data were recorded (in pairs whenever appropriate):

- | | |
|------------|------------|
| - Adrenals | - Brain |
| - Heart | - Kidneys |
| - Liver | - Lungs |
| - Ovaries | - Prostate |
| - Testes | - Thymus |

Statistical Analysis: The following analyses were conducted.

- Body weight gain, food consumption, and cholinesterase activity--ANOVA and William's test for intergroup comparisons of parametric data or Kruskal-Wallis test and Shirley's test for intergroup comparisons of nonparametric data
- Litter size, pup loss, litter weight, pup weight, sex ratio at birth, and developmental landmarks--Kruskal-Wallis test and Shirley's test for intergroup comparisons (or Fisher's Exact test if 75% of the values for a given variable consisted of one value)
- Organ weights--ANCOVA and William's test for intergroup comparisons
- Significance was judged at alpha = 0.05 or 0.01.

Compliance:

- A signed Statement of No Data Confidentiality Claim, dated January 13, 1992, was provided.
- A signed Statement of Compliance with EPA, OECD, Japanese MAFF, and the United Kingdom GLPs, dated January 10 and 13, 1992, was provided.
- A signed Quality Assurance Statement, dated January 10, 1992, was provided.

C. RESULTS

Test Material Analysis: Homogeneity/concentration analyses of the test compound in the diet revealed concentrations of 97.53%-99.28% of nominal values. Test diets were stable for 15 days in the freezer.

Parental Toxicity

Mortality: No compound-related mortalities were observed. Seven incidental deaths/moribund sacrifices in the F₁ generation were reported as follows: Among males, one animal at 15 ppm died during week 12 from a brain hemorrhage (resulting from injury). One additional male at 65 ppm died during week 34; necropsy did not reveal the cause of death. Among females, four animals in the control group and one at 65 ppm were sacrificed due to poor health status.

Clinical Observations: No compound-related clinical signs were observed in any sex and generation.

Body Weight: Compound-related effects in body weight were observed in females at 15 and/or 65 ppm during the gestation periods for both generations. Summaries of body weight from selected time intervals are presented in Tables 1, 2, and 3. (Summary and individual data on body weight gain, as well as standard deviations for body weight summary data, were not reported.)

In the F₀ generation during pre-mating, no significant decreases in body weight were observed for either sex (Table 1). Among males at termination, a 6%, 5%, and 7% increase in body weight was noted at 1, 15, and 65 ppm, respectively; among females during weeks 7-10, significant increases were noted at 15 and 65 ppm. The overall body weight gain for females during pre-mating was 112, 117, 124, and 126 g at 0, 1, 15, and 65 ppm, respectively (data not shown). During the gestation periods, body weight gain decreased nonsignificantly at 15 and 65 ppm in the first mating by 6%-16% and in the second mating by 2%-13% (Table 2). During the lactation periods, no consistent patterns were noted between groups in body weight gain (Table 3).

In the F₁ generation during pre-mating, no significant decreases in body weight were observed for either sex (Table 1). The overall body weight gain during pre-mating was 500, 518, 531, and 493 g for males and 237, 239, 242, and 246 g for females at 0, 1, 15, and 65 ppm, respectively (data not shown). During the gestation periods, body weight gain decreased nonsignificantly at 65 ppm in the first mating by 7%-20% and in the second mating by 16%-21% (Table 2). During the lactation periods, no consistent patterns were noted between groups in body weight gain (Table 3).

Water Consumption: Water consumption data were only recorded at the start and end of the pre-mating period for each generation (data not shown). It was significantly ($p < 0.05$) decreased in F₀ males during week 2 at 65 ppm and in F₁ females during weeks 1 and 2 at 65 ppm. It was significantly increased in F₀ females during pre-dosing week 1 at 1 ppm ($p < 0.05$) and pre-dosing weeks 1 and 2 at 15 and 65 ppm ($p < 0.01$) and during treatment week 1 at 1, 15, and 65 ppm. Based on these few data points and inconsistent results, the reviewers believe that no conclusions can be drawn regarding dimethoate's effect on water consumption.

Food Consumption: No significant compound-related effects on food consumption were observed for any sex and generation. Likewise, no consistent intergroup differences were observed in food conversion ratios (food consumption/body weight gain; data not shown).

Compound Intake: In the F₀ generation, mean compound intake during the pre-mating period was 0.06, 0.96, and 4.25 mg/kg/day for males and 0.07, 1.06, and 4.76 mg/kg/day for females at 1, 15, and 65 ppm, respectively. In the F₁ generation, mean compound intake during the pre-mating period was 0.10, 1.45, and 6.68 mg/kg/day for males and 0.10, 1.54, and 7.32 mg/kg/day for females at 1, 15, and 65 ppm, respectively.

Cholinesterase Activity: Compound-related effects in cholinesterase activities were observed at 15 and 65 ppm in both sexes and generations. Summaries of these effects are presented in Table 4.

In the F₀ generation for both sexes at 15 and 65 ppm, plasma and erythrocyte cholinesterase (P-CHE and E-CHE) during treatment weeks 8, 19, and 32 (termination) and brain cholinesterase (B-CHE) at term were consistently significantly decreased with the exceptions of P-CHE among males at 15 ppm during treatment weeks 8 and 19 and among females at 15 ppm during treatment week 8. Overall, the CHE decrements ranged from 11% to 48% at 15 ppm and from 26% to 68% at 65 ppm.

