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SCIENTIFIC DATA REVIEWS
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WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

July 8, 2004

Subject: EPA Id No.: 035001. Dimethoate: Review of the Cross Fostering Study (2004, MRID No.: 46214501).

DP Barcode No.: D296272
PC Code No.: 035001
TXR No.: 0052452

From: Elissa Reaves, Ph.D., Toxicologist
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To: Pat Dobak, Chemical Review Manager
Reregistration Branch I
Special Review and Reregistration Division (7508W)

Action Requested

Review the following study:

CITATION: Myers, D. P. (2004) Dimethoate Cross Fostering Study in CD Rats. Huntington Life Sciences, Ltd., Woolley Road, Alconbury, Huntington, Cambridgeshire, PE28 4HS, England. Laboratory report number CHV 089/033185, March 2, 2004. MRID 46214501.

Executive Summary: In a non-guideline cross fostering study (MRID 46214501), Dimethoate (99.1% a.i., batch # 20522-00) was administered by gavage to mated female Crl:CD®BR rats from gestation day (GD) 6 to post-natal day (PND) 10 at doses of 0 (100 dams), 3 mg/kg/day (25

RLC 7/1/04

dams) or 6 mg/kg/day (50 dams). Maternal animals were evaluated for mortality, clinical signs, body weight and body weight gain and reproductive parameters. A neurobehavioral screening in the hand and in the arena was conducted on GDs 12 and 18 and on PNDs 4 and 10. The maternal animals rearing a litter were sacrificed on PND 11 and subjected to gross necropsy. On PND 1 (approximately 6 hours after completion of parturition), approximately 50% of the control group litters containing 12 or more pups were cross fostered with dams treated at 3 or 6 mg/kg/day dimethoate (groups 1A and 1B, respectively). Approximately 25% of the litters were reared by their own control group dams (group 1C); the remainder of the dams were sacrificed and discarded without examination. Pups were not directly treated with dimethoate. All litters containing 12 or more pups from dams treated at 3 mg/kg/day dimethoate were cross fostered with control dams (group 2). In the 6 mg/kg/day group, approximately 50% of the litters containing 12 or more pups were cross fostered with control dams (group 3A); the remainder of the litters remained with the treated dams (group 3B). The target group size for cross fostering of at least 20 was achieved. Pup body weight and clinical observation data were recorded. Neurobehavioral screening including surface righting reflex, activity count and maximum pivoting angle was conducted on one male and one female offspring per litter per group on PNDs 4 and 10. Hematology and clinical chemistry parameters were assessed for 10 pups/sex/group. Offspring were sacrificed and necropsied on PND 11.

One dam at 6 mg/kg/day died on GD 16. Maternal clinical observations revealed an increase in the number of dams at 6 mg/kg/day which had hair loss on one or both forelimbs. There were no treatment-related effects on body weight and body weight gain during gestation. During lactation, minimal (9-13%) decreases in body weight gain were observed in dams treated postpartum with 3 and 6 mg/kg/day, and were considered only marginally adverse. The only effect of dimethoate treatment on reproductive performance appeared to be a higher proportion of 3 and 6 mg/kg/day dams with restlessness and scattering of their litters. Neurobehavioral assessments of dams did not identify any treatment-related effects.

An observed treatment-related increase in the number of pups with no milk in the stomach was observed at 3 and 6 mg/kg/day. Pup mortality was significantly increased early after cross-fostering (day 1-4) in groups 1B and 3B. However, pup mortality increased again from post-natal days 4-11 in groups 1A, 2, 3A, and 3B, suggesting that pup mortality was increased regardless of pre- or post-natal exposure to 3 or 6 mg/kg/day dimethoate. The incidence of total pup death (pre- plus postnatal) increased with a positive correlation to dose level and to the duration of treatment to the dams. Postnatal deaths appeared to be correlated to some extent with the incidences of maternal restlessness and litter scattering for groups 2, 3A, and 3B; however, these maternal behaviors were not the sole cause of pup mortality. Rather, a combination of pre and postnatal toxicity to pups and/or dams appears to have contributed to observed pup mortality. This study was not designed to distinguish between the maternal and offspring components of postnatal toxicity and mortality.

PND 1-11 pup body weight and body weight gain were decreased for groups treated postnatally with 6 mg/kg/day. Offspring neurobehavioral testing identified a delay in the PND 10 surface righting reflex of pups treated postnatally with 6 mg/kg/day. Treatment-related alterations in hematology measures included increased mean hematocrit and MCV levels, decreased mean MCHC values, and increased mean neutrophil and monocyte counts at 6 mg/kg/day. Clinical

chemistry findings included significant treatment-related increases in mean urea at 3 mg/kg/day(both sexes combined) and 6 mg/kg/day (males and females analyzed separately), and significant decreases in mean creatine phosphokinase levels (both sexes combined and females analyzed separately) for pups treated both pre- and post-natally with 6 mg/kg/day. Necropsy findings of pups that survived to termination on PND 11 were unremarkable and unrelated to treatment. At 3 and 6 mg/kg/day, there were an increased number of pups that died or were sacrificed for humane reasons prior to study termination and that were found to have no milk in the stomach.

The maternal toxicity LOAEL for dimethoate in rats is 3 mg/kg/day based on clinical observations of forelimb hairloss, marginal reductions in body weight gain, and increased incidences of restlessness and scattering of pups. The maternal toxicity NOAEL was not identified.

The offspring toxicity LOAEL for dimethoate in rats is 3 mg/kg/day based on reduced milk consumption, increased levels of urea in the blood, and increased mortality. The offspring NOAEL was not identified. While maternal toxicity appeared to be associated with the decreased postnatal survival in this study, direct pre- and postnatal toxicity of the offspring to dimethoate could not be disregarded as significant contributing factors to overall offspring mortality.

This study is classified **Acceptable/Non-guideline**; it was designed to assess the effect of maternal exposure to dimethoate during gestation and the post-natal period on offspring mortality.

COMPLIANCE: Signed and dated Flagging, GLP, Quality Assurance, and Data Confidentiality statements were provided.

DATA EVALUATION RECORD

DIMETHOATE/035001

STUDY TYPE: CROSS FOSTERING STUDY - RAT (NON-GUIDELINE)

MRID 46214501

Prepared for

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

Prepared by

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Life Sciences Division
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Task No. 34-2004

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TXR#: 0052452

DATA EVALUATION RECORD

STUDY TYPE: Cross Fostering Study (Non-Guideline) - Rat

PC CODE: 035001 **DP BARCODE:** D296272

TEST MATERIAL (PURITY): Dimethoate (99.1%w/w)

SYNONYMS: Phosphorodithioic acid, 0,0-dimethyl S-[2-methylamino)-2-oxoethyl]ester

CITATION: Myers, D. P. (2004) Dimethoate Cross Fostering Study in CD Rats. Huntington Life Sciences, Ltd., Woolley Road, Alconbury, Huntingdon, Cambridgeshire, PE28 4HS, England. Laboratory report number CHV 089/033185, March 2, 2004. MRID 46214501. Unpublished

SPONSOR: Cheminova A/S (EPA Company No. 4787), P.O. Box 9, DK-7620 Lemvig, Denmark.

EXECUTIVE SUMMARY: In a non-guideline cross fostering study (MRID 46214501), Dimethoate (99.1% a.i., batch # 20522-00) was administered by gavage to mated female Crl:CD®BR rats from gestation day (GD) 6 to post-natal day (PND) 10 at doses of 0 (100 dams), 3 mg/kg/day (25 dams) or 6 mg/kg/day (50 dams). Maternal animals were evaluated for mortality, clinical signs, body weight and body weight gain and reproductive parameters. A neurobehavioral screening in the hand and in the arena was conducted on GDs 12 and 18 and on PNDs 4 and 10. The maternal animals rearing a litter were sacrificed on PND 11 and subjected to gross necropsy. On PND 1 (approximately 6 hours after completion of parturition), approximately 50% of the control group litters containing 12 or more pups were cross fostered with dams treated at 3 or 6 mg/kg/day dimethoate (groups 1A and 1B, respectively). Approximately 25% of the litters were reared by their own control group dams (group 1C); the remainder of the dams were sacrificed and discarded without examination. Pups were not directly treated with dimethoate. All litters containing 12 or more pups from dams treated at 3 mg/kg/day dimethoate were cross fostered with control dams (group 2). In the 6 mg/kg/day group, approximately 50% of the litters containing 12 or more pups were cross fostered with control dams (group 3A); the remainder of the litters remained with the treated dams (group 3B). The target group size for cross fostering of at least 20 was achieved. Pup body weight and clinical observation data were recorded. Neurobehavioral screening including surface righting

reflex, activity count and maximum pivoting angle was conducted on one male and one female offspring per litter per group on PNDs 4 and 10. Hematology and clinical chemistry parameters were assessed for 10 pups/sex/group. Offspring were sacrificed and necropsied on PND 11.

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PND 1-11 pup body weight and body weight gain were decreased for groups treated postnatally with 6 mg/kg/day. Offspring neurobehavioral testing identified a delay in the PND 10 surface righting reflex of pups treated postnatally with 6 mg/kg/day. Treatment-related alterations in hematology measures included increased mean hematocrit and MCV levels, decreased mean MCHC values, and increased mean neutrophil and monocyte counts at 6 mg/kg/day. Clinical chemistry findings included significant treatment-related increases in mean urea at 3 mg/kg/day(both sexes combined) and 6 mg/kg/day (males and females analyzed separately), and significant decreases in mean creatine phosphokinase levels (both sexes combined and females analyzed separately) for pups treated both pre- and post-natally with 6 mg/kg/day. Necropsy findings of pups that survived to termination on PND 11 were unremarkable and unrelated to treatment. At 3 and 6 mg/kg/day, there were an increased number of pups that died or were sacrificed for humane reasons prior to study termination and that were found to have no milk in the stomach.

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NOAEL was not identified. While maternal toxicity appeared to be associated with the decreased postnatal survival in this study, direct pre- and postnatal toxicity of the offspring to dimethoate could not be disregarded as significant contributing factors to overall offspring mortality.

This study is classified **Acceptable/Non-guideline**; it was designed to assess the effect of maternal exposure to dimethoate during gestation and the post-natal period on offspring mortality.

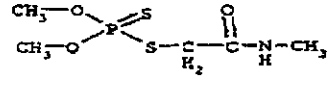
COMPLIANCE: Signed and dated Flagging, GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test material: Dimethoate

Description:	white solid
Lot/Batch #:	20522-00
Purity:	99.1 % a.i.
Compound Stability:	5 years
CAS # of TGAI:	60-51-5



2. Vehicle and/or positive control: reverse osmosis water

3. Test animals (P):

Species:	Rat	
Strain:	Crl:CD®BR	
Age at study initiation:	10-11 wks	
Wt. at study initiation:	200-314 g	
Source:	Charles River UK Limited, Margate, Kent, England	
Housing:	Individually or with litter in stainless steel grid or solid polypropylene cages	
Diet:	UAR VRF1 pelleted rodent diet (Usine d'Alimentation Rationale, France), *ad libitum*	
Water:	Tap water, *ad libitum*	
Environmental conditions:	**Temperature:**	19-23°C
	Humidity:	40-70%
	Air changes:	At least 15/hr
	Photoperiod:	12 hrs dark/12 hrs light
Acclimation period:	Minimum of eight days	

B. PROCEDURES AND STUDY DESIGN:

1. **In life dates**: Start: May 22, 2003; End: June 20, 2003

2. **General study design:** The objective of the study was to assess the effect of maternal exposure to dimethoate during gestation and the post-natal period on offspring mortality. The study was conducted to further interpret data on offspring survival from a developmental neurotoxicity study (MRID 45529703; TXR# 0050139). The general design of the developmental neurotoxicity study was followed. The maternal animals were mated and assigned to study. The test substance was administered to the maternal animals by gavage from gestation day (GD) 6 through postnatal day 10. The dams were subjected to a neurobehavioral screen on GDs 12 and 18 and lactation days (LDs) 4 and 10. On PND 1, some pups born to control dams were allocated to dimethoate-treated dams for rearing. Likewise, pups born to dimethoate-treated dams were assigned to control dams for fostering. Some pups remained with their control and dimethoate-treated dams. Offspring were terminated on PND 11 and were not directly treated with dimethoate.

