EPA Reviewer: Robert J. Mitkus, PhD **Signature:** Robert J. Mitkus
Toxicology Branch, Health Effects Division (7509C) **Date:** 7/13/05
EPA Work Assignment Manager: P.V. Shah, PhD **Signature:** P.V. Shah
Registration Action Branch 1, Health Effects Division (7509C) **Date:** 7/13/05

Template version 11/01

DATA EVALUATION RECORD

STUDY TYPE: Developmental Neurotoxicity Study - Rat; OPPTS 870.6300 (§83-6); OECD 426 (draft)

PC CODE: 101103 **DP BARCODE:** D300889
TXR#: 0052459 **SUBMISSION NO.:** Not provided

TEST MATERIAL (PURITY): Pymetrozine technical (99.3% a.i.)

SYNONYMS: (*E*)-4,5-dihydro-6-methyl-4-(3-pyridylmethyleneamino)-1,2,4-triazin-3(2*H*)-one

CITATION: Pinto, P.J. (2003) Pymetrozine technical (CGA 215944): Developmental neurotoxicity study in rats. Central Toxicology Laboratory, Cheshire, UK. Laboratory Study No.: RR0922, November 21, 2003. MRID 46170301. Unpublished.

Pinto, P.J. (2003) Pymetrozine technical (CGA 215944): Preliminary developmental neurotoxicity study in rats. Central Toxicology Laboratory, Cheshire, UK. Laboratory Study No.: RR0921, November 20, 2003. MRID 46170302. Unpublished.

SPONSOR: Syngenta Crop Protection, Inc., 410 Swing Road, Greensboro, NC

EXECUTIVE SUMMARY: In a developmental neurotoxicity study (MRIDs 46170301 and 46170302), Pymetrozine (CGA 215944, 99.3% a.i., Batch # P.301005) was administered in the diet to pregnant Alpk:APfSD Wistar-derived rats (30/dose) from gestation day (GD) 7 to lactation day (LD) 22 at nominal doses of 0, 100, 500, or 2500 ppm (equivalent to 0/0, 8.1/16.8, 38.7/82.6, and 173.1/NA mg/kg/day [gestation/lactation]). Dams were allowed to deliver naturally and were killed on LD 29. On postnatal day (PND) 5, litters were standardized to 8 pups/litter; the remaining offspring and dams were sacrificed and discarded without further examination. Subsequently, 1 pup/litter/group (at least 10 pups/sex/dose when available) were allocated to subsets for FOB, motor activity, acoustic startle response, learning and memory evaluation, and neuropathological examination.

At 2500 ppm, higher than expected mortality was observed during littering, resulting in insufficient numbers of litters for the F1 generation. Therefore, all surviving 2500 ppm parental females were sacrificed prior to scheduled termination.

At 2500 ppm (173.1 mg/kg/day), one dam was found dead on GD 7, and another dam was sacrificed on GD 24 due to difficult parturition. Additionally on GD 24, the following clinical signs of toxicity were noted in one or two dams per sign (affecting 6 total dams in this group): (i) distended abdomen; (ii) slight hunched posture; (iii) killed due to difficult parturition; (iv) pale; (v) sides pinched in; (vi) staining around nose; and (vii) subdued. Adjusted body weights were decreased (↓6-8%; $p \leq 0.01$) on GD 15 and 22, and body weight gains for the overall (GD 1-22) gestation period (calculated by the reviewers) were decreased by 18% compared to controls. During lactation, body weights remained decreased (↓5-9%; statistics not performed) in the surviving dams until the early termination of this group after LD 15. Food consumption was decreased in these animals during Weeks 2 and 3 of gestation (↓16-19%; $p \leq 0.01$) and throughout lactation until sacrifice (↓8-30%; statistics not performed). Total litter loss was experienced between birth and PND 5 by 4/15 treated dams compared to 2/30 controls, and gestation index (calculated by the reviewers) was decreased at this dose (79.3% treated vs 100% controls). This decrease is attributed to the five dams that were pregnant but were sacrificed on GD 23-24 because they had not littered and the one dam that experienced dystocia, resulting in 23 litters with live born out of 29 pregnant dams. This dose level was considered too high, based on excessive maternal toxicity, high pup mortality, and a lack of a sufficient number of pups to allow meaningful evaluation of developmental toxicity. Thus, the 22 surviving dams in this group were sacrificed for humane reasons before scheduled termination.

At 500 ppm (38.7 mg/kg/day), total litter loss was experienced between birth and PND 5 by 5/29 treated dams (17.2%) compared to 2/30 controls (6.7%). On GD 24, one dam with staining around the nose was sacrificed due to difficult parturition, and another dam was pale. Food consumption was decreased (↓21%; $p \leq 0.01$) during LD 1-5. However, body weights at this dose were comparable to controls throughout treatment.

At 100 ppm (8.1 mg/kg/day), no treatment-related effects were seen on survival, clinical signs, body weight, body weight gain, food consumption, or reproductive performances.

The maternal LOAEL is 38.7 mg/kg/day based on complete litter losses. The maternal NOAEL is 8.1 mg/kg/day.

Pymetrozine caused a dose-dependent increase in the number of pups dying during PND 1-5; 57 pups at 100 ppm , 95 pups at 500 ppm and 151 pups at 2500 ppm compared to 48 pups in the controls. This was due to the increase in the number of whole litter losses at 100 ppm (3 litters), 500 ppm (5 litters), and 2500 ppm (4 litters) compared to controls (2 litters). When whole litter losses are excluded, no treatment-related findings were observed on litter size or viability. On PND 1-3, the surviving 2500 ppm pups (85 pups in 9 litters) were sacrificed for humane reasons to terminate the high dose group.

Treatment had no adverse effects on body weight, body weight gain, food consumption, developmental land marks, clinical signs, FOB, motor activity, auditory startle reflex, learning and memory, brain weights or neuropathology.

Brain morphometry indicated the following differences ($p \leq 0.05$) from controls: (i) increased thickness of the corpus callosum in the 500 ppm males on PND 12 (↑15%) and in the ≥100 ppm males on PND 63 (↑9-13%); (ii) increased thickness of the inner granular and molecular layers of the pre-pyramidal fissure in the cerebellum in the 500 ppm males on PND 63 (↑6-19%); and (iii) increased thickness of the dorsal cortex in the ≥100 ppm females on PND 12 (↑9-10%).

The offspring LOAEL is 8.1 mg/kg/day (LDT) based on morphometric changes in the brains of female pups on PND 12 and male pups on PND 63. The offspring NOAEL is not established.

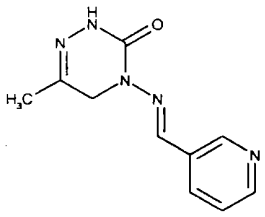
This study is classified **Acceptable/NonGuideline** and may be used for regulatory purposes. It does not, however, satisfy the guideline requirement for a developmental neurotoxicity study in rats (OPPTS 870.6300, §83-6); OECD 426 (draft) due to the inadequacies in the assessment of auditory startle in the offspring and the pending review of the of positive control data.

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

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Pymetrozine technical (CGA 215944)

Description:	White to light brown powder
Lot/Batch #:	P.301005
Purity:	99.3% a.i.
Compound Stability:	The test substance was stable in the diet for up to 37 days at room temperature.
CAS # of TGAI:	123312-89-0
Structure:	

2. Vehicle and/or positive control: Diet

3. Test animals (P)

Species:	Rat	
Strain:	Alpk:AP$_f$SD (Wistar-derived)	
Age at GD 1:	10-12 weeks	
Wt. at GD 1:	197-294 g (females)	
Source:	Rodent Breeding Unit (RBU), Alderly Park, Macclesfield, Cheshire, UK	
Housing:	Dams were housed individually until parturition and then with their litters until PND 29 in solid plastic cages with sawdust bedding. F1 animals were housed 4/sex/cage in wire mesh cages.	
Diet:	CT1 diet (Special Diet Services Limited, Witham, Essex, UK), *ad libitum*, except during testing of motor activity	
Water:	Tap water, *ad libitum*	
Environmental conditions:	**Temperature:**	22 ± 3°C
	Humidity:	30-70%
	Air changes:	≥15/hour
	Photoperiod:	12 hrs dark/ 12 hrs light
Acclimation period:	6 days prior to the start of dosing	

B. PROCEDURES AND STUDY DESIGN

1. In life dates - Start: 11/05/02 End: 09/12/03

2. Study schedule: The test substance was administered to maternal animals from gestation day (GD) 7 through lactation day (LD) 22. F1 pups were selected on post-natal day (PND) 5, weaned on PND 29, and assigned to subgroups in order to evaluate behavioral abnormalities, motor activity, auditory startle response, learning and memory, and neuropathology, including adverse changes in brain weight and morphometry.

3. Mating procedure: Maternal animals were mated by the supplier and examined for the presence of spermatozoa in a vaginal smear to verify positive mating. Dams were shipped to the performing laboratory the day on which positive mating was found, designated GD 1. Twenty

time-mated females were supplied on each of 6 days to the performing laboratory.

4. Animal assignment: Mated females were randomly assigned, blocked by arrival day, to dose groups as indicated in Table 1. Offspring were assigned to testing subgroups at the time of litter standardization on PND 5. However, it was not reported whether offspring were randomly assigned to testing subgroups.