In the F₁ generation for both sexes at 65 ppm, P-CHE and E-CHE during weeks 8, 15, 27, and 44 (termination) of age and B-CHE at term were consistently significantly decreased. At 15 ppm among males, E-CHE was consistently significantly decreased along with B-CHE at term. At 15 ppm for females, E-CHE during weeks 8, 15, and 27 of age, P-CHE during week 8 of age, and B-CHE at term were significantly decreased. Overall, the CHE decrements ranged from 12% to 43% at 15 ppm and from 19% to 71% at 65 ppm.

Among culled pups from the F₁ generation (data not shown), B-CHE in males was significantly decreased at 65 ppm.

Gross and Microscopic Pathology: No compound-related gross or histologic findings were observed for any sex and generation.

Organ Weights: No compound-related effects on organ weights were observed for any sex and generation. One incidental finding was noted: relative (% of body weight) heart weight was significantly ($p < 0.05$) increased at 65 ppm in F₁ males.

Reproductive Toxicity: Compound-related reproductive effects were observed at 15 and 65 ppm. Summaries of these effects are presented in Tables 5-9. Detailed results are presented in the text.

In the F₀ generation following the first mating (Table 5), slight decreases were observed in the mating index at 15 and 65 ppm. The number of live born pups/litter was significantly decreased at 65 ppm, and body weight for these pups was significantly decreased on lactation days 12 (data not shown), 16 (data not shown), and 21 (Table 5). Incidental increases in pup body weight were noted on day 0 at 15 and 65 ppm (Table 5). The mean age of attainment of the startle reflex was significantly ($p < 0.05$) increased among pups at 65 ppm (34.8 days post-coitus versus 34.3 days for controls; data not shown).

Following the F₀ second mating (Table 6), a decrease was observed in the fertility index at 65 ppm. At this same dosage level, pup body weight was significantly decreased on lactation days 4 (data not shown), 8 (Table 6), 12 (data not shown), 16 (data not shown), and 21 (Table 6).

In the F₁ generation following the first mating (Table 7), decreases were observed in the fertility index at all dosage levels. At 65 ppm, pup body weight was significantly decreased on lactation days 8 (Table 7),

12 (data not shown), 16 (data not shown), and 21 (Table 7). The mean age of attainment of the startle reflex was significantly ($p < 0.05$) increased among pups at 65 ppm (35.2 days post-coitus versus 34.5 days for controls; data not shown).

Following the F_1 second mating (Table 8), a decrease was observed in the fertility index at 65 ppm. The number of live pups/litter on lactation days 0 and 4 was significantly decreased at 65 ppm, and litter weight for these pups was significantly decreased on lactation days 12 (data not shown) and 16 (data not shown).

No compound-related clinical observations or gross malformations were noted in pups from any litter and generation. Likewise, no differences were observed in post-weaning development regarding the mean age of vaginal opening for females and cleavage of the balanopreputial skin fold for males.

D. REVIEWERS' DISCUSSION/CONCLUSIONS

Test Material Analyses: Concentration and homogeneity of the test material in the diet were confirmed to be within $\pm 5\%$ of nominal values. Stability data were only reported qualitatively; however, concentration analyses indicated that the test material was stable in the diet.

Parental Toxicity: Compound-related toxicity was observed at 15 and 65 ppm in both sexes and generations. It was manifested as significantly decreased cholinesterase activities in plasma, erythrocytes, and brain. In addition, for females during the gestation periods, slight body weight gain decreases were noted. No significant compound-related effects were noted in the rates of mortality and clinical, gross, and microscopic observations; in food consumption; and in organ weights.

Based on these results, the parental systemic toxicity NOEL and LOEL were 1 and 15 ppm, respectively.

Reproductive Toxicity: Compound-related reproductive toxicity was observed at 65 ppm. It was manifested as significantly decreased pup body weight during lactation in both sexes and generations. In addition, the litter size at birth among F_{1A} and F_{2B} litters was significantly decreased. The reviewers recalculated the mating index and fertility index as separate parameters (see Tables 5-8). There was an apparent effect on the fertility rate following F_{1B} , F_{2A} , and F_{2B} matings (this endpoint has not been statistically analyzed). The slightly decreased mating index at 15 and 65 ppm in the F_{1A} mating, was neither dose-related nor confirmed in later matings, and was therefore, not considered to be compound related.

In this study, pregnancy index (defined as % of surviving paired females that became pregnant) was reported by the study authors (see Table below).