3. **Mating procedure:** Females were paired 1:1 with males of the same strain and source. Each female was examined daily during the mating period to identify sperm cells in a vaginal smear or the presence of a copulatory plug. The day that either sperm or at least three copulation plugs was found was designated gestation day 0. During gestation (GD 0-17), up to four females were group housed in a stainless steel grid cage. During littering (GD17-PND 11), dams were housed individually in solid polypropylene cages.

4. **Animal assignment:** Females showing evidence of mating were allocated to group and cage position in the following order: for every seven females, four were allocated to the control group, one to the 3 mg/kg/day group and two to the 6 mg/kg/day group. The allocation was adjusted to prevent any stock male from providing more than one litter to any group. Dose groups are indicated in Table 1.

   On PND 1 (defined as occurring approximately 6 hours after completion of parturition), approximately 50% of the control group litters containing 12 or more pups were cross fostered with dams treated at 3 or 6 mg/kg/day dimethoate (Table 2, Groups 1A and 1B). Approximately 25% of the litters were reared by the control females (Group 1C); the remainder of the dams were sacrificed and discarded without examination. All litters containing 12 or more pups from dams treated at 3 mg/kg/day dimethoate were cross fostered with control dams (Group 2). In the 6 mg/kg/day group, approximately 50% of the litters containing 12 or more pups were cross fostered with control dams (Group 3A); the remainder of the litters remained with the treated dams (Group 3B). The target group size for cross fostering of at least 20 was achieved. Litters for cross fostering were, where possible, matched with a litter of a similar size (± 2 offspring); this occurred in all but two instances. Offspring for cross fostering received a tattoo mark on the left fore paw as a form of litter identification in addition to the toe tattoo for within litter identification. The two litters selected for cross fostering were mixed together in a separate cage for one minute before separation to the new foster parent.

Table 1. Study design for maternal animals			
Experimental parameter	Dose (mg/kg/day)		
	0	3	6
No. of maternal animals assigned (GDs 12 and 18)	100	25	50
No. subjected to neurobehavioral screening (PNDs 4 and 10)	75	25	50

Table 2. Study design for offspring			
Group	Maternal dosage (mg/kg/day)	Litter of origin (pre-natal maternal dosage) (mg/kg/day)	Number of litter units
1A	0	3*	23
1B	0	6*	24[a]
1C	0	0#	25
2	3	0*	23
3A	6	0*	24[a]
3B	6	6#	22

* Cross fostered
# Rearing own litter
[a] One litter allocated to cross fostering in error - dam and litter culled on Day 2

5. **Dose selection rationale:** The high dose of 6 mg/kg/day was selected based on the results of a dose-finding study (MRID 45529701). In this study, increased neonatal mortality, resulting in lower litter size and viability indices to PND 4 was observed at 6 mg/kg/day. The low dose of 3 mg/kg/day was selected based on results of a developmental neurotoxicity study (MRID 45529703). In that study, poor general condition/retarded development and/or increased pup mortality in some litters were reported at 3 mg/kg/day. Results from these studies are presented in separate DERs.

6. **Dosage administration:** All doses were administered once daily to maternal animals by gavage, on gestation day 6 through postnatal day 10, in a volume of 5 mL/kg of body weight/day. Individual dose volumes were based on the most recent body weight determination up to and including GD 17; the dose volume then remained constant to PND 1. From PND 1, dosing volumes were once again calculated based on the most recent body weight. Controls received reverse osmosis water (vehicle) only, at the same volume dosage as treated groups.

7. **Dosage preparation and analysis:** Formulations were prepared weekly. The highest required concentration (1.2 mg/mL) was prepared by mixing an appropriate amount of test substance with reverse osmosis water and mixing with a magnetic stirrer. The lower concentration (0.6 mg/mL) was then prepared by serial dilution. Dosing solutions were refrigerated for storage.

   Prior to the start of the study, stability of the test substance in water (0.02 and 2 mg/ml) was evaluated for a period of 2 days at room temperature and 15 days refrigerated (Huntingdon

Life Sciences Final Report No. CHV 069/003881). Homogeneity (top, middle, and bottom) was not evaluated. Single samples were taken from each dosing solution prepared for use during the first and last weeks of treatment; duplicate HPLC assays of each dosing solution were performed for concentration analysis.

Analytical Results:
Homogeneity analysis: not performed.

Stability analysis: The mean concentrations of dosing solutions remained within 4% of nominal after periods of 2 days at room temperature or 15 days refrigerated. (Reported in MRID 45529703)

Concentration analysis: The mean analytical concentrations of test solutions were within ± 3% of nominal. The precision of duplicate analyses was ≤2%.

The analytical data indicated that the difference between nominal and actual dosage to the study animals was acceptable. The adequacy of the mixing procedure could not be evaluated due to a lack of information on homogeneity of the dosing solution.

C. OBSERVATIONS:

1. In-life observations:

a. **Maternal animals:** Twice daily checks for mortality or moribundity and daily cage-side observations were conducted for maternal animals. Each animal was supposed to be subjected to a full physical examination pre-dosing and on GDs 0, 6, 14 and 20 and PNDs 1, 7 and 11. Errors made on GD 20 are discussed in this DER under STUDY DEFICIENCIES. Gross observations of the dams were conducted daily as follows: prior to treatment, as each animal was returned to the cage, at the end of dosing for each group, between 1 and 2 hours after completion of dosing, and as late as possible during the work day.

All females were subjected to detailed clinical observations outside the home cage prior to dosing; comments about behavior were made as free text. In addition, all females underwent neurobehavioral screening in the hand and in the arena on GD 12 and GD 18; allocated females rearing offspring to PND 11 were also screened on LDs 4 and 10. Neurobehavioral screening was not performed "blind," that is, testing was conducted with full knowledge of treatment group. The following observations were recorded and graded.

	NEUROBEHAVIORAL SCREENING
X	Signs of autonomic function, including: 1) Ranking of degree of lacrimation and salivation, with range of severity scores from none to marked 2) Presence or absence of piloerection and exophthalamus, 3) Ranking or count of urination and defecation 4) Pupillary function such as constriction of the pupil in response to light 5) Degree of palpebral closure, e.g., ptosis.
X	Description, incidence, and severity of any convulsions, tremors, or abnormal movements.
X	Description and incidence of posture and gait abnormalities.

Subjects were also scored for ease of removal from the cage and reactivity to handling. Observations of gait, grooming, palpebral closure, posture, activity counts, rearing counts, tremors, twitches, convulsions, urination, and defecation were made for one minute in an open field (653 x 500 mm) divided into six sectors.

Individual maternal body weight data were recorded on GDs 0, 3, 6, 10, 14, 17, and 20, then daily until parturition. During lactation, body weight data were recorded on days 1, 4, 7, and 11. Food consumption was not measured.

From GD 20, dams were checked 4 times/day for evidence of parturition. A visual assessment for the presence/absence of milk in the stomach of offspring was made, without disturbing the litter, prior to completion of parturition.

b. Offspring:

i. **Litter observations:** PND 1 was defined as occurring approximately six hours after completion of parturition. On that day, the following were recorded: litter size (live and dead), sex ratio, offspring body weight and visual assessment of presence/absence of milk in stomach. On PND 1-11, dams and offspring were observed five times/day for maternal behavior and clinical signs. At four of the time periods, visual assessments without handling were made for the following: dam and litter interaction appeared normal with offspring in one or two groups; offspring scattered in cage; dams restless; dam apparently ignoring litter; dead pups suspected; physical abuse of pups; and presence/absence of milk in pup stomachs. At the fifth time period, the entire litter was removed from the cage and all offspring examined individually. Pups were weighed individually on PNDs 4, 7 and 11.

ii. **Neurobehavioral screening:** One male and one female offspring per litter per group, where possible, were subjected to behavioral monitoring, as appropriate for the developmental stage, outside the home cage prior to dosing on PNDs 4 and 10. At least 22 males and 22 females/group were observed on PND 4. Neurobehavioral screening was not performed "blind," that is, testing was conducted with full knowledge of treatment group.

PND 4: A clear arena with a floor size of 30 x 20 cm and side walls of 4.5 cm was utilized. An FOB activity sheet (paper sheet marked with concentric circles) was placed underneath

the arena. The animal was then placed in the center of the FOB activity sheet and observed over a one-minute recording period. The following parameters were assessed: surface righting reflex, number of sections entered, maximum distance traveled, maximum pivoting angle, physical condition (skin color, physical abnormalities, cold-to-touch), locomotor incoordination, tremors, convulsions, and excessive backward movement. The arena was disinfected between each use to prevent activity from being influenced by olfactory cues from previous rats.

PND 10: The same arena was used as for postnatal day 4; however, the paper placed below the arena was divided into 9 equal segments. The animal was then placed in the center of the FOB activity sheet and observed over a one-minute recording period. The following parameters were assessed: surface righting reflex, number of sections entered, number of rearings, grooming, urination, physical condition (skin color, physical abnormalities, cold-to-touch), locomotor incoordination, tremors, convulsions, and excessive backward movement. The arena was disinfected between each use to prevent activity from being influenced by olfactory cues from previous rats.

iii. **Hematology and clinical chemistry**:

A. **Hematology:** The protocol directed that up to 2 males and 2 females from up to 10 litters per subgroup/group should be anesthesized with isoflurane without fasting on PND 11. The animals would then be decapitated and blood (0.5 mL) collected into EDTA anticoagulant. A complication developed when it was discovered that a significant proportion of samples were clotted. The problem was thought to result from pooling of samples. Therefore, individual samples of 0.2 mL were collected from male and female offspring from 10 litters in each of Groups 1A, 1B, 1C, 2, 3A and 3B. The CHECKED (X) parameters were examined.

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

B. **Clinical chemistry**: Up to 3 males and 3 females in each of the 10 liters per subgroup/group were anesthesized with isoflurane on PND 11 without fasting. The animals were then decapitated and one sample (0.7 mL) per sex per litter was collected into lithium heparin anticoagulant. The CHECKED (X) parameters were examined.

	ELECTROLYTES		OTHER
x	Calcium	x	Albumin
x	Chloride	x	Creatinine
	Magnesium	x	Urea nitrogen
x	Phosphorus	x	Total cholesterol
x	Potassium		Globulins
x	Sodium	x	Glucose (fasting)
	ENZYMES	x	Total bilirubin
x	Alkaline phosphatase (ALK)	x	Total protein (TP)
	Cholinesterase (ChE)	x	Triglycerides
x	Creatine phosphokinase		Serum protein electrophoresis
	Lactic acid dehydrogenase (LDH)	x	A/G Ratio (calculated)
x	Alanine aminotransferase (ALT/ SGPT)		
x	Aspartate aminotransferase (AST/ SGOT)		
	Gamma glutamyl transferase (GGT)		
	Sorbitol		
	Glutamate dehydrogenase		

2. **Postmortem observations:**

   a. **Maternal animals:** Females with no young were killed on Day 25 after mating. Females rearing a litter to PND 11 were killed on PND 11 and subjected to a macroscopic necropsy, which included examination of the mammary tissue and count of the number of implantation sites. Samples of the caudal and cranial mammary tissue and any abnormal tissues were retained for possible future histopathological examination. Dams not selected for cross fostering were sacrificed on PND 2 without examination. All dams were sacrificed with carbon dioxide inhalation.

   b. **Offspring:** Offspring not selected for blood sampling were killed by intraperitoneal sodium pentobarbital injection. Those selected for blood sampling were killed by decapitation. Offspring not assigned to cross fostering were sacrificed by an intraperitoneal sodium pentobarbital injection on PND 2. Offspring killed at termination on PND 11 or sacrificed for humane reasons were subjected to a macroscopic examination; a detailed examination of the gastrointestinal tract was performed. Abnormal tissues were retained in fixative. The cause of death was established, if possible.