TABLE 1. Study Design[a]

Parameter	Dose (ppm)			
	0	100	500	2500
Maternal Animals				
No. of maternal animals	30	30	30	30
FOB (GD 10 & 17; LD 2 & 9)	30	30	30	30
Offspring				
FOB (PND 5, 12, 22, 36, 46, & 61)	1pup/litter	1pup/litter	1pup/litter	1pup/litter
Motor activity (PND 14, 18, 22, & 60)	≥10 pups/sex	≥10 pups/sex	≥10 pups/sex	≥10 pups/sex[b]
Auditory startle test (PND 23 & 61)	≥10 pups/sex	≥10 pups/sex	≥10 pups/sex	≥10 pups/sex
Learning and memory (water maze) (PND 21 & 24) (PND 59 & 62)	 ≥10 pups/sex ≥10 pups/sex	 ≥10 pups/sex ≥10 pups/sex	 ≥10 pups/sex ≥10 pups/sex	 ≥10 pups/sex ≥10 pups/sex
Brain weight and neuropathology (PND 12 & 63)	10 pups/sex	10 pups/sex	10 pups/sex	10 pups/sex
Cholinesterase determinations	NA	NA	NA	NA

[a]Data obtained from pp. 20-26 and 1606-1638 of MRID 46170301.
[b]except on PND 14, when 3-4 pups/sex/dose were tested
NA=Not applicable

5. Dose selection rationale: Dose levels were chosen based on the results of a preliminary developmental neurotoxicity study in the rat (MRID 46170302), submitted concurrently. A summary of this range-finding study is included as Appendix in this DER.

6. Dosage administration: All doses were administered to maternal animals continuously in the diet from GD 7 through LD 22.

7. Dosage preparation and analysis: Test diets were prepared in 20 kg batches from 1000 g pre-mixes prepared for each dose level by mixing the appropriate amount of test substance with milled diet. The frequency of preparation was not stated, although the test diets were stored for up to 37 days at room temperature. Concentration analyses were performed on diets from all dose groups, prepared immediately prior to the study and during week 6 of the study. All concentrations were within 8% of nominal. However, concentration analyses were not

performed on diets from control groups, and no reason was provided. Additionally, in the batch prepared immediately prior to the study, homogeneity (top, middle, and bottom) and stability (37 days at room temperature) of the test substance in the diet were verified for 100 and 2500 ppm preparations. Homogeneity for each nominal concentration was within 2% of the overall mean measured concentration for that concentration. Concentration, homogeneity, and stability were not measured for test diets containing 500 ppm pymetrozine. No explanation was provided.

Results

Homogeneity: 99.5-109.5% nominal; 0.7-1.5% CV

Stability: The 2500 ppm diet averaged 83.2% initial concentration after 14 days at room temperature. Other than this exception, concentrations ranged from 92.3-105.1% initial concentration for up to 37 days at room temperature across the 100 and 2500 ppm test diets.

Concentration: 100.0-107.7% nominal

The analytical data indicated that the mixing procedure was adequate and that the variation between nominal and actual dosage to the study animals was acceptable.

C. OBSERVATIONS

1. In-life observations

a. Maternal animals: Cage-side observations were conducted twice daily. Detailed clinical examinations were performed at the same time that body weights were measured.

All rats were examined outside the home cage on GD 10 and 17 and LD 2 and 9 using a functional observation battery of tests which included, but were not limited to, the following:

	FUNCTIONAL OBSERVATIONS
X	Signs of autonomic function, including: 1) Ranking of degree of lacrimation and salivation, with range of severity scores from none to severe 2) Presence of absence of piloerection and exophthalmus, 3) Ranking or count of urination and defecation, including polyuria and diarrhea 4) Pupillary function such as constriction of the pupil in response to light, or a measure of pupil size 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.
X	Description and incidence of any unusual or abnormal behaviors, excessive or repetitive actions (stereotypies), emaciation, dehydration, hypotonia or hypertonia, altered fur appearance, red or crusty deposits around the eyes, nose, or mouth, and any other observations that may facilitate interpretation of the data.

Body weights (BW) and food consumption were recorded prior to testing, on GD 1, 7, 15, and 22; LD 1, 5, 8, 12, 15, and 22; and at termination (BW only). Food consumption (g/rat/day) was also reported for LD 18, 21, and 23.

b. Offspring

1) Litter observations: Each litter was examined as soon as possible (always within 24 hours) after completion of parturition (PND 1). The sex of each pup was recorded on PND 1 and 5. The body weight and clinical condition of each pup were recorded on PND 1, 5, 12, 18, 22, 29, 36, 43, 50, 57, and at termination (PND 63). In addition, daily checks for dead or abnormal pups were conducted.

On PND 5, litters were standardized to 8 pups (4/sex/litter, as nearly as possible), and selection of the F1 generation was carried out using litters comprised of 7 or 8 pups with at least 3 males and 3 females. Pups not selected for the F1 generation on PND 5 were killed and discarded.

2) Developmental landmarks: Beginning on PND 29, the selected F1 females were examined daily to determine the age at which vaginal opening occurred. Beginning on PND 41, the selected F1 males were examined daily to determine the age at which balanopreputial separation occurred.

3) Postweaning observations: Cage-side observations for mortality and clinical signs of toxicity were performed daily. Body weight measurements and detailed physical examination of each rat were conducted on PND 29, 36, 43, 50, 57, and prior to termination on PND 63.

4) Neurobehavioral evaluations

i) Functional observational battery (FOB): At least 10 rats/sex/dose (one male or one female per litter) were examined on PND 5, 12, 22, 36, 46, and 61 using a functional observational battery of tests. The FOB was conducted by a technician who was blind to the treatment groups and was comprised of the same parameters examined in the maternal rats (see above). No FOB was recorded, in error, for 14 animals on PND 46. However, because these rats were clinically observed on PND 43 and 50 and comprised a relatively small number of animals on a single day, this omission is not considered to compromise the validity of the study.

ii) Motor activity testing: Motor activity was evaluated in at least 10 rats/sex/dose (one male or one female per litter) on PND 14, 18, 22, and 60, using an automated recording apparatus (details not provided), which recorded small and large movements as activity counts. Each 50-minute session was divided into 10 sub-sessions of five-minute duration. The same offspring were evaluated at each time point, and each animal was returned to the same activity monitor when trials were repeated.

iii) Auditory startle reflex habituation: An auditory startle habituation test was conducted on at least 10 rats/sex/dose (one male or one female per litter) on PND 23 and 61, using an automated recording apparatus (details not provided). Fifty trials (5 blocks of 10 trials per day of testing) were performed per animal on each day of testing. The mean response amplitude and time to maximum amplitude were calculated on each block of 10 trials. There were some

failures of the recording equipment on both days, resulting in a lack of data for 3 rats/dose on PND 23, one control rat for trials 31-50 on PND 61, and three 500 ppm rats on PND 61.

iv) **Learning and memory testing:** Associative learning and memory were tested in at least 10 rats/sex/dose (one rat/sex/litter/dose) on PND 21 and 24 and a different set of at least 10 rats/sex/dose on PND 59 and 62. The test used a Y-shaped water maze with one escape ladder. The time taken to find the escape ladder was recorded for each trial. Animals were given 6 trials on either PND 21 or 59 (learning phase) and were retested three days later (PND 24 or 62) using the same procedure (memory phase). In order to assess swimming speed, each animal completed one trial in a straight channel immediately following the six trials of the learning and memory phases. Swimming times for the Y-maze and straight channel were reported. The percentage of successful trials in the Y-maze was calculated for each animal. The criterion for a successful trial was reaching the escape ladder in ≤ 10 seconds and ≤ 2.0x the straight channel time.

2. Postmortem observations

a. Maternal animals: Females with parturition difficulties and females that failed to litter were sacrificed by over exposure to halothane Ph. Eur. vapor followed by exsanguination and were subjected to a macroscopic examination (including an examination of the uterus to confirm pregnancy status). Microscopic examinations were not performed. Females with total litter loss or with litters not required for selection were sacrificed and discarded. At 2500 ppm, higher than expected mortality was observed during littering, resulting in insufficient numbers of litters for the F1 generation. Therefore, all surviving 2500 ppm-treated dams were sacrificed prior to scheduled termination and subjected to a macroscopic examination. The Sponsor subsequently met with scientists from the Agency to discuss continuing the study with the remaining dose groups and their sufficiency for assessment of developmental toxicity (see attached memo, Appendix 2). The maternal animals surviving in the other dose groups were sacrificed on PND 29 and discarded without examination.

b. Offspring: Pups that were found dead after maternal exposure to 2500 ppm pymetrozine, sacrificed intercurrently, or not selected on PND 5 were discarded without examination. All surviving 2500 ppm pups were also sacrificed and discarded without examination.

On PND 12, at least 10 pups/sex/group (one male or one female per litter) were euthanized by a rising concentration of carbon dioxide. The brain was immediately fixed in 10% neutral buffered formol saline and weighed after at least 24 hours fixation.