Guideline Series 83-4: Reproductive Toxicity

| Pregnancy Rate (%) (by study authors) | Dosage Levels (ppm) | | | |
|--|---------------------|-----|-----|------|
| | 0 | 1 | 15 | 65 |
| <u>F₀ generation</u> | | | | |
| First mating | 93 | 96 | 86 | 89 |
| Second mating | 89 | 93 | 89 | 71 |
| <u>F₁ generation</u> | | | | |
| First mating | 96 | 71* | 71* | 63** |
| Second mating | 73 | 67 | 58 | 50 |

^aOutside the historical range (range not reported)

*Significantly different from control (p-value not stated)

The study authors' pregnancy rates indicate that pregnancy may have been affected by the test compound at 65 ppm in the first generation, second mating; at 1, 15, and 65 ppm in the second generation, first mating; and at 15 and 65 ppm in the second generation, second mating. Historical control data for these parameters were not submitted which makes it difficult to determine the effect by the test compound since the pregnancy rate in the control group in the last mating was also low.

However, the above pregnancy rates, did not differentiate between dams that were pregnant but delivered no pups and females that were never pregnant (as confirmed by Salewski's method). These females were all considered by the authors to be nonpregnant. The reviewers recalculated the pregnancy rates based on individual data and confirmed pregnancy status at time of sacrifice (see Table below) and concluded that there was no compound-related effect on pregnancy rates. Even though the rates were decreased at 1 and 65 ppm in the second generation matings, there was no dose-response. Therefore, these decreases were considered to be spontaneous in nature.

| Pregnancy Rate (%) (by reviewers) | Dosage Levels (ppm) | | | |
|--------------------------------------|---------------------|-----|-----|----|
| | 0 | 1 | 15 | 65 |
| <u>F₀ generation</u> | | | | |
| First mating | 100 | 100 | 100 | 96 |
| Second mating | 100 | 100 | 100 | 96 |
| <u>F₁ generation</u> | | | | |
| First mating | 100 | 79 | 92 | 75 |
| Second mating | 100 | 79 | 92 | 75 |

A third mating in the last generation was conducted between animals that had previously been unsuccessful in mating and proven breeders (data not shown). When these results were included in the overall mating performance, the total number of males that failed to induce pregnancy was 2, 1, 2, and 2 in the F₀ generation and 0, 2, 3, and 3 in the F₁ generation at 0, 1, 15, and 65 ppm, respectively. For females it was 0,

0, 0, and 1 in the F₀ generation and 0, 5, 3, and 6 in the F₁ generation in these same dosage groups.

Based on decreased fertility in the F_{1B}, F_{2A}, and F_{2B} matings; decreased body weight during lactation in both sexes and generations; and decreased litter size at birth among F_{1A} and F_{2B} litters, the NOEL and LOEL for reproductive toxicity were 15 and 65 ppm, respectively.

Study/Reporting Deficiencies:

Body weight gain data for parental animals were not provided.

Insufficient historical control data were submitted.

Clinical signs were recorded only once a week.

Food consumption data were of limited use since the animals were not individually housed (except for pregnant females).

Standard deviations were not reported for several parameters.

Summary data of body weight during lactation were incorrect.

E. CLASSIFICATION: CORE Minimum Data.

Parental toxicity NOEL = 1 ppm (approximately 0.08 mg/kg/day)

Parental toxicity LOEL = 15 ppm (approximately 1.25 mg/kg/day based on decreased cholinesterase activity)

Reproductive toxicity NOEL = 15 ppm (approximately 1.25 mg/kg/day)

Reproductive toxicity LOEL = 65 ppm (approximately 5.75 mg/kg/day based on decreased fertility, live pups per litter, and pup body weight)

F. RISK ASSESSMENT: Not applicable

Guideline Series 83-4: Reproductive Toxicity

Table 1. Mean Body Weight (g) During the Premating Period in Rats Fed Dimethoate for Two Successive Generations^{a,b}

| Study Week | Dietary Levels (ppm) | | | |
|------------------------------|----------------------|-----|-------|-------|
| | 0 | 1 | 15 | 65 |
| <u>F₀ Males</u> | | | | |
| 0 | 279 | 279 | 281 | 284 |
| 3 | 416 | 416 | 422 | 415 |
| 6 | 493 | 490 | 496 | 494 |
| 9 | 545 | 540 | 544 | 547 |
| <u>F₀ Females</u> | | | | |
| 0 | 194 | 194 | 199 | 194 |
| 3 | 251 | 255 | 260 | 253 |
| 6 | 285 | 289 | 297** | 292** |
| 9 | 302 | 309 | 319** | 315** |
| <u>F₁ Males</u> | | | | |
| 6 | 220 | 226 | 228 | 205 |
| 9 | 393 | 409 | 417 | 383 |
| 12 | 507 | 524 | 533 | 491 |
| 15 | 573 | 590 | 604 | 557 |
| <u>F₁ Females</u> | | | | |
| 6 | 172 | 177 | 173 | 161 |
| 9 | 239 | 250 | 250 | 241 |
| 12 | 292 | 297 | 299 | 292 |
| 15 | 318 | 324 | 326 | 321 |

^aData were extracted from Study No. DTF 11/91154, Tables 4:0 and 4:1.