D. **DATA ANALYSIS**: A summary of the statistical procedures described in the study report follows:

1. **Statistical analyses:**

   a. **Summary of procedures described in study report:**

   For data from dam body weight and body weight change, offspring scattered in the cage, offspring with no milk apparent in the stomach, offspring cumulative body weight gain, neurobehavioral screening parameters (surface righting reflex, activity count, maximum

pivotal angle, maximum distance traveled) and hematology and chemistry data, there were three outcomes: the effect of maternal dosing up to birth on the offspring, the effect of maternal dosing after birth on offspring and the effect of cross fostering of the offspring. "The study design was such that none of the above effects could be directly observed. However, by using a general linear model, estimates and hypothesis tests for all three effects could be obtained." The data from most of these parameters were analyzed using SAS version 8.2; the parameters were analyzed separately and by separate sex, where appropriate. Data from number of days and number of occasions on which offspring were scattered in the cage and the number of occasions on which offspring were observed to have no milk in the stomach were analyzed by a Poisson regression.

For activity and rearing data from the neurobehavioral screening in maternal animals, the Bartlett's test for variance homogeneity was not significant; therefore the parametric analysis was applied. The F1 test for monotonicity of dose-response was not significant at the 1% level; therefore, the Williams' test for a monotonic trend was applied.

For dam restlessness data, there were two possible outcomes, the effect of the maternal dosing or the effect of cross fostering. The individual data for the number of days and number of occasions on which restlessness was observed were analyzed by a Poisson regression.

For offspring data, individual litter values were analyzed. There were three possible outcomes, as described above. For the offspring survival data prior to cross fostering, the number of post-implantation losses in each litter were modeled where, for each dam, implantations were trials and implantations that did not produce offspring were events. Offspring survival data on PND 1 was modeled where total births were trials and the deaths on PND 1 prior to cross fostering were events. A generalized linear model with a logit link function and dam as a random effect was used, testing for an effect of maternal dosing up to birth. Litter size was included because the generalized linear model includes the probability of death as the dependent variable. Offspring survival during PNDs 1-11 was similarly modeled where total live offspring on PND 1 was modeled as trials and deaths up to PND 11 as events. A generalized linear model with a logit link function and dam as a random effect was used to analyze these data, testing for the effects of maternal dosing on offspring up to birth, the effect of maternal dosing on offspring after birth and the effect of cross fostering on offspring. Litter size was included because the generalized linear model includes the probability of death as the dependent variable. The data were analyzed using SAS version 8.2.

b. Agency evaluation of statistical methodology:

General linear models

For some of the dam data (body weight and change in body weight) and offspring data (cumulative body weight, surface righting reflex, activity count, maximum pivoting angle, maximum distance traveled, hematology, and blood chemistry), general linear models (known more generally as used here as Ordinary Least Squares (OLS) regression or Classic Linear Regression (CLR)) were used to explore the relationship of the data to

maternal dose, post-natal maternal dose, and/or cross fostering (where appropriate). Although the results of the regression analyses may have been reported correctly, the analyses should be considered exploratory and not complete/conclusive. The analyses address the 1st order *linear* relationship of the data to dosing and cross fostering, but do not attempt to explore other possible relationships that can be modeled by general linear models by transforming (e.g. log transform, square root, etc.) the data or incorporating higher-order terms of the explanatory variables. Whether linear or non-linear, any type of regression relationships should be supported by residual diagnostics or at least graphical displays of the fitted and observed values.

Additionally the cross fostering effect was coded as a dummy variable (i.e. as zero or one), which is useful for determining changes in the *intercept* parameters of the regression models due to cross fostering. However, no interaction was modeled between cross fostering and maternal dose, or cross fostering and post-natal dose. By excluding the interaction terms of the dummy variable (i.e. cross fostering), changes in the *slope* parameters of the regression models due to cross fostering cannot be modeled.

Finally, analyzing maternal dose and post-natal maternal dose as continuous explanatory variables via linear regression is important for understanding the relationship between the data and the explanatory variables. However to determine significant differences in the responses of subjects at various doses, treating maternal dose and post-natal maternal dose as qualitative variables in an analysis of variance would be a valuable addition to an exploratory analysis of the data.

Logistic Regression

For the offspring survival data, logistic regression was used to explore the relationship of the data to maternal dose, post-natal maternal dose, and/or cross fostering (where appropriate). As with the data analyzed using general linear models, maternal dose and post-natal maternal dose were treated as continuous explanatory variables. As continuous explanatory variables, there is assumed to be a linear relationship between dosing (both maternal and post-natal maternal) and the logit of the response variables. If it is determined that the explanatory variables (maternal dose and post-natal maternal dose) are not linear in the logit, it would be helpful to treat them as qualitative variables in the logistic regression relationship to determine if there are significant differences in the responses of subjects at various doses.

2. **Indices:**

   a. **Reproductive indices:** The following reproductive indices were calculated from breeding and parturition records of animals in the study:

   Gestation index = (Number of live litters born/Number pregnant) x 100

   Gestation length was calculated as the number of gestation days up to and including the day on which offspring were first observed; GD 1 was the day of mating. Gestation lengths were reported to the nearest 0.25 days since parturition checks were performed four times daily.

b. **Offspring viability indices:** The following viability (survival) indices were calculated from lactation records of litters in the study:

Post-implantation survival index = (Total No. of offspring born/Total No. of implantation sites) × 100

Live birth index = (Number of live offspring at PND1/Total number of offspring born) × 100

3. **Positive and historical control data:** No positive or historical control data were submitted.

II. RESULTS:

A. MATERNAL ANIMALS:

1. **Maternal mortality and clinical and functional observations:** One dam treated with 6 mg/kg/day died on GD 16. Clinical signs prior to death included piloerection, hunched posture, underactivity, reduced body temperature, pallor and an aqueous pink discharge from the vagina on the day of death. On necropsy, the stomach contents were liquified, the cecum contents were firm and dehydrated, the spleen was slightly enlarged, the vagina was distended with red fluid and a large amount of red fluid was observed in both uterine horns; all 17 fetuses were dead but grossly normal. All other females survived to termination.

   The only possible treatment-related clinical sign noted during the physical examinations and observations during handling was an increase in the number of dams at 6 mg/kg/day which had hair loss on one or both forelimbs during the post-natal period (22/49 vs 16/100 controls).

2. **Maternal body weight:** Selected group mean body weight and body weight gain during gestation, on lactation day 1 and after the sub-grouping for cross-fostering are summarized in Tables 3 and 4. There were no treatment-related effects on body weight and body weight gain during gestation or on the first day of lactation. Dams treated with 6 mg/kg/day and rearing their own litters (group 3C) had a marginal weight loss (-1g) on LDs 1-4 compared with weight gain (10 g) in control animals rearing their own litters (group 1C). The weight gain in the 3B group was slightly lower than controls for LDs 4-7 (15 g vs 19 g for control group) but was higher than controls for LDs 7-11 (26 g vs 16 g for control group).

   Dams treated with 6 mg/kg/day and rearing control pups (group 3A) had lower body weight gain than control dams rearing their own litters (group 3B) during LDs 1-7 (21 g vs 30 g for the control group) but similar weight gain during LDs 7-11.

   Dams treated with 3 mg/kg/day and rearing control pups (group 2) had lower weight gain than controls (group 1C) during LDs 1-4 (1 g vs 10 g for control group). Weight gain was similar or slightly increased in comparison to controls during the remainder of lactation.

   The report stated that the regression coefficient for the effect of the dam dose on body weight change was significant and that the general linear model for maternal dose on body weight

gain during lactation was significant or highly significant. No further information was provided.

In summary, maternal body weight gain during gestation was not affected by treatment. During lactation, decreases in body weight gain were observed in treated dams (groups 2, 3A, and 3B), and to a lesser extent in control dams with treated pups, as compared to control dams with control pups (group 1C). A rebound in weight gain occurred during LD 7-11, resulting in overall body weight gain deficits of 9-13% in treated groups as compared to control group 1C. These effects on lactation body weight gain are minimal in magnitude (in rats weighing over 300 g, the control and treated group mean body weight gain values are only 4-11 g different for LD 1-4 and are only 4-6 g different for LD 1-11), and they lack a solid dose-response relationship; therefore, they are considered only marginally adverse.

Table 3. Selected mean (±SD) maternal body weight and body weight gain values during gestation[a]

Observations/study interval	Dose (mg/kg/day)		
	0 (n=97)	3 (n=25)	6 (n=49)
Body wt. Gestation day 0 (g)	259±22	260±23	259±25
Body wt. Gestation day 6 (g)	293±25	294±24	293±28
Body wt. Gestation day 14 (g)	337±29	338±29	336±32
Body wt. Gestation day 20 (g)	415±35	413±35	409±36
Wt. gain gestation days 0-6 (g)	34±7	33±5 (3)	33±7 (3)
Wt. gain gestation days 6-20 (g)	121±15	119±16 (2)	117±16 (3)
Body wt. lactation day 1 (g)	317±30	315±28	314±30

a Data obtained from Tables 10-11, pages 75-76, MRID 46214501.
Percent difference from control (group 1C) value calculated by reviewer and presented in parentheses.

Table 4. Selected mean (±SD) maternal body weight and body weight gain values during lactation[a]

Observations/study interval	Group					
	1C (n=25)	1A (n=23)	1B (n=23)	2 (n=23)	3A (n=23)	3B (n=22)
Body wt. LD 1 (g)	309±31	324±30	313±28	316±29	321±29	311±29
Body wt. LD 4 (g)	320±31	333±27	320±29	317±26	327±28	310±27
Body wt. LD 7 (g)	339±29	351±28	341±29	336±29	342±30	325±26
Body wt. LD 11 (g)	355±30	369±30	360±33	354±29	362±31	351±27
Wt. gain LDs 1-4 (g)	10±8	9±13	7±10	1±8	5±9	-1±10
Wt. gain LDs 4-7 (g)[b]	19	18	21	19	15	15
Wt. gain LDs 1-7 (g)	30±9	26±14	28±10	20±9	21±15	13±11
Wt. gain LDs 7-11 (g)[b]	16	18	19	18	20	26
Wt. gain LDs 1-11	45±12	45±16	47±13	39±14 (13)	41±13 (9)	40±15 (11)

a Data obtained from Table 12, page 77, MRID 46214501.
b Calculated by the reviewer using data from Table 12; standard deviations were not calculated.
Percent difference from control (group 1C) value calculated by reviewer and presented in parentheses.
LD = Lactation day
1A - dams in control group fostering pups from dams treated at 3 mg/kg/day
1B - dams in control group fostering pups from dams treated at 6 mg/kg/day

1C - dams in control group rearing own litter
2 - dams treated at 3 mg/kg/day fostering pups from a dam in the control group
3A - dams treated at 6 mg/kg/day fostering pups from a dam in the control group
3B - dams at the 6 mg/kg/day rearing own litter

3. Reproductive performance: A summary of reproductive performance for the maternal animals is presented in Table 5. There were no treatment-related effects on length of gestation, gestation index, the parturition process, or implantation rate.

Table 5. Reproductive performance [a]

Observation	Number of females/litters in group					
Dose	0			3 mg/kg/day	6 mg/kg/day	
Number mated	100			25	50	
With litters born	97			25	49	
Found dead during gestation	0			0	1	
Failed to litter - not pregnant	3			0	0	
Mean gestation duration (days)[b]	21.93 ± 0.35			21.86 ± 0.35	21.89 ± 0.34	
Mean (±SD) implantations/dam	15.9 ± 1.8 (n=71)			15.8 ± 1.7 (n=23)	16.4 ± 1.8 (n=45)	
Gestation index (%)	100			100	100	
Identity of treatment groups after birth	Group 1C	Group 1A	Group 1B	Group 2	Group 3A	Group 3B
Allocated to group	25	23	23	23	23	22
Rearing offspring to PND 11	25	23	23	23	23	22

a Data obtained from Tables 1, 13 -14 and 20, pages 59, 78 -79 and 85, MRID 46214501
b Calculated by the reviewer from data in Table 13, page 78
1A - dams in control group fostering pups from dams treated at 3 mg/kg/day
1B - dams in control group fostering pups from dams treated at 6 mg/kg/day
1C - dams in control group rearing own litter
2 - dams treated at 3 mg/kg/day fostering pups from a dam in the control group
3A - dams treated at 6 mg/kg/day fostering pups from a dam in the control group
3B - dams at the 6 mg/kg/day rearing own litter

Evaluation of maternal care and nurturing of pups: Data on maternal restlessness and offspring scattering are summarized in Table 6. Observations on pups with attached umbilicus or no milk in the stomach are presented in Table 7.