On PND 63, at least 10 pups/sex/group (one male or one female per litter) were sacrificed by over exposure to halothane Ph. Eur. vapor, and a cardiac blood sample was taken for the following hematology analyses:

X	Hemoglobin	X	Leukocytes (WBC)
X	Hematocrit	X	Leukocyte differential
X	Erythrocytes (RBC)	X	Mean cell volume (MCV)
X	Platelets	X	Mean cell hemoglobin (MCH)
X	Prothrombin time	X	Mean cell hemoglobin concentration (MCHC)
X	Activated partial thromboplastin time		

Additionally, a bone marrow smear was prepared from each animal but was not examined. The brains from these animals were then removed, weighed (before fixation), fixed, and stored. An additional 10 rats/sex/group (one male or one female per litter) were deeply anesthetized by intraperitoneal injection of sodium pentobarbitone, killed by perfusion fixation with formol saline, and were examined for neuropathology. After weighing, the following CHECKED (X) tissues were evaluated:

	CENTRAL NERVOUS SYSTEM		PERIPHERAL NERVOUS SYSTEM
X	**BRAIN**		**SCIATIC NERVE**
	Olfactory bulbs	X	Sciatic nerve (proximal)
	Frontal lobe		
	Parietal lobe		**OTHER**
	Midbrain with occipital and temporal lobe		Sural nerve
	Pons	X	Tibial nerve (proximal and distal)
	Medulla oblongata		Peroneal nerve
	Cerebellum	X	Lumbar dorsal root ganglion
	SPINAL CORD	X	Lumbar dorsal root fibers
X	Cervical swelling	X	Lumbar ventral root fibers
X	Lumbar swelling	X	Cervical dorsal root ganglion
	OTHER	X	Cervical dorsal root fibers
	Gasserian ganglia with nerve	X	Cervical ventral root fibers
	Pituitary gland		
X	Eyes (with retina and optic nerve)		
X	Skeletal muscle (gastrocnemius)		

Tissues from F1 animals sacrificed on PND 12 and 63 were embedded in paraffin, sectioned at 5 µm, and stained with hematoxylin and eosin. All tissues in the control, 100, and 500 ppm groups were examined – tissues from the 2500 ppm animals were not examined – using light microscopy for neuropathology, and an image analyzer was used for morphometric measurements of brain regions. The tibial and sciatic nerves were embedded in resin, sectioned, and stained with toluidine blue.

D. DATA ANALYSIS

1. Statistical analyses: Data were analyzed using the following statistical procedures:

Parameter	Statistical test[1]
Maternal body weights	Body weights on LD 1 only were analyzed by analysis of variance (ANOVA). Analysis of covariance (ANCOVA) was carried out for body weights on GD 15 and 22; body weights on GD 7 were used as the covariates. Body weights on LD1 were used as the covariate during lactation (other than LD 1). ANOVA (or ANCOVA) were followed by Student's t-test, if necessary, for pair-wise comparison of treated groups with controls.
Pup body weight [2]	Body weights on PND 1 and those selected on PND 5 were analyzed by ANOVA. Body weights on subsequent pre-cull days and post-cull days were adjusted for body weights on PND 1 or PND 5, respectively, and analyzed using ANCOVA. ANOVA (or ANCOVA) were followed by Student's t-test, if necessary, for pair-wise comparison of treated groups with controls.
Maternal food consumption, gestation length, litter size, motor activity, startle response, time to preputial separation, time to vaginal opening, swimming times, hematology	ANOVA followed by Student's t-test, if necessary.
Proportions of litters with gestation length <, =, or >22 days; whole litter loss; pups born live; pups surviving; litters with all pups born live; litters with all pups surviving; male pups; males with preputial separation, females with vaginal opening,	Fisher's Exact Test
Percentages of live born pups, pre-and post-cull pup survival, sex ratio, and successful swimming trials	ANOVA following the double arcsine transformation of Freeman and Tukey, followed by Student's t-test, if necessary.
Brain weight and morphometry	ANOVA and ANCOVA using the terminal body weight as the covariate followed by Student's t-test, if necessary.

[1] All statistical tests were 2-tailed.
[2] calculated separately for males and females for behavioral testing

Analyses of lactation (post-natal) body weights, food consumption, litter size, and pup survival are presented excluding whole litter losses.

2. Indices - Although the formulas were not provided, live birth index was reported as the percent of live born pups. No other indices were reported.

3. Positive control data - Positive control studies on the effect of buprenorphine on the tail flick response in rats (MRID 46012923), the effects of dizocilpine and mecamylamine on learning and memory in the water maze (MRID 46012924) as well as positive control data for motor activity, functional observational battery, and neuropathology previously submitted to the Agency are under review..

II. RESULTS

A. PARENTAL ANIMALS

1. Mortality and clinical and functional observations: Several dams were sacrificed prior to termination because they did not litter, suffered complete litter loss, or because there were insufficient numbers of pups – at least 7 pups with at least 3 pups/sex/litter are required. However, these findings were unrelated to dose.

At 500 ppm, one dam was sacrificed on GD 24 due to difficult parturition (Table 2). At this same dose and day, one dam was pale and another had staining around the nose. At 2500 ppm on GD 24, the following clinical signs were noted in 9 dams: (i) distended abdomen; (ii) slight hunched posture; (iii) difficult parturition; (iv) pale; (v) sides pinched in; (vi) staining around nose; and (vii) subdued. In addition, at 2500 ppm, one dam was found dead on GD 7; one dam was sacrificed on GD 24 due to difficult parturition (dystocia); and 22 animals were sacrificed before scheduled termination due to adverse effects, including high pup mortality, marked reductions in body weight, body weight gain, and food consumption and piloerection and hunched posture. There were no other treatment-related clinical or functional observations.

TABLE 2. Maternal Mortality and Clinical/Functional Observations [a]

Clinical observation	Dose (ppm)			
	0	100	500	2500
Found dead	0	0	0	1[c] (GD 7)
Sacrificed for humane reasons	0	0	0	22 (PND 1-17)
Sacrificed due to difficult parturition	0	0	1 (PND 2)[b]	1 (PND 2)
Distended abdomen	0	0	0	2 (PND 2)
Hunched posture - slight	0	0	0	2 (PND 2)
Pale	0	0	1 (PND 24)	1 (PND 2)
Sides pinched in	0	0	0	1 (PND 2)
Stained around nose	0	0	1 (PND 24)[b]	1 (PND 2)
Subdued	0	0	0	1 (PND 2)

[a] Data obtained from pages 47, 52, 53, 66-68, and 572-573 in MRID 46170301; n = 16-30.
[b] Observed in the same dam (#90)
[c] not pregnant

2. Body weight and food consumption: In the 2500 ppm dams, adjusted body weights were decreased (↓6-8%; $p \leq 0.01$) on GD 15 and 22, and body weight gains for the overall (GD 1-22) gestation period were decreased by 18% compared to controls (Table 3). During lactation, body weights remained decreased (↓5-9%; statistics not performed) in the surviving 2500 ppm dams until the early termination of this group after LD 15. Food consumption was decreased in these animals during Weeks 2 and 3 of gestation (↓16-19%; $p \leq 0.01$) and throughout lactation until sacrifice (↓8-30%; statistics not performed). The only finding at 500 ppm was a decrease (↓21%; $p \leq 0.01$) in food consumption during LD 1-5. However, mean body weights at this dose increased from LD 1-5. There were no other treatment-related effects on body weights, body weight gains, or food consumption during gestation or lactation. Selected group mean body weights and food consumption values for pregnant or nursing dams are summarized in the following table:

TABLE 3. Mean (±SD) Maternal Body Weight and Food Consumption [a]

Observations/study interval	Dose (ppm)			
	Control	100	500	2500 [b]
Gestation				
Body weight				
GD 1	257.0 ± 19.7	259.1 ± 19.0	258.3 ± 20.0	253.5 ± 19.0
GD 7	288.5 ± 20.4	292.0 ± 19.2	288.8 ± 19.8	292.2 ± 15.1
GD 15[c]	334.7	332.3	330.2	314.4** (↓6)
GD 22[c]	392.4	387.4	382.8	360.4** (↓8)
Body weight gain (GD 1-22)[d]	133.5	129.9	122.9	109.2 (↓18)
Food consumption				
Week 1	19.8 ± 2.3	20.2 ± 3.1	19.6 ± 3.5	20.2 ± 3.1
Week 2	26.6 ± 2.6	25.9 ± 3.2	25.3 ± 3.2	21.5 ± 3.8** (↓19)
Week 3	27.9 ± 3.8	28.4 ± 5.0	25.9 ± 4.3	23.3 ± 4.6** (↓16)
Lactation				
Body weight				
LD 1	301.7 ± 27.3	302.8 ± 29.8	301.5 ± 30.4	275.7 ± 31.1 (↓9)
LD 5[e]	312.4	313.8	313.4	298.2 ± 23.9 (↓5)
LD 29[e]	333.7	345.5* (↑4)	340.3	NA
Body weight gain (LD 1-29)[d]	33.1	40.7	39.3	NA
Food consumption				
LD 1-5	33.3 ± 10.3	29.8 ± 7.7	26.2 ± 6.8** (↓21)	23.3 ± 8.3 (↓30)
LD 5-8	42.2 ± 10.3	41.8 ± 8.3	40.0 ± 6.1	34.1 ± 15.4 (↓19)
LD 8-12	50.3 ± 9.3	50.6 ± 11.0	49.7 ± 5.9	41.7 ± 6.5 (↓17)
LD 12-15	55.8 ± 9.4	57.1 ± 9.5	59.8 ± 6.6	51.3 ± 10.4 (↓8)

[a]Data obtained from Tables 5 through 8 on pages 74-77 in MRID 46170301; n = 20-30, except at 2500 ppm where n = 7-29. Percent difference from controls is included in parentheses.
[b]Statistical analyses were not performed at 2500 ppm during lactation; thus, body weights in this group are unadjusted during the lactation period.
[c]Means are adjusted based on the body weight on GD 7.
[d]Calculated from the differences in unadjusted group mean body weights.
[e]Means are adjusted based on the body weight on LD 1, except at 2500 ppm where means are not adjusted because statistical analyses were not performed.
**Statistically different from the controls at $p \leq 0.01$
NA=Not available because 2500 ppm group was sacrificed prior to termination

3. Test substance intake: Based on maternal food consumption, body weight, and the nominal concentration in the diet, the mean test substance intake (mg/kg bw/day) during the gestation and lactation periods are presented in Table 4.