^bStandard deviations not reported

**Significantly different from control (p<0.01)

Table 2. Mean Body Weight Gain (g) During Gestation in Rats Fed Dimethoate for Two Successive Generations^{a,b}

| Gestation Days: | Dietary Levels (ppm) | | | |
|--|----------------------|-------|-------|-------|
| | 0 | 1 | 15 | 65 |
| <u>F₀ Generation - F_{1A} Litters</u> | | | | |
| 0 - 7 | 24.0 | 21.8 | 20.2 | 20.5 |
| 0 - 14 | 59.5 | 58.6 | 52.7 | 53.6 |
| 0 - 20 | 150.2 | 144.3 | 141.7 | 136.9 |
| <u>F₀ Generation - F_{1B} Litters</u> | | | | |
| 0 - 7 | 24.8 | 21.7 | 24.2 | 22.0 |
| 0 - 14 | 58.6 | 54.2 | 54.4 | 51.2 |
| 0 - 20 | 145.3 | 139.3 | 140.8 | 134.6 |
| <u>F₁ Generation - F_{2A} Litters^c</u> | | | | |
| 0 - 7 | 22.2 | 21.8 | 20.4 | 17.8 |
| 0 - 14 | 50.1 | 46.8 | 52.4 | 40.7 |
| 0 - 20 | 122.3 | 114.1 | 127.5 | 113.6 |
| <u>F₁ Generation - F_{2B} Litters</u> | | | | |
| 0 - 7 | 23.9 | 27.0 | 23.2 | 18.9 |
| 0 - 14 | 53.7 | 54.3 | 49.6 | 44.9 |
| 0 - 20 | 138.9 | 132.1 | 132.8 | 111.8 |

^aData were extracted from Study No. DTF 11/91154, Tables 7:0:1, 7:0:2, and 7:1:2.

^bStandard deviations not reported

^cSummary data missing from report; calculated by the reviewers

Table 3. Mean Body Weight Gain (g \pm S.D.) During Lactation in Rats Fed Dimethoate for Two Successive Generations^{a,b}

| Lactation Days: | Dietary Levels (ppm) | | | |
|--|----------------------|------------------|------------------|------------------|
| | 0 | 1 | 15 | 65 |
| <u>F₀ Generation - F_{1A} Litters</u> | | | | |
| 0 - 7 | 21.0 \pm 12.6 | 15.7 \pm 15.5 | 11.2 \pm 17.3 | 5.2 \pm 13.9 |
| 0 - 14 | 40.4 \pm 15.9 | 25.8 \pm 20.4 | 16.1 \pm 20.4 | 9.5 \pm 17.2 |
| 0 - 21 | 10.9 \pm 18.2 | 1.6 \pm 22.8 | -11.8 \pm 23.7 | -8.4 \pm 18.4 |
| <u>F₀ Generation - F_{1B} Litters</u> | | | | |
| 0 - 7 | 13.5 \pm 11.5 | 12.6 \pm 16.8 | -0.3 \pm 14.3 | -1.1 \pm 16.8 |
| 0 - 14 | 19.6 \pm 18.2 | 16.3 \pm 23.2 | -2.8 \pm 19.1 | -3.3 \pm 20.4 |
| 0 - 21 | -7.0 \pm 23.9 | -14.0 \pm 23.6 | -27.5 \pm 23.3 | -33.9 \pm 23.2 |
| <u>F₁ Generation - F_{2A} Litters</u> | | | | |
| 0 - 7 | 6.1 \pm 19.5 | 16.7 \pm 20.1 | 9.8 \pm 17.0 | 4.8 \pm 14.4 |
| 0 - 14 | 10.8 \pm 29.1 | 21.9 \pm 28.9 | 26.1 \pm 21.6 | 0.1 \pm 18.3 |
| 0 - 21 | -7.7 \pm 22.8 | -6.1 \pm 22.0 | 2.7 \pm 27.0 | -17.5 \pm 21.5 |
| <u>F₁ Generation - F_{2B} Litters</u> | | | | |
| 0 - 7 | -2.6 \pm 24.0 | 3.4 \pm 20.1 | 7.6 \pm 14.5 | -2.0 \pm 14.6 |
| 0 - 14 | -3.4 \pm 33.3 | 7.3 \pm 25.6 | 11.4 \pm 28.0 | -11.7 \pm 31.2 |
| 0 - 21 | -16.6 \pm 34.9 | -13.1 \pm 31.9 | 0.4 \pm 25.7 | -28.8 \pm 36.7 |

^aData were extracted from Study No. DTF 11/91154, Tables 7:0:1, 7:0:2, and 7:1:2 and individual data.

^bRecalculated by the reviewers owing to mistakes in summary tables

Guideline Series 83-4: Reproductive Toxicity

Table 4. Summary of Cholinesterase Activities in Rats Fed Dimethoate for Two Successive Generations^a