As noted above, there was no indication of treatment-related maternal toxicity or clinical signs during gestation, which might contribute to a lack of maternal care. However, during the lactation period, there was a higher proportion of dams at 3 and 6 mg/kg/day showing restlessness on 2 days or more, regardless of whether they were rearing their own litters (group 3B) or control offspring (groups 2 and 3A) (Table 6). Scattering of offspring in the cage on two or more days of lactation was also increased in dams at 3 and 6 mg/kg/day.

The number of pups with umbilicus still attached during the early perinatal period (PND 1) was increased in groups 1B (15), 3A (10), and 3B (13) compared to controls (4) (Table 7). However,

the number of pups with umbilicus attached after PND 1 was similar between control and treated groups and therefore did not suggest reduced maternal care of pups, even after cross-fostering.

During lactation, the incidence of pups with "no milk in the stomach" was increased in groups 2, 3A and 3B (15, 28, and 11, respectively) compared to control (group 1C: 4) (Table 7). It is noted that this finding is supported by pup necropsy results, specifically that the incidence of pups found dead after cross-fostering with no milk in the stomach was increased in groups 2, 3A, and 3B (14, 24, and 28 pups, respectively), as well as in group 1B (12 pups), compared to control (group 1C: 7 pups) (see Table 15 in this DER). It cannot be determined whether this finding is due to adverse effects on the dams or on the pups.

The report stated that the regression coefficients for the effect of the maternal dose on the number of days and occasions of restlessness and scattering were highly significant. No further information was provided.

In summary, the only effect of dimethoate treatment on reproductive performance appeared to be a higher proportion of 3 and 6 mg/kg/day dams with restlessness and scattering of their litters. An observed treatment-related increase in the number of pups with no milk in the stomach at 3 and 6 mg/kg/day could have resulted from either maternal or offspring toxicity.

Table 6. Incidence of maternal restlessness and offspring scattering[a]

Observation	Number of dams or litters affected [# observations/# days]					
	Group 1C (n=25)	Group 1A (n=23)	Group 1B (n=23)	Group 2 (n=23)	Group 3A (n=23)	Group 3B (n=22)
Maternal restlessness						
0 Days	15	13	15	8	3	1
1 Day	7 [7 obs/7 days]	10 [11 obs/10 days]	7 [8 obs/6 days]	6 [8 obs/6 days]	5 [6 obs/5 days]	6 [8 obs/5 days]
2-3 Days	3 [7 obs/6 days]	0	1 [4 obs/2 days]	8 [20 obs/19 days]	13 [40 obs/33 days]	12 [41 obs/32 days]
4 or more days	0	0	0	1 [6 obs/4 days]	3 [19 obs/12 days]	3 [24 obs/14 days]
Scattering of offspring						
0 Days	13	13	9	6	1	5
1 Day	6 [6 obs/6 days]	3 [3 obs/3 days]	6 [9 obs/7 days]	4 [6 obs/5 days]	3 [4 obs/3 days]	4 [6 obs/5 days]
2-3 Days	6 [17 obs/14 days]	4 [10 obs/10 days]	6 [14 obs/12 days]	8 [29 obs/19 days]	12 [53 obs/33 days]	7 [23 obs/17 days]
4 or more days	0	3 [19 obs/13 days]	1 [4 obs/4 days]	5 [36 obs/28 days]	7 [37 obs/30 days]	6 [37 obs/29 days]

a Data obtained from Table 19, page 84, MRID 46214501.
1A - dams in control group fostering pups from dams treated at 3 mg/kg/day
1B - dams in control group fostering pups from dams treated at 6 mg/kg/day
1C - dams in control group rearing own litter
2 - dams treated at 3 mg/kg/day fostering pups from a dam in the control group
3A - dams treated at 6 mg/kg/day fostering pups from a dam in the control group
3B - dams at the 6 mg/kg/day rearing own litter

Table 7. Observations of umbilicus attached and no milk in the stomach of pups (PND 1-11)

Clinical Sign	Group					
	1C	1A	1B	2	3A	3B
Umbilicus Attached [b]						
PND 1	4	5	15	1	10	13
PNDs 2-4	4	0	4	0	4	2
after PND 4	3	0	0	0	3	0
No Milk in Stomach						
Incidences of no milk in stomach [c]	4	3	4	15	28	11
Number of litters	4	3	4	9	13	9

Specific days of observation	2, 4, 5, 7	4, 5, 8	1, 5, 7	2,3,4,5,6, 7	1,3,4,5,6, 7,8,9	3,4,6,7

a Data extracted from Appendix 20, page 245-265,and Appendix 21, pp 270-279, MRID 46214501
b Number of observations of umbilicus still attached after cross-fostering of litters. Observations of offspring not allocated to cross-fostering include umbilicus attached for 15 control pups on PND 1, none for 3 mg/kg/day litters, and 5 pups for 6 mg/kg/day litters pre-PND 1.
c Observation of one or more pups in a litter with the finding at a scheduled observation time.
1A - dams in control group fostering pups from dams treated at 3 mg/kg/day
1B - dams in control group fostering pups from dams treated at 6 mg/kg/day
1C - dams in control group rearing own litter
2 - dams treated at 3 mg/kg/day fostering pups from a dam in the control group
3A - dams treated at 6 mg/kg/day fostering pups from a dam in the control group
3B - dams at the 6 mg/kg/day rearing own litter

4. **Maternal neurobehavioral screening:** Data are summarized in Table 8. The following were observed in females treated at 6 mg/kg/day:

   In the standard arena -

   a) There was a decrease in the proportion defecating and urinating compared to controls, especially on LDs 4 and 10.

   b) On GD 18, activity count was significantly lower compared to controls ($p \leq 0.01$); this was associated with an increase in the proportion of animals for which gait could not be assessed (4% treated vs. 27% controls).

   c) On LD 4, a slightly higher proportion of dams (18%) showed slightly elevated gait and/or hunched posture compared to controls (4%); a slightly higher proportion showed slightly elevated gait on LD 10 (9% treated vs. none in controls).

   In the hand-held evaluation -

   a) On removal from the home cage on LDs 4 and 10, a lower proportion of animals, compared to controls, showed a grade 3 response (some resistance or avoidance but no aggression) and a higher proportion showed a placid grade 2 response (easy - shows awareness but no avoidance or resistance).

   b) On LD 4, a slightly lower proportion of animals (25/45) showed a grade 3 reaction to handling (slightly awkward - some squirming or struggling) compared with controls (58/71) and a higher proportion showed a grade 2 response (easy - shows awareness but little or no resistance) compared to controls.

   c) On LDs 4 and 10, a higher proportion of animals showed hair loss on the forelimbs compared to controls (16-20/45 vs 13-16/71 controls).

At 3 mg/kg/day, observations in the hand revealed that on removal from the home cage on LDs 4 and 10 a slightly lower proportion of animals (3/23 and 5/23, respectively) had a grade 3 response (some resistance or avoidance but no aggression) compared to controls (20/71 and 23/71, respectively). A slightly higher proportion of animals at 3 mg/kg/day showed a grade 2 response (easy, shows awareness but no avoidance or resistance). On LD 4, a slightly lower proportion of females (13/23) at 3 mg/kg/day showed a grade 3 reaction to handling (slightly awkward, some squirming and struggling) compared to controls (58/71) and a slightly higher proportion had a grade 2 response (easy, shows awareness but little or no resistance) compared to controls. In the standard arena, there were no apparent differences between the behavior of control and 3 mg/kg/day dams.

Overall, these findings did not suggest a treatment-related effect on maternal behavior. In general, differences between control and treated groups were minimal and were seldom dose-related. When an endpoint was significantly different from control (e.g., decreased activity count on GD 18 at 6 mg/kg/day), it was not maintained or repeated at subsequent observation intervals. Evidence of reduced reactivity to handling of dams on LD 4 and/or 10 did not exhibit a consistent pattern of response over time within the treated groups, nor was a dose relationship apparent. Notably, no treatment-related alterations in behavior were observed during lactation, when observations of "restlessness" were reported for dams at 3 and 6 mg/kg/day. Since the neurobehavioral observations were conducted with full knowledge of treatment group, some uncertainty exists regarding the possible introduction of bias into the results.

Table 8. Maternal neurobehavioral screening results (incidence) [a]

Endpoint	Dose (mg/kg/day)		
	0	3	6
Arena Observations			
Posture	(n=100)	(n=25)	(n=50)
-GD 12 - Normal	100 (100)	25 (100)	50 (100)
-GD 18 - Normal	100 (100)	25 (100)	49 (100)
-LD 4	(n= 71)	(n=23)	(n=45)
Normal	71(100)	22 (96)	42 (93)
Hunched	0	1 (4)	3 (7)
-LD 10 - Normal	71 (100)	23 (100)	45 (100)
Gait (U=unable to assess, scale 0-3 where 0=normal, 3=markedly abnormal)			
-GD 12	(n=100)	(n=25)	(n=50)
0	92 (92)	25 (100)	46 (92)
1	8 (8)	0	4 (8)
-GD 18	(n=100)	(n=25)	(n=49)
U	27 (27)	6 (24)	23 (47)
0	72 (72)	19 (76)	26 (53)
1	1 (1)	0	0

Endpoint	Dose (mg/kg/day)		
	0	3	6
-LD 4	(n=71)	(n=23)	(n=45)
U	23 (32)	10 (44)	12 (27)
0	45 (63)	12 (52)	25 (56)
1	3 (4)	1 (4)	7 (16)
2	0	0	1 (2)
-LD 10	(n=71)	(n=23)	(n=45)
U	26 (37)	6 (26)	8 (18)
0	45 (63)	17 (74)	33 (73)
1	0	0	4 (9)
Activity Count (mean ± S.D.)	(n=100)	(n=25)	(n=49)
-GD 12	13.6 ± 3.8	14.0 ± 2.9	12.5 ± 2.9
-GD 18	7.3 ± 4.2	6.3 ± 3.2	5.1** ± 3.4
-LD 4	6.8 ± 4.9	5.3 ± 3.8	7.0 ± 4.3
-LD 10	6.5 ± 4.9	6.7 ± 4.6	7.5 ± 3.9
Elevated Gait (number affected)	(n=100)	(n=25)	(n=50)
-GD 12	4 (4)	0	3 (6)
-GD 18	1	0	0
	(n=71)	(n=23)	(n=45)
-LD 4	3 (4)	1 (4)	8 (18)
-LD 10	0	0	4 (9)
Urination (scale 0-3)			
-GD 12	(n=100)	(n=25)	(n=50)
0	79 (79)	17 (68)	44 (88)
1	12 (12)	3 (12)	4 (8)
2	3 (3)	4 (16)	0
3	6 (6)	1 (4)	2 (4)
-GD 18			
0	70 (70)	19 (76)	43 (86)
1	16 (16)	3 (12)	3 (6)
2	12 (12)	3 (12)	2 (4)
3	2 (2)	0	1 (2)
-LD 4	(n=71)	(n=23)	(n=45)
0	48 (68)	15 (65)	36 (80)
1	18 (25)	3 (13)	5 (11)
2	4 (6)	5 (22)	4 (9)
3	1 (1)	0	0
-LD 10			
0	54 (76)	19 (83)	42 (93)
1	14 (20)	3 (13)	2 (4)
2	3 (4)	1 (4)	1 (2)
Defecation count			
-GD 12	(n=100)	(n=25)	(n=50)
0	86 (86)	23 (92)	49 (98)
1-2	9 (9)	1 (4)	1 (2)