TABLE 4. Mean maternal test substance intake (mg/kg body weight/day)[a]

Parameter	Dose (ppm)		
	100	500	2500
Gestation	8.1	38.7	173.1
Lactation	16.8	82.6	NA

[a]Data were obtained from Appendix H on pages 211f. in MRID 46170301.
NA=Not available due to sacrifice of all animals in this group prior to scheduled termination

4. Reproductive performance: Total litter loss was experienced between birth and PND 5 by 5/29 dams at 500 ppm and 4/15 dams at 2500 ppm compared to 2/30 dams in the controls (Table 5). Gestation index was decreased at 2500 ppm (79.3%) compared to controls (100%). This decrease is attributed to the five dams that were pregnant but were sacrificed on GD 23-24, because they had not littered, and the one dam that experienced dystocia, resulting in 23 litters "with live born" out of 29 pregnant dams. There were no other treatment-related effects on reproductive performance.

TABLE 5. Reproductive performance[a]

Observation	Dose (ppm)			
	0	100	500	2500 [b]
Number mated	30	30	30	30
Number pregnant[c]	30	30	30	29
Number not pregnant	0	0	0	1
Number pregnant with no litters born[d]	0	0	0	5
Incidence of dystocia or other adverse clinical signs[g]	0	0	1	1
Number of litters (# with live born)	30	30	29	23
Gestation index (%)[e]	100	100	96.7	79.3
Number (%) with complete litter loss	2/30 (6.7%)	3/30 (10.0%)	5/29 (17.2%)	4/15 (26.7%)
Insufficient number or sex ratio of pups[f]	2	6	4	4
Total number of litters selected for F1	25/30	21/30	20/30	7/15
Mean (±SD) gestation duration (days)	22.1 ± 0.3	22.0 ± 0.0	22.0 ± 0.2	22.2 ± 0.5

[a]Data were obtained from pages 29, 78-80, and 719 in MRID 46170301.
[b]Statistical analyses were not performed at 2500 ppm.
[c]Calculated from data presented in this table
[d]Three dams were sacrificed on GD 23, and two dams were sacrificed on GD 24 because they did not litter, although pregnant (page 719, volume 4 of MRID 46170301).
[E]Gestation index = (# with pups born live/ # pregnant) x 100%.
[f]Sufficient number of pups was defined as at least 3 males and 3 females in a litter of at least 7 pups. Dams and litters not meeting this criteria were sacrificed.
[g]sacrificed

5. Maternal postmortem results: Macroscopic examinations (including examination of the uterus to confirm pregnancy status) were performed only on females with parturition difficulties (one 500 ppm dam and one 2500 ppm dam) and females which failed to litter (five 2500 ppm dams). Microscopic examinations were not performed.

B. OFFSPRING

1. **Viability and clinical signs:** Litter size and viability (survival) results from pups prior to selection on PND 5 are summarized in Table 6. Litter size and survival were not reported after culling on PND 5. No reason was provided for this. A dose-dependent increase in the number of pups dying during PND 1-5 was observed at 100 ppm (57 pups), 500 ppm (95 pups), and 2500 ppm (151 pups) compared to controls (48 pups), perhaps due to the increase in the number of whole litter losses at 100 ppm (3 litters), 500 ppm (5 litters), and 2500 ppm (4 litters) compared to controls (2 litters). On PND 1-3, the surviving 2500 ppm pups (85 pups in 9 litters) were sacrificed to terminate the high dose group. There were no other treatment-related clinical signs.

TABLE 6. Litter size and viability [a]

Observation	Dose (ppm)			
	Control	100	500	2500 [b]
Total number born	346	346	328	254
Number born live	335	339	321	246
Number born dead[c]	11	7	7	8
Sex Ratio Day 1 (% ♂)	48.5 ± 17.8	46.4 ± 17.0	53.8 ± 16.3	52.3 ± 19.2
Surviving Days 1-5 (%)[d]	92.9 ± 12.0	95.9 ± 12.6	90.4 ± 16.3	96.7 ± 5.1
Deaths Days 1-5 (#)[e]	48	57	95	151
Deaths Days 5-22 (#)	NR	NR	NR	NR
Mean litter size:				
Day 1[d]	11.5 ± 2.6	11.0 ± 3.2	10.8 ± 3.5	10.7 ± 2.4
Day 5[d, f]	10.6 ± 2.5	10.4 ± 3.2	9.4 ± 2.9*	10.6 ± 2.4
Day 5,12,18[d, g]	NR	NR	NR	NR
Day 22	NR	NR	NR	NR
Live birth index	95.7 ± 10.5	98.2 ± 4.4	97.8 ± 6.3	97.3 ± 5.8
Viability index (%)[c,d]	92.9 ± 12.0	95.9 ± 12.6	90.4 ± 16.3*	96.7 ± 5.1
Lactation index (%)	NR	NR	NR	NR

[a]Data obtained from p. 32 and Tables 10 through 14 on pages 79-83 in MRID 46170301.
[b] Statistical analyses were not performed at 2500 ppm.
[c] Viability index (%) = [# pups surviving to PND 5 (pre-cull)/# pups born live] x 100%
[d] Excluding whole litter loss
[e] obtained from Table 13 on page 82 of MRID 46170301; includes whole litter loss.
[f] Before standardization (culling).
[g] After standardization (culling).
*Statistically different from controls at $p \leq 0.05$
NR=Not reported

2. **Body weight:** Data for the 2500 ppm pups were not presented after PND 5 because this group was sacrificed prior to scheduled termination due to excessive maternal toxicity (Table 7). Based on the data presented, pre-weaning pup body weights of the treated groups were comparable to controls. Post-weaning body weights of the remaining treated groups were comparable to controls (Table 8).

TABLE 7. Mean (±SD) pre-weaning pup body weights (g)[a]

Post-natal Day	Dose (ppm)							
	0	100	500	2500 [b]	0	100	500	2500[b]
	Males				Females			
1	6.0 ± 0.7	5.9 ± 0.7	6.1 ± 0.8	5.9 ± 0.9	5.6 ± 0.5	5.6 ± 0.7	5.8 ± 0.7	5.7 ± 0.8
5[c, d]	9.6	9.3	9.3	9.3 ± 2.3	9.2	8.8	8.8	9.0 ± 2.0
5[e]	9.4 ± 1.1	8.9 ± 1.1	9.3 ± 1.9	NA	9.0 ± 1.1	8.4 ± 1.1	8.9 ± 1.7	NA
12[f]	21.8	22.0	21.8	NA	21.2	21.7	21.0	NA
18[f]	36.3	37.3	37.3	NA	35.0	36.2	35.6	NA
22[f]	49.3	50.5	50.3	NA	47.5	49.0	48.4	NA

[a]Data were obtained from Tables 15 and 19 on pages 84, 119, and 121 in MRID 46170301.
[b]Statistical analyses were not performed at 2500 ppm; thus, body weights in this group are unadjusted.
[c]Before standardization (culling)
[d]Means are adjusted based on the body weight on PND 1
[e]After standardization (culling)
[f]Means are adjusted based on the body weight on PND 5 (post-cull).

TABLE 8. Adjusted mean post-weaning pup body weights (g)[a]

Post-natal Day	Dose (ppm)					
	0	100	500	0	100	500
	Males			Females		
29	88.3	89.9	89.0	83.0	85.3	84.1
36	139.4	141.3	139.3	123.6	125.9	124.2
43	196.9	199.5	195.1	158.0	161.1	158.0
50	253.4	256.9	252.4	181.8	185.7	182.8
57	306.2	312.2	308.1	202.9	207.3	202.9
63	336.7	344.6	340.4	210.7	216.2	211.3

[a]Data were obtained from Table 19 on pages 119-122 in MRID 46170301. Means are adjusted based on the body weight on PND 5 (post-cull).

3. Developmental landmarks

a) Sexual maturation: Sexual maturation data are presented in Table 9. Time to preputial separation in males or vaginal opening in females was unaffected by treatment in the remaining treated groups.

TABLE 9. Mean (±SD) age of sexual maturation (days) [a]

Parameter	Dose (ppm)		
	0	100	500
N (M/F)	25/25	21/21	20/20
Preputial separation (males)	43.6 ± 1.3	43.7 ± 1.3	44.0 ± 1.1
Vaginal opening (females)	35.1 ± 1.8	34.9 ± 1.3	35.0 ± 1.5

[a]Data were obtained from Table 20 on pages 123-124 in MRID 46170301.

b) Physical landmarks: Physical landmarks were not evaluated. No reason was provided, given that treatment-related effects were observed.

4. Behavioral assessments

a) Functional observational battery: No abnormalities in either sex were detected in any of the parameters examined in the functional observational battery on PND 5, 12, 22, 36, 46, or 61.

b) Motor activity: There were no treatment-related effects on total activity in males or females during any of the time points (Table 10a). Sub-session data indicated that there was no evidence of habituation in females, and activity levels remained high throughout the 50-minute session in both sexes for each of the days tested. Mean motor activity was increased 8- to 12-fold ($p \leq 0.05$) compared to controls in the 500 ppm males on PND 14 during the 36-40 and 41-45 minute intervals (Table 10b). There were no other statistically significant differences in the sub-session motor activity data in the males. In the 500 ppm females, mean motor activity was increased ($p \leq 0.05$) by 396% on PND 14 during the 11-15 minute interval and by 284% on PND 18 during the 16-20 minute interval relative to controls (Table 10c). However, these increases are not treatment-related because comparable increases (↑70-875%; $p \leq 0.05$), which were not dose-related, were observed in the 100 ppm females on PND 14 and 22 and no differences were noted across dose in overall motor activity counts.