| Parameter | | Dietary Levels (ppm) | | | |
|---|--------------------|----------------------|------|-------------------------|--------------------------|
| | | 0 | 1 | 15 | 65 |
| <u>F₀ Generation - Males</u> | | | | | |
| Prenate 1 (Age: 15 weeks) | P-CHE ^b | 0.43 | 0.43 | 0.40 (7) ^e | 0.31 ^{**} (28) |
| | E-CHE ^c | 1.74 | 1.73 | 1.31 ^{**} (25) | 0.62 ^{**} (64) |
| Prenate 2 (Age: 26 weeks) | P-CHE | 0.46 | 0.47 | 0.43 (7) | 0.34 ^{**} (26) |
| | E-CHE | 1.69 | 1.74 | 1.24 ^{**} (27) | 0.69 ^{**} (59) |
| Termination (Age: 39 weeks) | P-CHE | 0.56 | 0.54 | 0.50 [*] (11) | 0.39 ^{**} (30) |
| | E-CHE | 1.69 | 1.65 | 1.41 ^{**} (17) | <0.56 ^{**} (67) |
| | B-CHE ^d | 5.89 | 5.63 | 4.83 ^{**} (18) | 2.38 ^{**} (60) |
| <u>F₀ Generation - Females</u> | | | | | |
| Prenate 1 (Age: 15 weeks) | P-CHE | 1.39 | 1.33 | 1.25 (10) | 0.96 ^{**} (31) |
| | E-CHE | 1.83 | 1.95 | 1.17 ^{**} (36) | 0.83 ^{**} (55) |
| Prenate 2 (Age: 26 weeks) | P-CHE | 1.36 | 1.25 | 1.17 ^{**} (14) | 0.92 ^{**} (32) |
| | E-CHE | 1.65 | 1.79 | 0.86 ^{**} (48) | 0.53 ^{**} (68) |
| Termination (Age: 39 weeks) | P-CHE | 1.56 | 1.52 | 1.34 [*] (14) | 1.06 ^{**} (32) |
| | E-CHE | 1.65 | 1.58 | 0.95 ^{**} (42) | <0.58 ^{**} (65) |
| | B-CHE | 5.94 | 6.02 | 4.03 ^{**} (32) | 2.24 ^{**} (62) |
| <u>F₁ Generation - Males</u> | | | | | |
| Age: 8 weeks | P-CHE | 0.49 | 0.47 | 0.46 (6) | 0.33 ^{**} (33) |
| | E-CHE | 1.58 | 1.61 | 1.18 ^{**} (25) | 0.68 ^{**} (57) |
| Prenate 1 (Age: 15 weeks) | P-CHE | 0.46 | 0.46 | 0.44 (4) | 0.36 ^{**} (22) |
| | E-CHE | 1.46 | 1.53 | 1.21 ^{**} (17) | <0.54 ^{**} (63) |
| Prenate 2 (Age: 27 weeks) | P-CHE | 0.51 | 0.51 | 0.49 (4) | 0.40 ^{**} (22) |
| | E-CHE | 1.48 | 1.58 | 1.19 ^{**} (20) | <0.58 ^{**} (61) |
| Termination (Age: 44 weeks) | P-CHE | 0.54 | 0.54 | 0.51 [*] (6) | 0.44 ^{**} (19) |
| | E-CHE | 1.70 | 1.92 | 1.29 ^{**} (24) | <0.59 ^{**} (65) |
| | B-CHE | 7.87 | 8.13 | 5.64 ^{**} (28) | 3.07 ^{**} (61) |
| <u>F₁ Generation - Females</u> | | | | | |
| Age: 8 weeks | P-CHE | 1.01 | 1.00 | 0.89 ^{**} (12) | 0.60 ^{**} (41) |
| | E-CHE | 1.65 | 1.71 | 1.20 ^{**} (27) | 0.51 ^{**} (69) |
| Prenate 1 (Age: 15 weeks) | P-CHE | 1.47 | 1.41 | 1.29 (12) | 0.89 ^{**} (39) |
| | E-CHE | 1.57 | 1.68 | 1.11 ^{**} (29) | 0.59 ^{**} (62) |
| Prenate 2 (Age: 27 weeks) | P-CHE | 1.56 | 1.60 | 1.43 (8) | 0.93 ^{**} (40) |
| | E-CHE | 1.68 | 1.61 | 0.95 ^{**} (43) | 0.51 ^{**} (70) |
| Termination (Age: 44 weeks) | P-CHE | 1.59 | 1.76 | 1.55 (3) | 1.05 ^{**} (34) |
| | E-CHE | 1.70 | 1.74 | 1.40 (18) | <0.56 ^{**} (67) |
| | B-CHE | 6.73 | 6.61 | 4.73 ^{**} (30) | 1.97 ^{**} (71) |

^aData were extracted from Study No. DTF 11/91154 Tables 11a-11j.

^bPlasma cholinesterase

^cErythrocyte cholinesterase

^dBrain cholinesterase

^ePercent change from control

*Significantly different from control (p<0.05)

**Significantly different from control (p<0.01)

Table 5. Summary of Effects of Dietary Administration of Dimethoate on F_{1A} Reproductive Parameters, Offspring Survival, and Pup Body Weight^a