Endpoint	Dose (mg/kg/day)		
	0	3	6
3-4	3 (3)	0	0
5-6	2 (2)	0	0
7-8	0	1 (4)	0
-GD 18			(n=49)
0	82 (82)	23 (92)	44 (88)
1-2	8 (8)	1 (4)	1 (2)
3-4	7 (7)	1 (4)	2 (4)
5-6	3 (3)	0	1 (2)
7-8	0	0	1 (2)
-LD 4	(n=71)	(n=23)	(n=45)
0	59 (83)	21 (91)	43 (96)
1-2	8 (11)	2 (9)	0
3-4	4 (6)	0	1 (2)
5-6	0	0	1 (2)
-LD 10			
0	63 (89)	23 (100)	45 (100)
1-2	4 (6)	0	0
3-4	3 (4)	0	0
7-8	1 (1)	0	0
In hand observations			
Reactivity to handling (scale of 1-5)			
-GD 12	(n=100)	(n=25)	(n=50)
Grade 2	46 (46)	12 (48)	20 (40)
Grade 3	54 (54)	13 (52)	30 (60)
-GD 18			(n=49)
Grade 2	84 (84)	18 (72)	39 (80)
Grade 3	16 (16)	7 (28)	10 (20)
-LD 4	(n=71)	(n=23)	(n=45)
Grade 2	13 (18)	10 (43)	20 (44)
Grade 3	58 (82)	13 (57)	25 (56)
-LD 10			
Grade 2	7 (10)	2 (9)	8 (18)
Grade 3	64 (90)	21 (91)	37 (82)

Endpoint	Dose (mg/kg/day)		
	0	3	6
Removal from cage (scale of 1 to 5)			
-GD 12	(n=100)	(n=25)	(n=50)
Grade 2	65 (65)	16 (64)	31 (62)
Grade 3	35 (35)	9 (36)	19 (38)
-GD 18			(n=49)
Grade 2	92 (92)	23 (92)	43 (88)
Grade 3	8 (8)	2 (8)	6 (12)
-LD 4	(n=71)	(n=23)	(n=45)
Grade 2	51 (72)	20 (87)	40 (89)
Grade 3	20 (28)	3 (13)	5 (11)
-LD 10			
Grade 2	48 (68)	18 (78)	36 (80)
Grade 3	23 (32)	5 (22)	9 (20)
Hair Loss - forelimb(s) (Number affected)	(n=100)	(n=25)	(n=50)
-GD 12	5 (5)	0	0
-GD 18	7 (7)	1 (4)	4 (8)
	(n=71)	(n=23)	(n=45)
-LD 4	13 (18)	2 (9)	16 (36)
-LD 10	16 (23)	3 (13)	20 (44)

a Data obtained from Tables 4-9, pages 64-74, MRID 46214501
** Statistically significant when compared to control, $p<0.01$
(Percentage calculated by the reviewer and rounded off to the nearest whole number; all groups may not total 100%).

4. **Maternal postmortem results:** No treatment-related effects were noted at necropsy, except for an increased proportion of females at 6 mg/kg/day with forelimb hair loss, which was also noted during in-life clinical observations and neurobehavioral screening.

B. OFFSPRING:

1. **Offspring viability and clinical signs:** Litter and offspring mortality prior to and following cross-fostering are summarized in Tables 9 and 10, respectively. The number and distribution (across litters) of dead pups in each group are presented in Tables 11 and 12, respectively. Table 13 presents a summary of pup mortality in relationship to maternal observations of restlessness or scattering of litters. Pup mortality in litters with 4 or more incidences of maternal restlessness or scattering of the litter are presented in Table 14.

   When the control and treated animals selected for cross fostering were evaluated, there was a slight increase in the percentage of pup deaths at 6 mg/kg/day on Day 1 prior to sub-grouping (2.6 vs. 1.6 in control group) (Table 9). The mean number of implantations, total litter size on Day 1 and live litter size on Day 1 were comparable between treated and control groups. The post-implantation survival index and live birth index were similar between the treated and control groups.

Table 9. Litter and offspring mortality up to day 1 [a]

Observation	Number of females/litters in group		
Dose	0	3 mg/kg/day	6 mg/kg/day
Mean total litter size (Day 1)	15.1±2.0 (n=97)	15.1±2.5 (n=25)	15.1±2.2 (n=49)
Mean live litter size (Day 1)	14.8±2.0 (n=97)	14.8±2.5 (n=25)	14.7±2.3 (n=49)
Mean number of deaths (Day 1)	0.2±0.6 (n=97)	0.3±0.6 (n=25)	0.4±0.8 (n=49)
% Deaths (Day 1)	1.6±3.5 (n=97)	1.7±4.0 (n=25)	2.6±5.1 (n=49)
Post-implantation survival index (%)	96.1 (n=71)	95.3 (n=23)	94.2 (n=45)
Live birth index (%)	98.4 (n=97)	98.3 (n=25)	97.4 (n=49)

[a] Data obtained from Tables 14 and 15, pages 79-80, MRID 46214501.

Table 10. Litter size and viability after cross-fostering [a]

Observation	Group					
	1C	1A	1B	2	3A	3B
Number of litters	25	23	23	23	23	22
Mean no. of implantations	15.7±1.7	15.8±1.7	16.4±1.9	16.1±1.8	15.7±2.0	16.5±1.8
Sex Ratio Day 1 (% ♂)	52.2±12.4	45.5±11.0	48.9±12.2	47.2±10.2	45.9±13.3	50.6±10.7
Total litter size Day 1	15.0±1.7	15.1±1.9	15.3±1.8	15.3±1.9	15.3±1.8	15.5±2.0
Mean litter size:						
Day 1	14.7±1.6	14.8±2.0	14.7±1.8	15.0±1.7	15.1±1.9	15.2±2.2
Day 4	14.6±1.7	14.7±1.8	14.2±2.0	15.0±1.7	14.9±2.0	14.2±2.2
Day 7	14.5±1.7	14.6±1.8	14.2±1.9	14.8±1.6	14.6±2.0	14.0±1.8
Day 11	14.5±1.7	14.4±1.8	14.2±1.9	14.7±1.6	13.9±1.9	13.8±1.8
Mean No. Deaths Day 1 % Deaths Day 1	0.3±0.5 1.8±2.9	0.3±0.6 2.0±4.2	0.5±1.1 3.2±6.6	0.3±0.8 1.8±4.4	0.1±0.5 0.8±3.0	0.3±0.5 2.2±3.3
Mean No. Deaths Days 1-11 b % Deaths Days 1-11 b	0.2±0.4 1.4±3.0	0.4±0.6 2.5±3.6	0.6±1.7 3.4±9.4	0.4±0.6 2.5±3.6	1.2±1.3 7.9±8.1	1.4±1.7 8.8±9.4

a Data obtained from Tables 20-21, pages 85-86, and unnumbered text table on page 47, MRID 46214501.
b Does not include deaths observed on Day 1.
1A - dams in control group fostering pups from dams treated at 3 mg/kg/day
1B - dams in control group fostering pups from dams treated at 6 mg/kg/day
1C - dams in control group rearing own litter
2 - dams treated at 3 mg/kg/day fostering pups from a dam in the control group
3A - dams treated at 6 mg/kg/day fostering pups from a dam in the control group
3B - dams at the 6 mg/kg/day rearing own litter

Detailed findings for each dose/treatment group are summarized in the following section:

a) 6 mg/kg/day group offspring reared by their dams (group 3B)

Compared to controls, offspring mortality was slightly increased during PNDs 1-11 in 6 mg/kg/day offspring reared by their dams (group 3B) and 6 mg/kg/day offspring reared by control dams (group 1B): 1.4 offspring/litter were sacrificed or found dead in group 3B compared to 0.2 control (group 1C) offspring/litter reared by their own dams and 0.6 offspring/litter in the 6 mg/kg/day group cross-fostered with control dams (group 1B)

(Table 10). Table 11 shows an increase in the total number of postnatal offspring deaths in group 3B as compared to group 1C controls (38 pups of 16 litters versus 12 pups of 12 litters). The number of dams with no dead pups was decreased for group 3B compared to group 1C controls (Table 12). Litter 139 at 6 mg/kg/day (group 3B) was especially large (23 pups) and had a high level of pup mortality (7 deaths). The effect of maternal dose on offspring survival was still apparent when this litter was excluded.

Two or more offspring in a total of 9 litters were found dead or sacrificed during PNDs 1-11 at 6 mg/kg/day (group 3B) compared to no litters in controls (group 1C) and one litter each in groups 1A, 1B and 2. The litter size on PND 11 was 13.8 for group 3B compared with 14.5 for controls (group 1C) (Table 10). The sex ratio in group 3B remained constant to PND 11 indicating that there was no preferential mortality of either sex (Table 10). A large number of pups in the 6 mg/kg/day group (3B) were sacrificed for humane reasons due to poor condition, such as cold to touch, underactivity or little/no milk apparent in stomach; the cause of death was not established. In-life observations indicate offspring in group 3B had no milk in the stomach on 11 occasions (9 litters) compared to 3-4 occasions in groups 1A-1C (Table 7). Absence of milk in the stomach was the principal necropsy finding among offspring in group 3B (28 pups) (Table 19). In group 3B, the number of fostered pups that died was increased for litters with high rates of maternal restlessness and scattering of pups (Tables 13 and 14).

b) Control group offspring cross-fostered to dams treated at 6 mg/kg/day (group 3A)

A slight increase in mean offspring mortality rate during PNDs 1-11 was observed in group 3A when compared to controls (group 1C) and 6 mg/kg/day offspring reared by control dams (group 1B): 1.2 offspring/litter (7.9% offspring) were found dead or sacrificed compared to 0.2 control offspring/litter (1.4% offspring) and 0.6 offspring/litter (3.4% offspring) in group 1B (Table 10). The total number of postnatal offspring deaths in group 3A (Table 11) was increased as compared to group 1C controls (31 pups of 15 litters versus 12 pups of 12 litters). The number of dams with no dead pups was decreased for group 3A compared to group 1C controls (8 versus 13; Table 12). Two or more offspring were found dead or killed in a total of 8 litters during PNDs 1-11 compared to no litters in the control group and one litter each in groups 1A, 1B and 2 (Table 12). This resulted in a lower litter size on PND 11, 13.9 compared to 14.5 in the control group. The sex ratio was not affected (Table 10) and no total litters were lost. In-life observations indicate offspring with no milk in the stomach were noted on 28 occasions (13 litters) in group 3A compared to 3-4 times in groups 1A-1C (Table 7). No milk in the stomach was the principal necropsy finding among offspring in group 3A (24 pups) (Table 19). The number of group 3A pups that died after fostering was increased for litters with high rates of maternal restlessness and scattering of pups (Tables 13 and 14).

c) Control group offspring cross-fostered to females treated at 3 mg/kg/day (group 2)

The offspring mortality rate for PNDs 1-11 was 0.4 offspring/litter (2.5% offspring), which was the same as for the 3 mg/kg/day offspring cross-fostered to control females (group 1A) and similar to 0.2 offspring/litter (1.4% offspring) rate for controls (group 1C)

(Table 10). The total number of postnatal offspring deaths in group 2 (Table 11) was slightly increased as compared to group 1C controls (16 pups of 11 litters versus 12 pups of 12 litters). The number of dams with no dead pups was similar for group 2 compared to group 1C controls (12 versus 13; Table 12). The sex ratio was not affected (Table 10), and no total litters were lost. In-life observations indicate offspring with no milk in the stomach were noted 15 times (9 litters) in group 2 compared to 3-4 times in groups 1A-1C (Table 7), and lack of milk in the stomach was a necropsy observation for 14 pups in group 2 (Table 19). In group 2, the number of fostered pups that died was increased for litters with maternal restlessness and scattering of pups (Tables 13 and 14).

d) 3 mg/kg/day group offspring (group 1A) or 6 mg/kg/day group offspring (group 1B) cross-fostered to control group females

The offspring mortality rate for PNDs 1-11 was 0.4 offspring/litter (2.5% offspring) for group 1A and 0.6 offspring/litter (3.4% offspring) for group 1B as compared to 0.2 offspring/litter (1.4% offspring) for control litters (group 1C) (Table 10). Table 11 shows an increase in the total number of postnatal offspring deaths in group 1B as compared to group 1C controls (25 pups of 10 litters versus 12 pups of 12 litters). The number of dams with no dead pups was similar for group 1B and group 1C controls (Table 12). The higher overall mortality rate in group 1B was due in part to a high mortality rate in litter 126 reared by control dam 19. A total of 8 offspring died during PNDs 1-11 compared to 0 or 1 offspring in all other litters in this group. The cause of death was not established in these offspring. Excluding data from litter 126 would result in a group mean mortality rate of 0.2 offspring/litter (1.6% offspring), which is similar to the controls. Nevertheless, the number of litters with only one dead/missing pup was decreased in group 1B as compared to control group 1C (5 versus 12, Table 12), and the number of litters with greater than 1 pup death was increased in group 1B as compared to control group 1C (5 versus 0, Table 12). This suggests that the increased offspring mortality observed in group 1B may have been related to prenatal treatment, and was not solely due to the deaths in a single litter. It is noted, however, that the number of litters with pup mortalities was not increased in group 1B as compared to group 1C. There was no effect on sex ratio (Table 10) and no instances of total litter loss.