TABLE 10a. Mean (±SD) motor activity data (total number of movements/50 minutes)[a]

Test Day	Dose (ppm)		
	0	100	500
Males			
PND 14	30.4 ± 26.6 (87.5)	53.9 ± 72.3 (134)	110.7 ± 158.1 (143)
PND 18	103.8 ± 78.5 (75.6)	109.3 ± 138.3 (126.5)	86.8 ± 112.7 (130)
PND 22	298.9 ± 167.9	318.4 ± 201.1 (63.2)	324.3 ± 125.9
PND 60	505.7 ± 146.5	468.2 ± 199.1	480.8 ± 136.7
Females			
PND 14	52.9 ± 70.3 (133)	83.5 ± 77.6 (92.9)	117.9 ± 118.4 (100)
PND 18	90.9 ± 107.0 (118)	61.8 ± 60.0 (97)	115.3 ± 126.4 (110)
PND 22	295.2 ± 104.1	332.5 ± 145.2 (43.7)	325.8 ± 179.4
PND 60	528.1 ± 75.3	538.9 ± 131.2	576.9 ± 106.0

[a]Data were obtained from Table 21 on pages 125-132 in MRID 46170301; n = 10-13; select % coefficients of variation in parentheses

TABLE 10b. Mean (± SD) sub-session motor activity in males (# movements/5 minute sub-session)[a]

Interval (min)	Dose (ppm)		
	0	100	500
Post-natal day (PND) 14			
1-5	5.2 ± 5.1	11.0 ± 11.1	10.9 ± 13.9
6-10	1.6 ± 3.3	3.3 ± 8.8	7.9 ± 15.4
11-15	7.5 ± 13.1	2.8 ± 2.9	13.4 ± 25.1
16-20	3.5 ± 5.9	2.9 ± 5.6	11.4 ± 18.1

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Interval (min)	Dose (ppm)		
	0	100	500
21-25	3.4 ± 5.9	7.2 ± 11.7	7.8 ± 13.8
26-30	3.3 ± 7.5	9.3 ± 19.4	11.4 ± 15.8
31-35	1.8 ± 3.0	4.3 ± 9.9	9.7 ± 19.0
36-40	1.5 ± 1.9	3.3 ± 6.5	14.6 ± 23.4* (↑873)
41-45	1.2 ± 1.5	4.0 ± 9.7	15.6 ± 27.2* (↑1200)
46-50	1.4 ± 2.0	5.8 ± 10.1	8.0 ± 15.1
PND 18			
1-5	18.1 ± 20.3	18.6 ± 24.1	17.4 ± 18.0
6-10	15.5 ± 15.6	15.8 ± 24.5	11.9 ± 18.5
11-15	3.9 ± 8.8	14.4 ± 22.0	9.9 ± 14.9
16-20	4.0 ± 7.0	6.4 ± 17.2	6.9 ± 12.8
21-25	11.3 ± 20.7	12.1 ± 23.7	7.9 ± 11.9
26-30	9.5 ± 18.8	10.9 ± 14.0	7.7 ± 16.6
31-35	6.9 ± 12.2	4.5 ± 10.1	9.0 ± 16.6
36-40	8.0 ± 14.5	6.6 ± 17.9	8.3 ± 14.7
41-45	12.9 ± 18.6	7.4 ± 12.6	3.6 ± 8.6
46-50	13.7 ± 20.1	12.6 ± 20.7	4.2 ± 12.2

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Interval (min)	Dose (ppm)		
	0	100	500
PND 22			
1-5	38.3 ± 22.2	42.9 ± 23.3	47.1 ± 20.3
6-10	36.9 ± 21.8	43.6 ± 24.1	32.3 ± 18.1
11-15	27.3 ± 26.0	32.6 ± 21.4	30.3 ± 16.7
16-20	31.8 ± 24.1	23.8 ± 22.7	37.6 ± 23.3
21-25	27.8 ± 24.0	31.1 ± 32.3	33.1 ± 20.1
26-30	31.0 ± 26.5	24.9 ± 29.5	32.1 ± 17.7
31-35	29.4 ± 26.6	31.5 ± 29.2	40.3 ± 27.2
36-40	26.8 ± 26.8	33.8 ± 30.6	26.5 ± 23.4
41-45	23.0 ± 25.9	27.5 ± 29.7	22.8 ± 23.8
46-50	26.6 ± 24.5	26.7 ± 32.2	22.2 ± 32.6
PND 60			
1-5	62.5 ± 17.3	63.6 ± 22.2	64.0 ± 25.8
6-10	69.3 ± 13.2	57.2 ± 24.1	60.8 ± 21.7
11-15	61.6 ± 24.8	58.5 ± 24.9	55.8 ± 20.4
16-20	54.8 ± 26.7	46.5 ± 28.4	48.6 ± 28.2
21-25	49.4 ± 24.5	32.1 ± 31.8	39.4 ± 22.8
26-30	48.8 ± 26.6	44.1 ± 31.1	44.4 ± 29.0
31-35	29.5 ± 27.1	41.9 ± 32.7	40.3 ± 24.8
36-40	36.8 ± 31.2	49.8 ± 25.1	48.8 ± 23.3
41-45	46.5 ± 25.8	43.4 ± 19.1	39.3 ± 28.9
46-50	46.5 ± 29.3	31.1 ± 31.2	39.4 ± 29.3

[a]Data were obtained from Table 21 on pages 125, 127, 129, and 131 in MRID 46170301; n = 10-12. Significant percent difference from controls included in parentheses.
*Statistically different from controls at $p \leq 0.05$

TABLE 10c. Mean (± SD) sub-session motor activity in females (# movements/5 minute sub-session)[a]

Interval (min)	Dose (ppm)		
	0	100	500
Post-natal day (PND) 14			
1-5	7.8 ± 12.0	6.8 ± 8.8	10.0 ± 11.7
6-10	3.9 ± 8.7	5.7 ± 8.4	12.7 ± 20.3
11-15	2.8 ± 4.3	6.1 ± 8.8	13.9 ± 20.7* (↑396)
16-20	6.5 ± 13.9	10.1 ± 19.1	8.4 ± 12.3
21-25	5.6 ± 16.5	10.6 ± 20.2	19.4 ± 24.3
26-30	5.5 ± 9.7	7.7 ± 9.0	9.0 ± 11.9
31-35	7.8 ± 14.9	9.5 ± 15.0	11.3 ± 18.2
36-40	6.5 ± 12.7	10.5 ± 16.4	13.6 ± 16.1
41-45	1.2 ± 2.4	11.7 ± 14.0* (↑875)	8.4 ± 11.6
46-50	5.2 ± 8.0	4.7 ± 7.7	11.2 ± 12.0
PND 18			
1-5	11.9 ± 13.4	15.6 ± 24.7	18.5 ± 23.0
6-10	11.7 ± 14.1	8.3 ± 12.3	14.6 ± 20.0
11-15	11.1 ± 18.8	9.5 ± 14.0	17.8 ± 26.5
16-20	5.5 ± 10.0	5.4 ± 8.6	21.1 ± 28.3* (↑284)
21-25	5.2 ± 14.1	9.7 ± 21.2	14.2 ± 25.9
26-30	7.7 ± 18.9	3.5 ± 5.4	10.4 ± 17.9
31-35	6.7 ± 17.1	1.5 ± 2.2	3.3 ± 6.6
36-40	10.8 ± 20.8	1.3 ± 2.3	1.5 ± 4.4
41-45	11.1 ± 18.0	2.2 ± 3.0	4.4 ± 7.1
46-50	9.3 ± 19.3	4.7 ± 9.0	9.5 ± 17.7
PND 22			
1-5	29.2 ± 19.2	49.5 ± 24.8* (↑70)	42.5 ± 25.5
6-10	23.2 ± 20.2	32.3 ± 23.5	36.5 ± 22.7
11-15	23.3 ± 17.5	33.9 ± 26.8	35.2 ± 23.7
16-20	24.2 ± 22.3	28.7 ± 26.8	24.7 ± 17.7
21-25	37.7 ± 19.2	32.8 ± 26.1	38.3 ± 22.2
26-30	46.0 ± 20.6	38.1 ± 27.5	34.1 ± 29.3
31-35	38.0 ± 20.5	35.5 ± 32.7	31.6 ± 28.1
36-40	20.5 ± 21.2	30.8 ± 29.0	22.0 ± 21.3
41-45	28.6 ± 31.7	21.5 ± 22.8	30.4 ± 27.8
46-50	24.5 ± 24.2	29.4 ± 26.0	30.5 ± 26.3

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Interval (min)	Dose (ppm)		
	0	100	500
PND 60			
1-5	66.3 ± 12.1	71.1 ± 9.6	67.4 ± 15.8
6-10	65.2 ± 9.4	72.4 ± 11.9	70.4 ± 15.3
11-15	58.7 ± 12.1	62.8 ± 20.1	60.6 ± 11.8
16-20	48.2 ± 16.0	50.4 ± 24.2	57.3 ± 12.9
21-25	52.7 ± 15.2	41.8 ± 23.7	55.0 ± 14.5
26-30	47.6 ± 18.4	42.7 ± 29.2	52.4 ± 19.9
31-35	45.9 ± 22.8	49.5 ± 25.0	53.5 ± 26.6
36-40	44.5 ± 25.5	52.2 ± 23.4	53.9 ± 19.7
41-45	44.5 ± 20.8	51.5 ± 19.7	53.3 ± 22.7
46-50	54.5 ± 17.3	44.6 ± 21.0	53.1 ± 22.0

[a]Data were obtained from Table 21 on pages 126, 128, 130, and 132 in MRID 46170301; n = 10-13. Significant percent difference from controls included in parentheses.
*Statistically different from controls at $p \leq 0.05$

c) **Auditory startle reflex habituation:** No treatment-related differences were observed in peak amplitude (Table 11a) or latency (Table 11b) of auditory startle response. However, while habituation arguably occurred for males at PND 61, the data show that it likely did not occur at PND 23 for males and on either day for females. Technical failure of the equipment was reported for both days (PND 23 and 61).