| Parameter | Dietary Levels (ppm) | | | |
|--------------------------------------|----------------------|------|------------------|--------------------------------------|
| | 0 | 1 | 15 | 65 |
| No. matings (F ₀ parents) | 28 | 28 | 28 | 28 |
| Mating index (%) ^b | 86 | 82 | 79 | 79 |
| Fertility index (%) ^c | 92 | 100 | 91 | 91 |
| Gestation index (%) ^d | 100 | 100 | 100 | 96 |
| Gestation length (days) | 22.0 | 22.0 | 22.2 | 22.0 |
| No. females with liveborn pups | 26 | 27 | 24 | 24 |
| Total no. live pups | | | | |
| Day 0 | 421 | 409 | 367 | 355 |
| Day 4 precull | 398 | 395 | 360 | 347 |
| Day 21 | 206 | 215 | 189 | 190 |
| Mean no. live pups/litter | | | | |
| Day 0 | 16.2 | 15.1 | 15.3 | 14.2 ^{**} (25) ^e |
| Day 4 precull | 15.3 | 14.6 | 15.0 | 14.5 (24) |
| Day 21 | 7.9 | 7.9 | 7.9 | 7.9 (24) |
| Live birth index (%) ^f | 99 | 99 | 99 | 100 |
| Viability index (%) ^g | 93 | 96 | 98 | 98 |
| Lactation index (%) ^h | 99 | 99 | 98 | 99 |
| Mean pup body weight (g) | | | | |
| Day 0 | 6.1 | 6.3 | 6.5 [*] | 6.3 [*] |
| Day 8 | 19.7 | 20.4 | 20.3 | 18.0 ^{**} |
| Day 21 | 60.2 | 61.4 | 59.9 | 53.4 ^{**} |
| Sex ratio (% male day 0) | 54 | 50 | 48 | 49 |

^aData were extracted from Study No. DTF 11/91154 Tables 8:0:1 and 12:0:1 and individual animal data.

^bMating index: No. sperm-positive females expressed as % of No. mated females; calculated by the reviewers

^cFertility index: No. females delivering a litter expressed as % of No. sperm-positive females; calculated by the reviewers

^dGestation index: No. females delivering a live litter expressed as % of No. females delivering a live or dead litter; calculated by the reviewers

^eNumber of litters; includes one dam with a total litter loss postpartem

^fLive birth index: Percentage of pups born alive based on No. of total pups born; calculated by the reviewers

^gViability index: Percentage of pups surviving four days based on No. of live pups born; calculated by the reviewers

^hLactation index: Percentage of pups surviving 21 days based on No. of pups on day 4 postcull; calculated by the reviewers

^{*}Significantly different from control (p<0.05)

^{**}Significantly different from control (p<0.01)

Table 6. Summary of Effects of Dietary Administration of Dimethoate on F_{1B} Reproductive Parameters, Offspring Survival, and Pup Body Weight^a

| Parameter | Dietary Levels (ppm) | | | |
|--------------------------------------|----------------------|------|------|--------|
| | 0 | 1 | 15 | 65 |
| No. matings (F ₀ parents) | 28 | 28 | 28 | 28 |
| Mating index (%) ^b | 75 | 93 | 82 | 79 |
| Fertility index (%) ^c | 95 | 92 | 96 | 77 |
| Gestation index (%) ^d | 100 | 100 | 100 | 100 |
| Gestation length (days) | 22.4 | 22.2 | 22.1 | 22.3 |
| No. females with liveborn pups | 25 | 26 | 25 | 20 |
| Total no. live pups | | | | |
| Day 0 | 369 | 379 | 350 | 282 |
| Day 4 precull | 362 | 373 | 343 | 275 |
| Day 21 | 199 | 201 | 190 | 153 |
| Mean no. live pups/litter | | | | |
| Day 0 | 14.8 | 14.6 | 14.0 | 14.1 |
| Day 4 precull | 14.5 | 14.3 | 13.7 | 13.8 |
| Day 21 | 8.0 | 7.7 | 7.6 | 7.7 |
| Live birth index (%) ^f | 99 | 98 | 99 | 99 |
| Viability index (%) ^g | 97 | 96 | 97 | 97 |
| Lactation index (%) ^h | 99 | 99 | 99 | 96 |
| Mean pup body weight (g) | | | | |
| Day 0 | 6.7 | 6.5 | 6.7 | 6.6.. |
| Day 8 | 21.4 | 21.5 | 21.3 | 18.8** |
| Day 21 | 63.7 | 64.8 | 63.9 | 56.6** |
| Sex ratio (% male day 0) | 50 | 50 | 45 | 51 |

^aData were extracted from Study No. DTF 11/91154, Tables 8:0:2 and 12:0:2 and individual animal data.

^bMating index: No. sperm-positive females expressed as % of No. mated females; calculated by the reviewers

^cFertility index: No. females delivering a litter expressed as % of No. sperm-positive females; calculated by the reviewers

^dGestation index: No. females delivering a live litter expressed as % of No. females delivering a live or dead litter; calculated by the reviewers

^eLive birth index: Percentage of pups born alive based on No. of total pups born; calculated by the reviewers

^fViability index: Percentage of pups surviving four days based on No. of live pups born; calculated by the reviewers

^gLactation index: Percentage of pups surviving 21 days based on No. of pups on day 4 postcull; calculated by the reviewers