The report states that the regression coefficient was highly significant for 1) the effect of the maternal dose on offspring survival after birth and 2) the effect of the maternal dose on milk status after birth. Although the report indicated a significant difference from control for specific dose groups (2, 3A, or 3B), no information on the method of group-wise comparisons was provided.

In summary, pup mortality was significantly increased early after cross-fostering (day 1-4) in groups 1B and 3B. However, pup mortality increased again from post-natal days 4-11 in groups 1A, 2, 3A, and 3B, suggesting that pup mortality was increased regardless of pre- or post-natal exposure to 3 or 6 mg/kg/day dimethoate. The incidence of total pup death (pre- plus postnatal) increased with a positive correlation to dose level and to the duration of treatment to the dams. Postnatal deaths appeared to be correlated to some extent with the incidences of maternal restlessness and litter scattering for groups 2, 3A, and 3B; however, these maternal behaviors were not the sole cause of pup mortality. Rather, a combination of

pre- and postnatal toxicity to pups and/or dams appears to have contributed to observed pup mortality. This study was not designed to distinguish between the maternal and offspring components of postnatal toxicity and mortality.

Table 11. Pup mortality [dead/missing pups (litters)] [a]

Postnatal Day	Group					
	1C	1A	1B	2	3A	3B
No. litters	25	23	23	23	23	22
Day 1 b	7 (7)	7 (5)	12 (6)	7 (4)	3 (2)	7 (7)
PND 1-4 c	3 (3)	2 (1)	12 (5)	2 (2)	6 (6)	21 (11)
PND 1-4 d	10 (10)	9 (6)	24 (9)	9 (5)	9 (7)	28 (14)
PND 4-7	1 (1)	3 (3)	1 (1)	3 (3)	6 (6)	6 (4)
PND 7-11	1 (1)	4 (4)	0 (0)	4 (4)	16 (10)	4 (4)
PND 4-11	2 (2)	7 (7)	1 (1)	7 (6)	22 (12)	10 (6)
PND 1-11c	5 (5)	9 (8)	13 (6)	9 (8)	28 (14)	31 (13)
PND 1-11 d	12 (12)	16 (10)	25 (10)	16 (11)	31 (15)	38 (16)

a Data obtained from Tables 20-21, pages 85-86, and unnumbered text table on page 47, MRID 46214501.
b Includes stillborn and other nonviable pups
c Without Day 1 stillborn and other nonviable pups
d Includes Day 1 stillborn and other nonviable pups
1A - dams in control group fostering pups from dams treated at 3 mg/kg/day
1B - dams in control group fostering pups from dams treated at 6 mg/kg/day
1C - dams in control group rearing own litter
2 - dams treated at 3 mg/kg/day fostering pups from a dam in the control group
3A - dams treated at 6 mg/kg/day fostering pups from a dam in the control group
3B - dams at the 6 mg/kg/day rearing own litter

Table 12. Distribution of pup deaths [no. of dams with dead/missing pups] [a]

No. of dead/missing pups b	Group					
	1C	1A	1B	2	3A	3B
No. litters	25	23	23	23	23	22
0	13	13	13	12	8	6
1	12	5	5	8	6	6
2	0	4	2	1	3	4
3	0	1	1	2	5	3
4	0	0	0	0	1	2
5	0	0	1	0	0	0
6	0	0	0	0	0	0
7	0	0	0	0	0	1
8	0	0	1	0	0	0

a Data obtained from Appendix 22, pages 281-286, MRID 46214501.
b Includes stillborn and other nonviable pups
1A - dams in control group fostering pups from dams treated at 3 mg/kg/day
1B - dams in control group fostering pups from dams treated at 6 mg/kg/day
1C - dams in control group rearing own litter
2 - dams treated at 3 mg/kg/day fostering pups from a dam in the control group
3A - dams treated at 6 mg/kg/day fostering pups from a dam in the control group
3B - dams at the 6 mg/kg/day rearing own litter

Table 13. Pup mortality after cross-fostering and occurring before or after restlessness or scattering in litters [a]

Group	Pup death **before** day of restlessness or scattering		Pup death **on or after** day of restlessness or scattering		Pup death **without** restlessness or scattering		Total # dead pups [b]
	Dams	Dead pups	Dams	Dead pups	Dams	Dead pups	
1C	4	4	1	1	0	0	**5**
1A	1	1	4	4	3 [c]	4 [c]	**9**
1B	5	8	1	4	1 [c]	1 [c]	**13**
2	2	2	5	6	1 [c]	1 [c]	**9**
3A	1	1	13	27	0	0	**28**
3B	6	8	9	23	0	0	**31**

a Data obtained from Appendix 20, 21and 22, pages 245-286, MRID 46214501
b Includes all pups that were live born and died between PND 1-11 (regardless of observations of restless or scattering)
c Death of the pup was without observations for dam restlessness or offspring scattering
1A - dams in control group fostering pups from dams treated at 3 mg/kg/day
1B - dams in control group fostering pups from dams treated at 6 mg/kg/day
1C - dams in control group rearing own litter
2 - dams treated at 3 mg/kg/day fostering pups from a dam in the control group
3A - dams treated at 6 mg/kg/day fostering pups from a dam in the control group
3B - dams at the 6 mg/kg/day rearing own litter

Table 14. Pup mortality in litters with 4 or more days of restlessness or scattering [a]

Endpoint	Group											
	1C		1A		1B		2		3A		3B	
	Dams	Dead pups	Dams	Dead pups	Dams	Dead pups	Dams	Dead pups	Dams	Dead pups	Dams	Dead pups
Restlessness	0	0	0	0	0	0	1	0	3	3	3	14
Scattering	0	0	3	2	1	0	5	8	7	12	6	16
Combined	0	0	3	2	1	0	6	8	9	14	7	20

a Data obtained from Appendix 21 and 22, pages 270-286, MRID 46214501.
1A - dams in control group fostering pups from dams treated at 3 mg/kg/day
1B - dams in control group fostering pups from dams treated at 6 mg/kg/day
1C - dams in control group rearing own litter
2 - dams treated at 3 mg/kg/day fostering pups from a dam in the control group
3A - dams treated at 6 mg/kg/day fostering pups from a dam in the control group
3B - dams at the 6 mg/kg/day rearing own litter

2. **Offspring body weight:** Pup body weight and body weight gain data are summarized in Tables 15 (males) and 16 (females). Mean body weight at birth (PND 1) was similar among all groups, for males and for females, regardless of maternal dose.

Body weight gain on PNDs 1-11 was decreased in male and female offspring of the 6 mg/kg/day group reared by their own dam (group 3B) compared to control offspring reared by their own dams (group 1C) and 6 mg/kg/day offspring reared by control dams (group 1B). Overall body weight gains of males and females in group 3B were reduced 15% and 16%, respectively, compared to group 1C, with absolute body weights lower after PND 1.

Male and female control offspring cross-fostered to dams treated at 6 mg/kg/day (group 3A) also had decreased body weight gain for PNDs 1-11 when compared to controls (group 1C) and 6 mg/kg/day offspring reared by control dams (group 1B). Overall body weight gains of both sexes were 20% lower than Group 1C offspring, with absolute body weights lower after PND1.

A marginal decrease in body weight gain in male and female control offspring reared by females at 3 mg/kg/day (group 2), compared to controls (group 1C) and 3 mg/kg/day offspring reared by control dams (group 1A), was observed after PND 4. Overall body weight gains in males and females of group 2 were 8% and 7%, respectively, lower than group 1C offspring, with absolute body weights marginally lower on PNDs 7 and 11.

Body weight and body weight gain in male and female offspring from the 3 mg/kg/day group offspring (group 1A) and 6 mg/kg/day offspring (group 1B) reared by control group females were similar to controls (group 1C).

The study report stated that the regression coefficient for the effect of maternal dose after birth on pup body weight gain was very highly significant ($p \leq 0.001$) in males and females; however, the study author dismissed the effect in group 2 due to the minimal nature of the response and the lack of an apparent response until after PND 4. The regression coefficient for the effect of cross-fostering on offspring body weight gain was reported to be not significant.

Agency reviewers agreed with the study authors that decreased PND 1-11 pup body weight and body weight gain values for groups 3A and 3B demonstrated an adverse response to treatment. For these two groups, body weight gains were decreased 20% and 16%, respectively, as compared to control. Decreases of a lesser magnitude observed in group 2 (7% for PND 1-11) were not considered adverse, although they may have been treatment-related.

Table 15. Mean (±SD) pup body weights and body weight gain (g) in males[a]

Day of age	Group					
	1C	1A	1B	2	3A	3B
Body weight (g)						
1	6.3±0.5	6.3±0.5	6.4±0.6	6.3±0.6	6.5±0.6	6.4±0.6
4	8.8±0.6	9.1±0.7	8.8±0.9	8.8±0.7	8.3±0.9	8.3±1.1
7	12.9±1.1	13.2±1.3	13.1±1.3	12.5±1.4	11.3±1.4 (88)	11.6±1.6 (90)
11	19.9±1.7	20.2±2.3	20.1±2.0	18.8±2.2	17.3±2.4 (87)	18.0±2.4 (90)
Body weight gain (g)						
1-4	2.5±0.5	2.7±0.7	2.4±0.7	2.5±0.8	1.8±0.7	1.8±0.8
4-7[b]	4.1	4.1	4.3	3.7 (90)	3.0 (73)	3.3 (80)
7-11[b]	7.0	7.1	7.0	6.3 (90)	6.1 (86)	6.4 (91)
1-11	13.6±1.5	13.9±2.1	13.7±1.9	12.5±2.4 (92)	10.9±2.4 (80)	11.5±2.1 (85)

a Data obtained from Tables 22-23, pages 87-88, and unnumbered text table on page 47, MRID 46214501
b Calculated by the reviewer using mean data from Table 22, page 87, MRID 46214501; standard deviations were not calculated
[Percentage of control value (group 1C) calculated by the reviewer]
1A - dams in control group fostering pups from dams treated at 3 mg/kg/day
1B - dams in control group fostering pups from dams treated at 6 mg/kg/day
1C - dams in control group rearing own litter
2 - dams treated at 3 mg/kg/day fostering pups from a dam in the control group
3A - dams treated at 6 mg/kg/day fostering pups from a dam in the control group
3B - dams at the 6 mg/kg/day rearing own litter