TABLE 11a. Mean (± SD) Peak amplitude (Vmax) of auditory startle reflex[a]

Post-natal Day	Repetition	Dose (ppm)		
		0	100	500
Males				
PND 23	1-10	357.5 ± 181.7	262.4 ± 102.5	281.4 ± 95.7
	11-20	252.1 ± 107.2	208.3 ± 55.2	230.7 ± 71.6
	21-30	210.1 ± 67.0	179.6 ± 62.5	223.2 ± 92.1
	31-40	224.0 ± 118.7	179.5 ± 62.6	215.8 ± 78.1
	41-50	205.6 ± 67.6	159.1 ± 55.7	193.5 ± 48.0
PND 61	1-10	1070.0 ± 338.3	1268.6 ± 729.1	1042.6 ± 174.4
	11-20	945.3 ± 305.7	939.2 ± 244.9	795.2 ± 165.1
	21-30	781.7 ± 142.6	742.7 ± 290.7	615.9 ± 196.0
	31-40	764.4 ± 186.5	638.1 ± 154.8	643.5 ± 278.3
	41-50	675.5 ± 274.8	614.4 ± 167.9	586.2 ± 213.9
Females				
PND 23	1-10	331.1 ± 202.0	287.9 ± 171.9	405.2 ± 374.1
	11-20	297.2 ± 124.3	221.2 ± 103.2	249.6 ± 191.7
	21-30	229.1 ± 105.1	216.6 ± 91.8	230.3 ± 145.1
	31-40	218.3 ± 67.9	219.5 ± 85.7	219.7 ± 130.3
	41-50	204.2 ± 70.7	201.7 ± 82.7	183.1 ± 110.7
PND 61	1-10	799.0 ± 274.0	936.7 ± 514.1	671.5 ± 231.1
	11-20	662.1 ± 319.9	669.7 ± 388.1	568.1 ± 267.8
	21-30	627.8 ± 293.4	738.7 ± 348.2	539.3 ± 251.4

Post-natal Day	Repetition	Dose (ppm)		
		0	100	500
	31-40	555.1 ± 320.4	620.9 ± 304.3	398.8 ± 207.7
	41-50	576.5 ± 278.3	606.3 ± 322.9	428.8 ± 191.2

[a]Data were obtained from Tables 22 on pages 133-134 in MRID 46170301; n = 8-12.

TABLE 11b. Mean (± SD) time to peak amplitude (ms)[a]

Post-natal Day	Repetition	Dose (ppm)		
		0	100	500
Males				
PND 23	1-10	26.2 ± 8.0	28.1 ± 3.2	25.8 ± 4.7
	11-20	22.4 ± 7.4	22.7 ± 3.6	21.4 ± 3.2
	21-30	20.9 ± 3.4	24.7 ± 6.9	23.8 ± 7.4
	31-40	22.4 ± 6.3	22.0 ± 2.7	20.1 ± 1.6
	41-50	23.8 ± 10.2	23.5 ± 3.5	21.2 ± 4.1
PND 61	1-10	28.1 ± 6.6	31.1 ± 9.6	27.8 ± 4.7
	11-20	25.3 ± 3.0	24.0 ± 3.3	25.6 ± 3.2
	21-30	25.2 ± 3.7	26.4 ± 1.9	26.2 ± 3.1
	31-40	25.5 ± 4.3	26.6 ± 3.3	27.9 ± 3.1
	41-50	26.4 ± 5.5	26.2 ± 2.2	26.5 ± 4.2
Females				
PND 23	1-10	27.0 ± 9.7	26.4 ± 5.6	27.5 ± 8.7
	11-20	23.3 ± 6.6	21.3 ± 2.1	21.4 ± 1.1
	21-30	22.3 ± 3.3	20.6 ± 4.8	23.0 ± 4.1
	31-40	23.5 ± 7.2	20.1 ± 2.0	22.1 ± 3.9
	41-50	24.8 ± 7.2	21.1 ± 4.2	22.1 ± 4.3
PND 61	1-10	27.0 ± 4.1	26.2 ± 2.5	25.7 ± 3.3
	11-20	26.5 ± 3.6	26.5 ± 3.7	25.9 ± 2.9
	21-30	28.1 ± 4.5	24.0 ± 2.5* (↓15)	25.0 ± 3.6
	31-40	25.5 ± 1.9	25.1 ± 6.3	26.1 ± 3.4
	41-50	27.0 ± 4.6	26.3 ± 2.9	25.0 ± 4.4

[a]Data were obtained from Table 23 on pages 135-136 in MRID 46170301; n = 8-12. Significant percent difference from controls included in parentheses.
*Statistically different from controls at p≤0.05

d) Learning and memory testing: No treatment-related differences were observed in the water maze tests at either age (around weaning or PND 60). Several instances of increased (p≤0.05) swimming times were noted in the females, for example, during Trial 5 on PND 21 in the 100 and 500 ppm groups (↑52 and 60%, resp.) and during Trial 4 on PND 24 in the 500 ppm group (↑64%). A similar increase was noted in the 100 ppm males during Trial 1 on PND 21 (↑39%; p≤0.05) that was not dose-related (Table 12a).

On PND 59 the mean time taken to complete Trial 1 was longer for subsequent trials, but not all subsequent trials showed a decrease from one another (Table 12b). In addition, variability was high around each measure of memory on PND 62 and actually increased in some cases, e.g., from Trial 4 to 5 in females on PND 62. Swimming times for the treated groups were comparable to controls during all trials of both the learning and memory phases for both sexes on PND 59.

The mean percent successful swimming trials in the water maze are reported in Table 12c. The statistically significant decrease in the mean percentage of swimming trials completed in less than 10 seconds in the memory phase by the PND 62 males and the PND 24 females was not considered to be biologically significant based on the review of individual data (See Appendix I).

TABLE 12a. Mean (± SD) swimming times (s) in Y-water maze around weaning [a]

Session/Parameter		Dose (ppm)		
		0	100	500
Males				
Learning phase (PND 21)	Straight channel	3.99 ± 4.31	3.89 ± 1.55	3.62 ± 1.54
	Trial 1	13.23 ± 6.68	18.38 ± 8.61*(↑39)	15.24 ± 8.58
	Trial 2	12.74 ± 9.03	14.15 ± 7.49	11.21 ± 8.36
	Trial 3	11.08 ± 6.79	12.55 ± 6.44	12.31 ± 8.74
	Trial 4	8.56 ± 5.48	11.38 ± 6.31	12.63 ± 9.06
	Trial 5	8.59 ± 5.94	9.49 ± 5.69	8.24 ± 6.92
	Trial 6	8.09 ± 6.80	10.84 ± 5.33	7.43 ± 6.58
Memory phase (PND 24)	Straight channel	2.82 ± 1.18	2.69 ± 0.74	2.88 ± 1.23
	Trial 1	7.22 ± 5.55	6.58 ± 3.40	7.98 ± 5.35
	Trial 2	4.60 ± 2.41	3.98 ± 1.75	5.19 ± 3.72
	Trial 3	3.32 ± 1.41	4.84 ± 3.07	4.32 ± 3.36
	Trial 4	3.97 ± 3.00	4.44 ± 3.02	3.73 ± 1.66
	Trial 5	4.54 ± 3.12	4.18 ± 2.54	4.56 ± 3.59
	Trial 6	3.96 ± 2.35	3.64 ± 1.69	3.33 ± 1.58
Females				
Learning phase (PND 21)	Straight channel	4.11 ± 3.89	4.01 ± 1.75	4.77 ± 3.39
	Trial 1	16.14 ± 8.24	16.50 ± 8.01	15.23 ± 8.37
	Trial 2	8.88 ± 4.66	10.65 ± 7.64	10.11 ± 6.87
	Trial 3	10.93 ± 8.55	11.35 ± 6.98	11.12 ± 8.22
	Trial 4	8.12 ± 5.21	9.24 ± 5.73	9.94 ± 8.35
	Trial 5	6.68 ± 2.98	10.13 ± 6.15* (↑52)	10.70 ± 7.72* (↑60)
	Trial 6	6.55 ± 4.80	8.88 ± 7.64	10.32 ± 7.40
Memory phase (PND 24)	Straight channel	3.18 ± 1.80	3.03 ± 1.25	3.80 ± 2.30
	Trial 1	7.79 ± 5.18	6.82 ± 3.14	9.70 ± 6.84
	Trial 2	4.33 ± 3.73	4.58 ± 2.45	4.88 ± 4.55
	Trial 3	3.74 ± 2.08	3.83 ± 2.12	4.94 ± 3.80
	Trial 4	3.66 ± 1.51	3.40 ± 1.38	6.00 ± 5.23* (↑64)
	Trial 5	3.74 ± 1.42	4.41 ± 2.66	4.53 ± 3.14
	Trial 6	5.31 ± 2.65	4.20 ± 2.40	4.50 ± 4.80

[a]Data were obtained from Table 24 on page 137-140 in MRID 46170301; n = 19-25. Percent difference from controls, calculated by the reviewers, is included in parentheses.
*Statistically different from controls at $p \leq 0.05$

TABLE 12b. Mean (± SD) swimming times (s) in water maze around PND 60[a]