** Significantly different from control (p<0.01)

Table 7. Summary of Effects of Dietary Administration of Dimethoate on F_{2A} Reproductive Parameters, Offspring Survival, and Pup Body Weight^a

| Parameter | Dietary Levels (ppm) | | | |
|--------------------------------------|----------------------|------|------------------------|--------------------|
| | 0 | 1 | 15 | 65 |
| No. matings (F ₁ parents) | 24 | 24 | 24 | 24 |
| Mating index (%) ^b | 79 | 83 | 75 | 79 |
| Fertility index (%) ^c | 100 | 85 | 83 | 74 |
| Gestation index (%) ^d | 100 | 100 | 100 | 100 |
| Gestation length (days) | 22.1 | 21.9 | 21.9 | 22.1 |
| No. females with liveborn pups | 23 | 17 | 17 | 15 |
| Total no. live pups | | | | |
| Day 0 | 279 | 199 | 247 | 180 |
| Day 4 precull | 269 | 194 | 220 | 161 |
| Day 21 | 163 | 125 | 117 | 98 |
| Mean no. live pups/litter | | | | |
| Day 0 | 12.1 | 11.7 | 14.5 (17) ^e | 12.0 (15) |
| Day 4 precull | 11.7 | 11.4 | 14.0 (15) | 11.3 (14) |
| Day 21 | 7.1 | 7.4 | 7.8 (15) | 7.0 (14) |
| Live birth index (%) ^f | 99 | 99 | 97 | 100 |
| Viability index (%) ^g | 95 | 96 | 89 | 89 |
| Lactation index (%) ^h | 99 | 100 | 98 | 93 |
| Mean pup body weight (g) | | | | |
| Day 0 | 6.4 | 6.5 | 6.3 | 6.3 |
| Day 8 | 19.3 | 19.3 | 18.0 | 15.3 ^{**} |
| Day 21 | 58.6 | 58.8 | 58.1 | 47.0 ^{**} |
| Sex ratio (% male day 0) | 50 | 45 | 51 | 49 |

^aData were extracted from Study No. DTF 11/91154, Tables 8:1:1 and 12:1:1 and individual animal data.

^bMating index: No. sperm-positive females expressed as % of No. mated females; calculated by the reviewers

^cFertility index: No. females delivering a litter expressed as % of No. sperm-positive females; calculated by the reviewers

^dGestation index: No. females delivering a live litter expressed as % of No. females delivering a live or dead litter, calculated by the reviewers

^eNumber of litters

^fLive birth index: Percentage of pups born alive based on No. of total pups born; calculated by the reviewers

^gViability index: Percentage of pups surviving four days based on No. of live pups born; calculated by the reviewers

^hLactation index: Percentage of pups surviving 21 days based on No. of pups on day 4 postcull; calculated by the reviewers

^{**}Significantly different from control (p<0.01)

Table 8. Summary of Effects of Dietary Administration of Dimethoate on F_{2B} Reproductive Parameters, Offspring Survival, and Pup Body Weight^a

| Parameter | Dietary Level (ppm) | | | |
|--------------------------------------|---------------------|------|------------------------|-------|
| | 0 | 1 | 15 | 65 |
| No. matings (F ₁ parents) | 22 | 24 | 24 | 24 |
| Mating index (%) ^b | 68 | 63 | 54 | 63 |
| Fertility index (%) ^c | 87 | 100 | 85 | 67 |
| Gestation index (%) ^d | 100 | 100 | 100 | 100 |
| Gestation length (days) | 22.2 | 21.8 | 22.2 | 22.4 |
| No. females with liveborn pups | 16 | 16 | 14 | 12 |
| Total no. live pups | | | | |
| Day 0 | 222 | 213 | 184 | 120 |
| Day 4 precull | 221 | 210 | 164 | 118 |
| Day 21 | 127 | 124 | 93 | 80 |
| Mean no. live pups/litter | | | | |
| Day 0 | 13.9 | 13.3 | 12.8 (14) ^e | 10.0* |
| Day 4 precull | 13.8 | 13.1 | 12.6 (13) | 9.8* |
| Day 21 | 7.9 | 7.8 | 7.2 (13) | 6.7 |
| Live birth index (%) ^f | 99 | 100 | 97 | 100 |
| Viability index (%) ^g | 98 | 99 | 86 | 98 |
| Lactation index (%) ^h | 99 | 99 | 95 | 98 |
| Mean pup body weight (g) | | | | |
| Day 0 | 6.4 | 6.2 | 6.6 | 6.8 |
| Day 8 | 19.8 | 19.3 | 19.4 | 19.7 |
| Day 21 | 58.5 | 57.2 | 57.6 | 54.0 |
| Sex ratio (% male day 0) | 54 | 49 | 47 | 51 |

^aData were extracted from Study No. DTF 11/91154, Tables 8:1:2 and 12:1:2 and individual data.

^bMating index: No. sperm-positive females expressed as % of No. mated females; calculated by the reviewers

^cFertility index: No. females delivering a litter expressed as % of No. sperm-positive females; calculated by the reviewers

^dGestation index: No. females delivering a live litter expressed as % of No. females delivering a live or dead litter; calculated by the reviewers

^eNumber of litters

^fLive birth index: Percentage of pups born alive based on No. of total pups born; calculated by the reviewers

^gViability index: Percentage of pups surviving four days based on No. of live pups born; calculated by the reviewers

^hLactation index: Percentage of pups surviving 21 days based on No. of pups on day 4 postcull; calculated by the reviewers

*Significantly different from control (p<0.05)

JELLINEK, SCHWARTZ,
CONNOLLY & FRESHMAN, INC.