Table 16. Mean (±SD) pup body weights and body weight gain (g) in females [a]						
Day of age	Group					
	1C	1A	1B	2	3A	3B
Body weight (g)						
1	6.1±0.5	6.0±0.6	6.1±0.5	5.9±0.6	6.1±0.6	6.1±0.5
4	8.5±0.6	8.6±0.8	8.4±0.9	8.4±0.7	7.8±0.9	7.8±1.0
7	12.5±1.1	12.7±1.4	12.5±1.3	11.9±1.2	10.8±1.5	11.1±1.5
11	19.3±1.9	19.5±2.3	19.2±2.1	18.2±2.2 (94)	16.7±2.2 (87)	17.1±2.1 (89)
Body weight gain (g)						
1-4	2.4±0.4	2.7±0.6	2.4±0.7	2.4±0.8	1.7±0.6 (71)	1.8±0.7 (75)
4-7[b]	4.0	4.0	4.1	3.6 (88)	3.0 (75)	3.2 (83)
7-11[b]	6.8	6.8	6.7	6.3 (93)	5.9 (87)	6.0 (88)
1-11	13.2±1.6	13.6±2.1	13.2±2.0	12.3±2.3 (93)	10.6±2.2 (80)	11.1±1.9 (84)

a Data obtained from Tables 24-25, pages 89-90, and an unnumbered text table on page 47, MRID 46214501
b Calculated by the reviewer using mean data from Table 24, page 89, MRID 46214501; standard deviations were not calculated
[Percentage of control value (group 1C) calculated by the reviewer]
1A - dams in control group fostering pups from dams treated at 3 mg/kg/day
1B - dams in control group fostering pups from dams treated at 6 mg/kg/day
1C - dams in control group rearing own litter
2 - dams treated at 3 mg/kg/day fostering pups from a dam in the control group
3A - dams treated at 6 mg/kg/day fostering pups from a dam in the control group
3B - dams at the 6 mg/kg/day rearing own litter

4. **Offspring neurobehavioral screening:** Selected pup neurobehavioral screening data are summarized in Table 17. There were no adverse neurobehavioral findings in the control (group 1C) or 3 mg/kg/day dams fostering control pups (group 2). Noteworthy findings in pups from the other treated groups are described as follows:

   a) 6 mg/kg/day group offspring reared by their dams (group 3B)

   The mean activity count in males was slightly greater than the controls (group 1C) on PND 4. On PND 10, 9/21 (43%) males took more than two seconds in a surface righting trial (i.e., Grades 2 and 3) compared to 3/25 (12%) of controls (group 1C). Four females took more than two seconds to complete surface righting compared to no controls (group 1C).

   b) Control offspring cross-fostered to dams treated at 6 mg/kg/day (group 3A)

   A greater mean maximum pivoting angle and activity count was observed among males on PND 4. On PND 10, 9/23 (39%) of males took more than two seconds to show a surface righting reflex compared to 3/25 (12%) of controls (group 1C).

   c) 3 mg/kg/day group offspring (group 1A) or 6 mg/kg/day group offspring (group 1B) cross-fostered to control group females

On PND 10, 2/23 (9%) of females in group 1A and 3/23 (13%) in group 1B took more than two seconds in righting reflex trials compared with no controls (group 1C).

The study report indicated that the regression coefficients for the effect of the maternal dose up to and after birth for mean activity count and maximum pivoting angle were not significant. The regression coefficients for the effect of maternal dose after birth on surface righting reflex were significant.

The data (Table 17) clearly demonstrate a treatment-related delay in surface righting reflex in group 3A and 3B male and female pups at PND10. The incidence of Grade 1 responses (immediate; up to 2 seconds) was decreased and the incidence of Grade 2 (slow; 3-5 seconds) and 3 (failed; more than 5 seconds) responses was increased in these two treated groups as compared to control. It is noted that no control (group 1C) pups were observed with Grade 3 responses on PND 10, while 3 group 3A males and 4 group 3 pups (2/sex) were observed with Grade 3 responses. For group 2, Grade 3 responses in 1 pup/sex were also suggestive of a treatment-related response, but were not supported by the pattern of grade 2 responses across other groups.

There was no clear dose response pattern observed in mean activity count and pivoting angle data; therefore, agency reviewers did not interpret these data to be indicative of an adverse treatment-related effect. The evaluation of the mean activity count and maximum pivoting angle data was made difficult by the high level of variability in the reported results. The standard deviations were very large compared to the means. This could suggest, for example, problems or inconsistencies in laboratory procedures, the possibility that the scoring methods applied may not have been the most appropriate method for the endpoint, or especially in the case of activity counts, that the variability may have been related to normal developmental events, such as eye-opening in the pups. The age and time of individual pup eye opening was not reported; therefore, the relationship of eye opening to activity score cannot be evaluated.

In summary, the offspring neurobehavioral testing identified a delay in the surface righting reflex of group 3A and 3B male and female pups on PND 10. Slight delays in the PND 10 surface righting reflex of group 2 pups were considered equivocal.

TABLE 17. Selected neurobehavioral screening results for offspring [a]

	Group					
	1C	1A	1B	2	3A	3B
Males						
Surface righting reflex (scale of 1 to 3) -PND 4	(n=25)	(n=23)	(n=23)	(n=23)	(n=23)	(n=22)b
Grade 1	7 (28)	4 (17)	8 (35)	7 (30)	5 (22)	2 (9)
Grade 2	7 (28)	8 (35)	9 (39)	7 (30)	11 (48)	7 (32)
Grade 3	11 (44)	11 (48)	6 (26)	9 (39)	7 (30)	13 (59)
-PND 10						
Grade 1	22 (88)	19 (83)	21 (91)	18 (78)	14 (61)	12 (57)
Grade 2	3 (12)	3 (13)	2 (9)	4 (17)	6 (26)	7 (33)
Grade 3	0 (0)	1 (4)	0 (0)	1 (4)	3 (13)	2 (10)
Activity count (mean)						
-PND 4	0.4±2.0	1.0±1.8	1.5±1.8	1.1±2.0	1.4±3.0	1.0±1.4
-PND 10	5.6±4.1	5.2±4.6	4.6±3.2	5.5±3.8	4.7±4.5	5.0±4.3
Maximum pivoting angle (mean)						
-PND 4	16.2±72.2	19.6±48.6	21.5±32.9	19.6±42.5	39.1±102.7	18.4±26.6
Females						
Surface righting reflex (scale of 1 to 3)	(n=24)	(n=23)	(n=23)	(n=23)	(n=23)	(n=22)
-PND 4						
Grade 1	5 (21)	8 (35)	5 (22)	5 (22)	4 (17)	10 (45)
Grade 2	13 (54)	8 (35)	9 (39)	5 (22)	6 (26)	2 (9)
Grade 3	6 (25)	7 (30)	9 (39)	13 (57)	13 (57)	10 (45)
-PND 10						
Grade 1	24 (100)	21 (91)	20 (87)	22 (96)	22 (96)	18 (82)
Grade 2	0	2 (9)	3 (13)	0	1 (4)	2 (9)
Grade 3	0	0	0	1 (4)	0	2 (9)
Activity count (mean)						
-PND 4	2.0±2.5	2.7±3.5	1.8±1.8	1.5±1.6	2.2±2.5	2.0±2.5
-PND 10	6.9±3.6	7.8±5.7	5.7±5.4	6.7±3.8	7.7±6.0	5.5±3.3
Maximum pivoting angle (mean)						
-PND 4	43.1±69.6	76.3±106.3	41.1±55.8	37.2±42.2	58.7±71.1	61.4±90.6

a Data obtained from Tables 26-27, pages 91-94, and unnumbered text table on page 47, MRID 46214501
b n=10 for male pups on PND 10.
(Percentage calculated by the reviewer and rounded off to the nearest whole number; all groups may not total 100%)
1A - dams in control group fostering pups from dams treated at 3 mg/kg/day
1B - dams in control group fostering pups from dams treated at 6 mg/kg/day
1C - dams in control group rearing own litter
2 - dams treated at 3 mg/kg/day fostering pups from a dam in the control group
3A - dams treated at 6 mg/kg/day fostering pups from a dam in the control group
3B - dams at the 6 mg/kg/day rearing own litter

5. Offspring hematology and clinical chemistry: Selected hematology and clinical chemistry data are summarized in Table 18.

a. **Hematology:** The mean hematocrit values in male and female offspring in the 6 mg/kg/day group reared by their own dams (group 3B) and control offspring reared by dams at 6 mg/kg/day (group 3A) were higher than in groups 1A-1C. The mean MCHC values in male and female offspring in group 3B were slightly lower than groups 1A-1C. The mean MCV values in male and female offspring of groups 3B and 3A were slightly higher compared to groups 1A-1C. Among male offspring in groups 3B and 3A, there were slight increases in the neutrophil and monocyte counts compared to groups 1A-1C. Eosinophil and basophil counts were also higher in males of groups 3B and 3A compared to controls (group 1C); however, there was marked inter-animal variability. It is noted that parameters such as total protein, albumin, and creatinine were not increased, and therefore do not indicate that the altered hematology parameters in 3A and 3B were the result of dehydration but are instead the result of post-natal exposure to dimethoate.

b. **Clinical chemistry:** Urea and creatine phosphokinase (CPK) results are presented in Table 18. Urea levels were higher in male and female offspring of dams dosed at 6 mg/kg/day (group 3B), control offspring reared by dams at 6 mg/kg/day (group 3A) and control offspring reared by dams at 3 mg/kg/day (group 2). Creatine phosphokinase levels in males and females of group 3B were lower than other groups. Statistical analysis (conducted by Agency reviewers) revealed that mean urea increases were significant ($p \leq 0.05$) as compared to control for groups 2, 3A, and 3B when data for both sexes were combined, and for groups 3A and 3B when the data were considered separately by sex. Additionally, mean creatine phosphokinase levels were statistically significant for group 3B (both sexes combined and females analyzed separately) as compared to control values.

The study report stated that the regression coefficients for the effect of maternal dose after birth were significant for hematocrit, MCHC, MCV, neutrophil counts, monocyte counts (males), urea, and CPK (females). The regression coefficient for the effect of pre-natal maternal dose on MCHC values was also significant for females.

In summary, treatment-related alterations in hematology measures included increased mean hematocrit and MCV levels, decreased mean MCHC values, and increased mean neutrophil and monocyte counts in groups 3A and 3B. Significant treatment-related alterations in clinical chemistry parameters included increases in mean urea for group 2 (both sexes combined) and for groups 3A and 3B (for males and females analyzed separately), and significant decreases in mean creatine phosphokinase levels for group 3B (both sexes combined and females analyzed separately).

Table 18. Selected hematology and clinical chemistry results for offspring [a]

	Group					
	1C	1A	1B	2	3A	3B
Hematology parameters- males						
HCT (L/L)	0.29±.0.03	0.29±0.02	0.29±0.03	0.30±0.01	0.31±0.02	0.31±0.03
MCHC (g/dL)	30.5±1.1	30.7±1.0	30.9±1.2	30.9±0.5	30.1±0.6	29.6±1.1
MCV(fL)	85.4±3.9	84.6±3.4	84.4±5.4	86.3±4.6	88.4±4.1	89.8±5.1
Neutrophils [b] ($x10^9$/L)	0.70±0.40	0.66±0.67	0.55±0.53	0.84±0.57	0.99±0.35	1.24±0.44
Monocytes [b] ($x10^9$/L)	0.21±0.14	0.30±0.32	0.25±0.25	0.39±0.29	0.43±0.15	0.53±0.14
Hematology parameters - females						
HCT (L/L)	0.29±0.02	0.29±0.01	0.30±0.02	0.30±0.03	0.31±0.02	0.30±0.03
MCHC (g/dL)	30.7±0.7	30.4±0.6	30.6±0.7	30.8±0.9	30.3±0.8	29.7±0.8
MCV(fL)	85.5±1.9	85.9±2.1	85.4±2.4	86.0±3.2	88.9±3.2	89.0±5.6
Clinical chemistry parameters - males						
Urea (mmol/L)	6.67±1.35	7.10±2.59	7.35±1.38	8.59±2.18	8.90±1.94	10.26*±3.13
CPK (U/L)	10223± 4948	10306± 5569	11552± 4197	8591±1472	10491±2226	7336±1352
Clinical chemistry parameters - females						
Urea (mmol/L)	7.51±1.56	8.16±1.86	8.20±1.22	9.35±2.25	9.58±1.60	11.32*±2.88
CPK (U/L)	12184± 3871	10592± 3513	11594± 2204	9507± 2941	11776±4468	6798*±2398
Clinical chemistry parameters - combined sexes c						
Urea (mmol/L)	7.09±1.48	7.63±2.26	7.78±1.34	8.97*±2.19	9.24*±1.76	10.79*±2.98
CPK (U/L)	11204± 4439	10449± 4534	11573± 3263	9049±2312	11133±3498	7067±1915

a Data obtained from Tables 28-29, pages 95-110, and an unnumbered table on page 47, MRID 46214501
b Hematology sample size = 8, 7, 7, 8, 6, and 9 for 1C, 1A, 1B, 2, 3A, and 3B, respectively; clinical chemistry sample size = 10/sex/group.
c Calculated by reviewer.
* Statistically significant as compared to control values, $p \leq 0.05$, by Dunnett's test; analysis conducted by reviewer.
1A - dams in control group fostering pups from dams treated at 3 mg/kg/day
1B - dams in control group fostering pups from dams treated at 6 mg/kg/day
1C - dams in control group rearing own litter
2 - dams treated at 3 mg/kg/day fostering pups from a dam in the control group
3A - dams treated at 6 mg/kg/day fostering pups from a dam in the control group
3B - dams at the 6 mg/kg/day rearing own litter

6. **Offspring postmortem results:** The necropsy findings of pups that survived to termination on PND 11 were unremarkable and unrelated to treatment. Pups sacrificed prior to PND 11 for humane reasons were found to have no milk in the stomach. The number of dead pups from dams treated either with 3 or 6 mg/kg and found to have no milk in the stomach post-fostering was increased (Groups 2, 3A, and 3B) compared to control (Group 1C). Necropsy findings for each group are tabulated in Table 19.