Session/Parameter		Dose (ppm)		
		0	100	500
Males				
Learning phase (PND 59)	Straight channel	3.11 ± 1.53	3.41 ± 2.16	2.91 ± 1.57
	Trial 1	8.28 ± 3.06	10.34 ± 4.14	10.33 ± 5.90
	Trial 2	5.54 ± 2.80	5.91 ± 3.20	6.30 ± 4.49
	Trial 3	4.28 ± 1.67	6.55 ± 5.58	5.57 ± 4.62
	Trial 4	4.14 ± 2.14	5.15 ± 2.72	4.61 ± 2.26
	Trial 5	5.13 ± 3.90	4.33 ± 2.50	4.21 ± 2.06
	Trial 6	4.56 ± 2.29	4.26 ± 2.32	4.58 ± 2.25
Memory phase (PND 62)	Straight channel	2.24 ± 0.61	2.75 ± 1.25	2.70 ± 1.64
	Trial 1	4.34 ± 2.71	4.47 ± 2.37	4.68 ± 1.74
	Trial 2	3.93 ± 2.37	3.45 ± 1.41	5.39 ± 5.56
	Trial 3	4.68 ± 3.27	4.97 ± 4.00	4.41 ± 2.78
	Trial 4	4.54 ± 3.48	5.32 ± 2.71	6.95 ± 6.56
	Trial 5	5.67 ± 3.72	6.59 ± 5.43	7.50 ± 6.50
	Trial 6	5.42 ± 3.55	5.53 ± 3.09	7.67 ± 5.85
Females				
Learning phase (PND 59)	Straight channel	2.38 ± 0.79	2.64 ± 0.69	2.88 ± 1.90
	Trial 1	10.59 ± 4.50	12.09 ± 5.21	8.32 ± 2.84
	Trial 2	6.56 ± 2.95	6.41 ± 4.92	5.29 ± 2.86
	Trial 3	5.32 ± 4.07	5.44 ± 3.97	6.60 ± 4.60
	Trial 4	4.35 ± 1.94	5.11 ± 2.37	5.09 ± 1.98
	Trial 5	4.16 ± 1.61	4.85 ± 2.46	4.36 ± 2.21
	Trial 6	3.81 ± 2.14	4.61 ± 2.37	4.77 ± 3.41
Memory phase (PND 62)	Straight channel	2.26 ± 1.01	2.58 ± 1.17	2.52 ± 1.10
	Trial 1	5.61 ± 3.13	5.38 ± 3.15	3.74 ± 1.33
	Trial 2	4.93 ± 3.77	4.60 ± 3.65	3.89 ± 2.50
	Trial 3	6.19 ± 6.71	4.39 ± 3.79	4.39 ± 2.96
	Trial 4	5.90 ± 3.64	4.22 ± 3.25	7.57 ± 7.34
	Trial 5	8.13 ± 7.03	6.23 ± 4.73	8.06 ± 8.01
	Trial 6	5.71 ± 4.36	5.51 ± 6.69	7.73 ± 5.72

aData were obtained from Table 24 on page 141-144 in MRID 46170301; n = 16-23. Percent difference from controls, calculated by the reviewers, is included in parentheses.

TABLE 12c. Mean (± SD) percent of successful swimming trials in water maze[a]

Session	Criterion	Dose (ppm)		
		0	100	500
Males				
Learning phase (PND 21)	≤ 10 seconds	60.0 ± 18.6	39.7 ± 22.7** (↓39)	58.8 ± 22.5
	≤ 2 x straight channel time	38.0 ± 29.5	29.4 ± 25.8	45.6 ± 25.4
Memory phase (PND 24)	≤ 10 seconds	94.7 ± 7.9	93.7 ± 9.8	89.5 ± 11.4
	≤ 2 x straight channel time	68.7 ± 20.6	68.3 ± 27.8	71.9 ± 21.6
Learning phase (PND 59)	≤ 10 seconds	92.0 ± 9.9	84.2 ± 19.8	89.5 ± 14.9
	≤ 2 x straight channel time	64.5 ± 27.7	60.8 ± 30.2	55.3 ± 27.2
Memory phase (PND 62)	≤ 10 seconds	91.7 ± 12.3	90.0 ± 12.6	80.6 ± 19.2* (↓12)
	≤ 2 x straight channel time	58.3 ± 21.7	66.7 ± 25.4	55.6 ± 24.3
Females				
Learning phase (PND 21)	≤ 10 seconds	65.3 ± 19.8	57.1 ± 17.1	56.7 ± 22.6
	≤ 2 x straight channel time	44.0 ± 27.6	42.1 ± 23.9	49.2 ± 30.3
Memory phase (PND 24)	≤ 10 seconds	92.7 ± 9.7	95.2 ± 7.7	84.2 ± 18.3* (↓9)
	≤ 2 x straight channel time	70.0 ± 23.1	77.0 ± 20.7	77.5 ± 22.5
Learning phase (PND 59)	≤ 10 seconds	87.0 ± 16.7	84.2 ± 13.8	89.6 ± 14.8
	≤ 2 x straight channel time	48.1 ± 27.9	54.2 ± 25.9	49.0 ± 23.9
Memory phase (PND 62)	≤ 10 seconds	83.3 ± 15.1	89.2 ± 14.6	86.5 ± 15.2
	≤ 2 x straight channel time	54.6 ± 22.7	61.7 ± 22.4	58.3 ± 23.6

aData were obtained from Table 25 on page 145-160 in MRID 46170301; n = 16-25. Percent difference from controls, calculated by the reviewers, is included in parentheses.
*Statistically different from controls at p≤0.05
**Statistically different from controls at p≤0.01

5. Postmortem results

a) Hematology: At 500 ppm, the number of monocytes was increased (↑44%; p≤0.05) in the males, while the numbers of leukocytes and lymphocytes were decreased (↓19-22%; p≤0.05) in the females (Table 13). In addition, small decreases (3-4%) in hemoglobin, hematocrit, and red blood cells were observed at 100 ppm, but not at 500 ppm. There were no other dose-related hematological findings.

TABLE 13. Selected mean (± SD) hematology parameters in rats on PND 63[a]

Parameter	Dose (ppm)		
	0	100	500
Males			
Monocytes (10^9/L)	0.148 ± 0.049	0.190 ± 0.145	0.213 ± 0.075* (↑44)
Females			
Leukocytes (10^9/L)	5.60 ± 0.62	5.32 ± 0.76	4.53 ± 1.28* (↓19)
Lymphocytes (10^9/L)	4.25 ± 0.51	3.94 ± 0.59	3.32 ± 1.02* (↓22)

aData were obtained from Table 26 on pages 162 and 164 in MRID 46170301; n = 11-13. Percent difference from controls, calculated by the reviewers, is included in parentheses.
*Statistically different from controls at p≤0.05

b) Brain weights: Absolute brain weights and brain weights relative to body weight and adjusted for body weight of the remaining treated groups were comparable to controls at PND 12 and PND 63 (pre- and post-perfusion fixation) in both sexes (Table 14).

TABLE 14. Mean (±SD) brain weights in F_1 rats[a]

Post-natal Day	Parameter		Dose (ppm)		
			0	100	500
Males					
PND 12	Terminal body weight (g)		21.8 ± 3.2	20.9 ± 2.3	22.0 ± 3.5
	Brain	absolute (g)	1.09 ± 0.07	1.10 ± 0.07	1.14 ± 0.08
		relative to bw (%)	5.07 ± 0.53	5.30 ± 0.54	5.29 ± 0.82
		adjusted for bw	1.09	1.10	1.13
PND 63 (pre-perfusion)	Terminal body weight (g)		342.5 ± 24.2	338.4 ± 27.1	342.5 ± 30.8
	Brain	absolute (g)	2.00 ± 0.07	1.96 ± 0.10	1.97 ± 0.07
		relative to bw (%)	0.58 ± 0.03	0.58 ± 0.04	0.58 ± 0.05
		adjusted for bw	1.99	1.97	1.97
PND 63 (post-perfusion)	Terminal body weight (g)		345.7 ± 30.8	353.5 ± 26.3	349.4 ± 21.7
	Brain	absolute (g)	1.87 ± 0.09	1.89 ± 0.12	1.95 ± 0.11
		relative to bw (%)	0.54 ± 0.05	0.54 ± 0.04	0.56 ± 0.03
		adjusted for bw	1.87	1.88	1.95
Females					
PND 12	Terminal body weight (g)		21.2 ± 2.2	20.6 ± 3.7	19.9 ± 2.5
	Brain	absolute (g)	1.07 ± 0.05	1.08 ± 0.09	1.08 ± 0.06
		relative to bw (%)	5.08 ± 0.41	5.32 ± 0.65	5.45 ± 0.52
		adjusted for bw	1.06	1.08	1.09
PND 63 (pre-perfusion)	Terminal body weight (g)		214.4 ± 18.7	217.3 ± 17.7	210.5 ± 23.0
	Brain	absolute (g)	1.84 ± 0.07	1.83 ± 0.08	1.86 ± 0.10
		relative to bw (%)	0.86 ± 0.06	0.85 ± 0.07	0.89 ± 0.06
		adjusted for bw	1.84	1.82	1.86
PND 63 (post-perfusion)	Terminal body weight (g)		204.8 ± 13.7	218.2 ± 24.4	211.2 ± 16.3
	Brain	absolute (g)	1.76 ± 0.07	1.78 ± 0.12	1.79 ± 0.07
		relative to bw (%)	0.86 ± 0.06	0.82 ± 0.06	0.85 ± 0.05
		adjusted for bw	1.78	1.76	1.79

aData obtained from Tables 27 and 28 on pages 165-167 in MRID 46170301. Percent difference from controls, calculated by the reviewers, is included in parentheses; n = 9-13.

b) Neuropathology

1) **Macroscopic examination:** No macroscopic findings were reported.

2) **Microscopic examination:** There were no dose-related microscopic findings aside from a non-statistically significant increase in demyelination of the proximal tibial nerve at 500 ppm (90%) relative to controls (60%).