1015 15th Street, N.W., Suite 500
Washington, D.C. 20005

Telephone (202) 789-8181
Fax (202) 789-8243 / 789-8244

Hand Delivered

422515- 00

March 17, 1992

Ms. Lois Rossi
Chief, Reregistration Branch
Special Review and Reregistration
Division (H-7508W)
Office of Pesticide Programs
U.S. Environmental Protection Agency
2800 Crystal Drive
Crystal Station 1, Third Floor
Arlington, VA 22202

Attention: Mr. William Crutchfield

Re: Dimethoate Rat Reproduction Study (Rejection Number 140)

Dear Lois:

In response to your February 9, 1992, PRN 86-5 rejection letter and on behalf of the Dimethoate Task Force (DTF, Dr. Wolfgang Biegel, Chair, Selztalstrasse 151, D-6507 Ingelheim, Germany), I am submitting four copies of the missing pages 137, 340, and 345 for the study listed below:

42251501 • The Effects of Dimethoate on Reproductive Function of Two-Generations in the Rat (Volumes I, II, and III).

You also listed page 577 as missing. There is no page 577, but the total number of pages in the completed report is 577. A flagging statement was added (page 4a). This addition increased the total number of pages in the report from 576 to 577, but the final page number is 576.

rec'd
3/18/92

If you have any questions, please call me at (202) 789-3330.

Sincerely,

A handwritten signature in black ink that reads "Diane Allemang". The signature is written in a cursive style with a large, looped initial "D".

Diane Allemang
JSCF & Co., Inc.
Authorized Representative of
the Dimethoate Task Force

Enclosures

JELLINEK, SCHWARTZ,
CONNOLLY & FRESHMAN, INC.

1015 15th Street, N.W., Suite 500
Washington, D.C. 20005

Telephone (202) 789-8181
Fax (202) 789-8243 / 789-8244

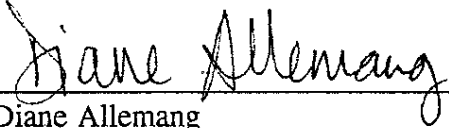
TRANSMITTAL DOCUMENT

Submitters: Dimethoate Task Force
Dr. Wolfgang Biegel, Chair
Selztalstrasse 151
D-6507 Ingelheim, Germany

Regulatory Action: Dimethoate Reregistration

Transmittal Date: March 17, 1992

Pages Submitted: 137, 340, and 345 for the study "The Effects of Dimethoate on Reproductive Function of Two-Generations in the Rat" (Volumes I,II, and III)

Authorized Representative: 
Diane Allemang
JSCF & Co., Inc. ¹
1015 15th Street, NW Suite 500
Washington, DC 20005
(202) 789-8181

¹All correspondence relating to these documents should be directed to JSCF & Co., Inc.

JELLINEK, SCHWARTZ,
CONNOLLY & FRESHMAN, INC.

1015 15th Street, N.W., Suite 500
Washington, D.C. 20005

Telephone (202) 789-8181
Fax (202) 789-8243 / 789-8244
Telex 5106001897 Cable JSCF USA

HAND DELIVERED

January 31, 1992

Ms. Lois Rossi
Chief, Reregistration
Office of Pesticide Programs
U.S. Environmental Protection Agency
2805 Jefferson Davis Highway
Crystal Station 1, Room F33J2
Arlington, VA 22202

Re: Supplement to MRID 41939801, Dimethoate 12-Month Dietary Study in Beagle Dogs
and Dimethoate Rat Reproduction Study

Dear Lois:

On behalf of the Dimethoate Task Force (DTF, Dr Wolfgang Biegel, Chair,
Selztalstrasse 151, D-6507 Ingelheim, Germany), I am submitting four copies of the
following items:

- Individual Clinical Observation Supplement to MRID 41939801 Dimethoate
12-Month Dietary Study in Beagle Dogs (Repeated Daily Dosage for 52
Weeks); and
- The Effect of Dimethoate on Reproductive Function of Two-Generations in the
Rat (Volumes I, II, and III).

Please call me at (202) 789-3330 if you have any questions regarding this letter.

Sincerely,



Diane Allemang
JSCF & Co., Inc.

Authorized Representative of
the Dimethoate Task Force

cc: Dr. W. Biegel, DTF Chairman

010065

TRANSMITTAL DOCUMENT

Submitters: Dimethoate Task Force
Dr. Wolfgang Biegel, Chair
Selztalstrasse 151
D-6507 Ingelheim, Germany

Regulatory Action: Dimethoate Reregistration

Transmittal Date: January 31, 1992

Studies Submitted: Study 1 of 2:
42192301 Individual Clinical Observation Supplement to
MRID 41939801, Dimethoate 12-Month
Dietary Study in Beagle Dogs (Repeated
Daily Dosage for 52 Weeks)

Study 2 of 2:
42251501 The Effect of Dimethoate on Reproductive
Function of Two-Generations in the Rat
(Volumes I, II, and III)

Authorized Representative: Diane Allemang
Diane Allemang
JSCF & Co., Inc. ¹

1015 15th Street, NW Suite 500
Washington, DC 20005
(202) 789-8181

¹All correspondence relating to these documents should be directed to JSCF & Co., Inc.