Table 19. Pup necropsy observations - no milk in the stomach

Clinical Sign	Group					
	1C	1A	1B	2	3A	3B
No. dead/missing pups - PND 1-11[b]	12 (12)	16 (10)	25 (10)	16 (11)	31 (15)	38 (16)
Pre-Fostering - No milk in stomach	6	4	5	2	2	6
Post-Fostering - No milk in stomach	1	4	7	12	22	22
Total No. pups with no milk in stomach	7	8	12	14	24	28

a Data extracted from Appendix 20, pp. 245-265, MRID 46214501
b Includes all pup deaths (i.e., both pre- and post-fostering)
1A - dams in control group fostering pups from dams treated at 3 mg/kg/day
1B - dams in control group fostering pups from dams treated at 6 mg/kg/day
1C - dams in control group rearing own litter
2 - dams treated at 3 mg/kg/day fostering pups from a dam in the control group
3A - dams treated at 6 mg/kg/day fostering pups from a dam in the control group
3B - dams at the 6 mg/kg/day rearing own litter

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS: The study author concluded that the excess mortality in pups of treated dams and the behavioral and clinical effects observed were associated with post-natal rearing by dimethoate-treated dams. It was concluded that the excess mortality was not associated with exposure of offspring *in utero*.

B. REVIEWER COMMENTS:

Maternal toxicity:

Treatment of maternal animals with 3 and 6 mg/kg/day of dimethoate produced marginal effects during gestation, with the exception of one death. One dam at 6 mg/kg/day died on GD 16. The necropsy findings did not identify other causes; therefore, the death is considered treatment-related. The only possible treatment-related finding on the neurobehavioral screening during gestation was a statistically significant lower mean activity count in females at 6 mg/kg/day, which was also associated with an increase in the proportion of animals for which gait could not be assessed. Maternal body weight and body weight gain were unaffected by treatment during gestation; maternal body weight was comparable to controls on lactation day 1. During lactation, decreases in body weight gain were observed in treated dams (groups 2, 3A, and 3B), and to a lesser extent in control dams with treated pups, as compared to control dams with control pups (group 1C). A rebound in weight gain occurred during LD 7-11, resulting in overall body weight gain deficits of 9-13% in treated groups as compared to control group 1C. These effects on lactation body weight gain are minimal in magnitude (in rats weighing over 300 g, the control and treated group mean body weight gain values are only 4-11 g different for LD 1-4 and are only 4-6 g different for LD 1-11), and they lack a solid dose-response relationship; therefore, they are considered only marginally adverse.

There were no treatment-related effects on length of gestation, gestation index or implantation rate. A higher proportion of dams at 3 and 6 mg/kg/day either rearing their own litters or control pups (groups 3A and 3B) showed restlessness two or more days during lactation. Scattering of offspring in the cage on two or more days of lactation was also increased at 3 and 6 mg/kg/day (groups 2, 3A and 3B). While these findings are suggestive of a reduced level of typical maternal nurturing behavior, it cannot be determined whether the dams were exhibiting a direct behavioral response to treatment or whether they were responding to adverse treatment-related effects in their young (e.g., reduced body temperature, activity, or ability to nurse). Additionally, these findings were not supported by other indicator data, such as the similarity between control and treated dams in the incidence of pups with retained umbilicus. It is also noted that there was the potential for bias in these subjective observations since neurobehavioral assessments were conducted with full knowledge of treatment group.

Sporadic increases in various findings were observed in the neurobehavioral screening of dams during lactation. Overall, these findings did not suggest a treatment-related effect on maternal behavior. In general, differences between control and treated groups were minimal and were seldom dose-related. When an endpoint was significantly different from control (e.g., decreased activity count on GD 18 at 6 mg/kg/day), it was not maintained or repeated at subsequent observation intervals. Notably, no treatment-related alterations in behavior were observed during lactation, when observations of "restlessness" were reported for dams at 3 and 6 mg/kg/day. Since the neurobehavioral observations were conducted with full knowledge of treatment group, some uncertainty exists regarding the possible introduction of bias into the results.

Offspring toxicity:

Pup mortality was significantly increased early after cross-fostering (day 1-4) in groups 1B and 3B. However, pup mortality increased again from post-natal days 4-11 in groups 1A, 2, 3A, and 3B, suggesting that pup mortality was increased regardless of pre- or post-natal exposure to 3 or 6 mg/kg/day dimethoate. The incidence of total pup death (pre- plus postnatal) increased with a positive correlation to dose level and to the duration of treatment to the dams. Postnatal deaths appeared to be correlated to some extent with the incidences of maternal restlessness and litter scattering for groups 2, 3A, and 3B; however, these maternal behaviors were not the sole cause of pup mortality. Rather, a combination of pre and postnatal toxicity to pups and/or dams appears to have contributed to observed pup mortality. This study was not designed to distinguish between the maternal and offspring components of postnatal toxicity and mortality.

Decreased PND 1-11 pup body weight and body weight gain values for groups 3A and 3B demonstrated an adverse response to treatment. For these two groups, body weight gains were decreased 20% and 16%, respectively, as compared to control. Decreases of a lesser magnitude observed in group 2 (7% for PND 1-11) were not considered adverse, although they may have been treatment-related.

Offspring neurobehavioral testing identified a delay in the surface righting reflex of group 3A and 3B male and female pups on PND 10. Slight delays in the PND 10 surface righting reflex of group 2 pups were considered equivocal.

Treatment-related alterations in hematology measures included increased mean hematocrit and MCV levels, decreased mean MCHC values, and increased mean neutrophil and monocyte counts in groups 3A and 3B. Parameters such as total protein, albumin, and creatinine were not increased, and therefore do not indicate that the altered hematology parameters in 3A and 3B were the result of dehydration (as proposed by the study author) but are instead the result of post-natal exposure to dimethoate. Significant treatment-related alterations in clinical chemistry parameters included increases in mean urea for group 2 (both sexes combined) and for groups 3A and 3B (for males and females analyzed separately), and significant decreases in mean creatine phosphokinase levels for group 3B (both sexes combined and females analyzed separately).

Growth retardation and reduced survival of pups reared by treated dams appear to be correlated to effects on maternal behavior. However, this study did not disprove the possibility of a direct effect of pre- and/or postnatal exposure with dimethoate on offspring toxicity. Uncertainty remains regarding quantification of dimethoate (or omethoate) in the milk of lactating rats.

The maternal toxicity LOAEL for dimethoate in rats is 3 mg/kg/day based on clinical observations of forelimb hairloss, marginal reductions in body weight gain, and increased incidences of restlessness and scattering of pups. The maternal toxicity NOAEL was not identified.

The offspring toxicity LOAEL for dimethoate in rats is 3 mg/kg/day based on reduced milk consumption, increased levels of urea in the blood, and increased mortality. The offspring NOAEL was not identified. While maternal toxicity appeared to be associated with the decreased postnatal survival in this study, direct pre- and postnatal toxicity of the offspring to dimethoate could not be disregarded as significant contributing factors to overall offspring mortality.

C. STUDY DEFICIENCIES:

1) There was no dose group in this study with dams treated at 3 mg/kg/day rearing their own litters. While this did not compromise the results or analysis of the study findings, it prevented a comprehensive evaluation of the inter-relationship of treatment-related effects on dams and pups at 3 mg/kg/day and did not allow a comparison with the results of the developmental neurotoxicity study with dimethoate.

2) Neurobehavioral assessments were not conducted "blind," that is, they were conducted with full knowledge of treatment group, thereby introducing an element of bias into the subjective observations.

3) The only statistics report (pages 404-409 of MRID 46214501) submitted with the study is a reanalysis after exclusion of the results from litters 126 and 139. The analyses for maternal data are not included in this report and not all offspring data are discussed. For example, the study report (page 43) indicates that offspring in group 3A were noted to have no milk in the stomach on a greater number of occasions compared to groups 1A-1C;

the regression coefficient for the effect of maternal dose after birth was highly significant ($p<0.01$). This parameter is not discussed in the statistical reanalysis report.

Additionally, the statistical analyses performed were exploratory and incomplete, and do not adequately support the conclusions presented in the study report.

4) The following errors occurred during the study:

a) Fifteen dams were over or under dosed by ± 11% on PND 4, including 3 in group 1A, 4 in group 1B, 2 in group 2, 5 in group 3A and 1 in group 3B.

b) The physical examinations scheduled for GD 20 were not performed on control group females 41-79, 3 mg/kg/day group females 110-119 and 6 mg/kg/day group females 144-163. Examinations for control group females 80-100, 3 mg/kg/day group females 120-125 and 6 mg/kg/day females 164-175 were performed post-dosing rather than pre-dosing, as scheduled.

c) Milk status was not recorded for one litter at completion of parturition and for nine litters on PND 1.

d) One of the scheduled maternal/litter observations for PND 1 was not done.

e) One of the scheduled maternal/litter observations for one day for one litter and two of the scheduled observations on one day for another litter during PNDs 2-11 were not made.

f) Errors made during cross-fostering on PND 1 in six litters included:

1) Offspring in control litter 34 were cross-fostered to 6 mg/kg/day group dam 143 and offspring in the 6 mg/kg/day group litter 143 were cross-fostered to control dam 34. Litter 143 should not have been cross-fostered since it only contained 11 live offspring, whereas the protocol required 12 for cross-fostering. The dams and litters were culled on PND 2.

2) In litter 86, a female toe-marked 13 was found dead on PND 3. On PND 4, male 6 was not present but a second female toe-marked 13 was found. In litter 164, it was noted on PND 4 that there were two males toe-marked 6 and no female with a toemark 13. Data for these animals were not reported since it was not possible to determine their litter of origin. The litter data for PND 1 was unaffected since it was recorded before the cross-fostering.

3) In litter 59, male 1 was not present on PND 4 and an extra female toe-marked 17 was found. In litter 151, male 2 was found dead on PND 2 but was found to be present on PND 4 and female 17 was missing. Data on these animals were not reported for offspring signs, necropsy findings and mortalities or for litter data for PNDs 1-11 of age.

DATA FOR ENTRY INTO ISIS

Cross Fostering Study - rats (non-guideline)

PC code	MRID #	Study type	Species	Duration	Route	Dosing method	Dose range mg/kg/day	Doses tested mg/kg/day	NOAEL mg/kg/day	LOAEL mg/kg/day	Target organ(s)	Comments
035001	46214501	cross fostering	rats	GD 6 - PND 10	oral	gavage	3-6	0, 3, 6	not identified	3	FOB findings, body weight gain	Maternal
035001	46214501	cross fostering	rats	GD 6 - PND 10	oral	gavage	3-6	0, 3, 6	not identified	3	growth retardation	Offspring

13544

R100747

Chemical:	**Dimethoate**
PC Code:	**035001**
HED File Code	**13000 Tox Reviews**
Memo Date:	**07/08/2004**
File ID:	**TX0052452**
Accession Number:	**412-04-0243**

HED Records Reference Center
08/13/2004