3) **Brain morphometry:** Brain morphometry indicated the following differences ($p \leq 0.05$) from controls (Table 15): (i) increased thickness of the corpus callosum in the 500 ppm males on PND 12 (↑15%) and in the ≥100 ppm males on PND 63 (↑9-13%); (ii) increased thickness of the inner granular and molecular layers of the pre-pyramidal fissure in the cerebellum in the 500 ppm males on PND 63 (↑6-19%); and (iii) increased thickness of the dorsal cortex in the ≥100 ppm females on PND 12 (↑9-10%). The height of the cerebellum in males was decreased in males at 100 ppm. There were no other dose-related differences in brain morphometry in either sex at either age.

TABLE 15. Mean (±SD) morphometric measurements in F_1 rats[a]

Parameter		PND	Dose (ppm)		
			0	100	500
Males					
Corpus callosum (4C)	Thickness	12	0.60 ± 0.06	0.64 ± 0.09	0.69 ± 0.12* (↑15)
		63	0.32 ± 0.02	0.35 ± 0.05* (↑9)	0.36 ± 0.03* (↑13)
Cerebellum pre-pyramidal fissure	Thickness of inner granular layer	63	144 ± 21	162 ± 30	172 ± 33* (↑19)
	Thickness of molecular layer	63	206.5 ± 14.1	209.9 ± 12.7	219.8 ± 16.1* (↑6)
Females					
Dorsal cortex (5AB)	Thickness	12	1.00 ± 0.07	1.10 ± 0.07** (↑10)	1.09 ± 0.09* (↑9)

a Data were obtained from Table 30 on pages 170-185 of MRID 46170301; n = 9-10. Percent difference from control (calculated by reviewers) is presented in parentheses.
*Statistically different from controls at $p \leq 0.05$
**Statistically different from controls at $p \leq 0.01$

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: Excessive maternal toxicity was observed at 2500 ppm; thus, this group was sacrificed prior to scheduled termination. Based on the remaining dose groups, it was concluded that the maternal/offspring LOAELs were 500 ppm based on: (i) decreased maternal body weights and food consumption during late gestation; (ii) increased mortality of offspring (including five complete litter losses and an increased number of pups that were found dead or missing and presumed dead); (iii) slight reductions in PND 5 (pre-cull) litter size and total litter weight; and (iv) proportion of pups surviving PND 1-5. No evidence of developmental neurotoxicity was observed at doses up to 500 ppm.

B. REVIEWER COMMENTS

At 2500 ppm, one dam was found dead on GD 7, and another dam was sacrificed on GD 24 due to difficult parturition. Additionally on GD 24, the following clinical signs of toxicity were noted in one or two dams per sign (affecting 6 total dams in this group): (i) distended abdomen; (ii) slight hunched posture; (iii) killed due to difficult parturition; (iv) pale; (v) sides pinched in; (vi) staining around nose; and (vii) subdued. Adjusted body weights were decreased (↓6-8%; $p \leq 0.01$) on GD 15 and 22, and body weight gains for the overall (GD 1-22) gestation period (calculated by the reviewers) were decreased by 18% compared to controls. During lactation, body weights remained decreased (↓5-9%; statistics not performed) in the surviving dams until the early termination of this group after LD 15. Food consumption was decreased in these animals during Weeks 2 and 3 of gestation (↓16-19%; $p \leq 0.01$) and throughout lactation until sacrifice (↓8-30%; statistics not performed). Total litter loss was experienced between birth and PND 5 by 4/15 treated dams compared to 2/30 controls, and gestation index (calculated by the reviewers) was decreased at this dose (79.3% treated vs 100% controls). This decrease is attributed to the five dams that were pregnant but were sacrificed on GD 23-24 because they had not littered and the one dam that experienced dystocia, resulting in 23 litters with live born out of 29 pregnant dams. This dose level was considered too high, based on excessive maternal toxicity, high pup mortality, and a lack of a sufficient number of pups to allow meaningful evaluation of developmental toxicity. Thus, the 22 surviving dams in this group were sacrificed for humane reasons before scheduled termination.

At 500 ppm on GD 24, one dam with staining around the nose was sacrificed due to difficult parturition, and another dam was pale. Food consumption was decreased (↓21%; $p \leq 0.01$) during LD 1-5. However, body weights at this dose were comparable to controls throughout treatment. Total litter loss was experienced between birth and PND 5 by 5/29 treated dams (17.2%) compared to 2/30 controls (6.7%).

The maternal LOAEL is 38.7 mg/kg/day based on complete litter losses. The maternal NOAEL is 8.1 mg/kg/day.

Litter size and survival were not presented after culling on PND 5. A dose-dependent increase in the number of pups dying during PND 1-5 was observed at 100 ppm (57 pups), 500 ppm (95 pups), and 2500 ppm (151 pups) compared to controls (48 pups), due to the increase in the number of whole litter losses at 100 ppm (3 litters), 500 ppm (5 litters), and 2500 ppm (4 litters) compared to controls (2 litters). When whole litter losses are excluded, no treatment-related findings were observed on litter size or viability. On PND 1-3, the surviving 2500 ppm pups (85 pups in 9 litters) were sacrificed for humane reasons to terminate the high dose group.

There were no treatment-related effects on pup body weight, body weight gain, food consumption, clinical signs, developmental landmarks, FOB, total motor activity, auditory startle response, learning and memory, brain weight, or neuropatholgy at any dose level. Brain morphometry indicated the following differences ($p \leq 0.05$) from controls: (i) increased thickness of the corpus callosum in the 500 ppm males on PND 12 (↑15%) and in the ≥100 ppm males on PND 63 (↑9-13%); (ii) increased thickness of the inner granular and molecular layers of the pre-

pyramidal fissure in the cerebellum in the 500 ppm males on PND 63 (↑6-19%); and (iii) increased thickness of the dorsal cortex in the ≥100 ppm females on PND 12 (↑9-10%). **The offspring LOAEL is 8.1 mg/kg/day based on increased morphometric measurements in PND 63 males and PND 12 females. The offspring NOAEL is not established.**

This study is classified **Acceptable/Non guideline** and may be used for regulatory purposes. It does not, however, satisfy the guideline requirement for a developmental neurotoxicity study in rats (OPPTS 870.6300, §83-6); OECD 426 (draft). This study is classified as non-guideline due to the deficiencies listed below.

C. STUDY DEFICIENCIES: The following study deficiencies were noted:

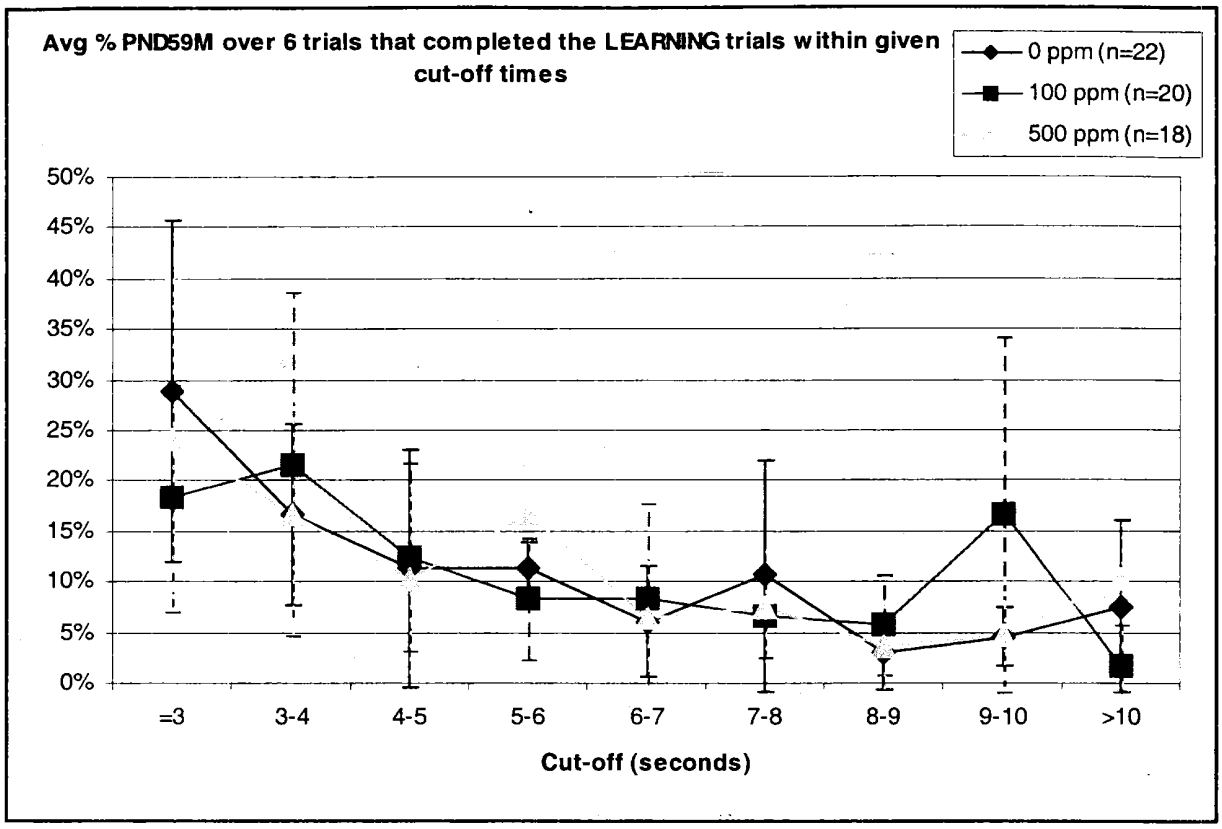
1. Concentration, homogeneity, and stability were not measured for test diets containing 500 ppm pymetrozine. No explanation was provided.

2. There was technical failure of the recording equipment for auditory startle on both days, resulting in a lack of data for 3 rats/dose on PND 23, one control rat for trials 31-50 on PND 61, and three 500 ppm rats on PND 61.

APPENDIX I

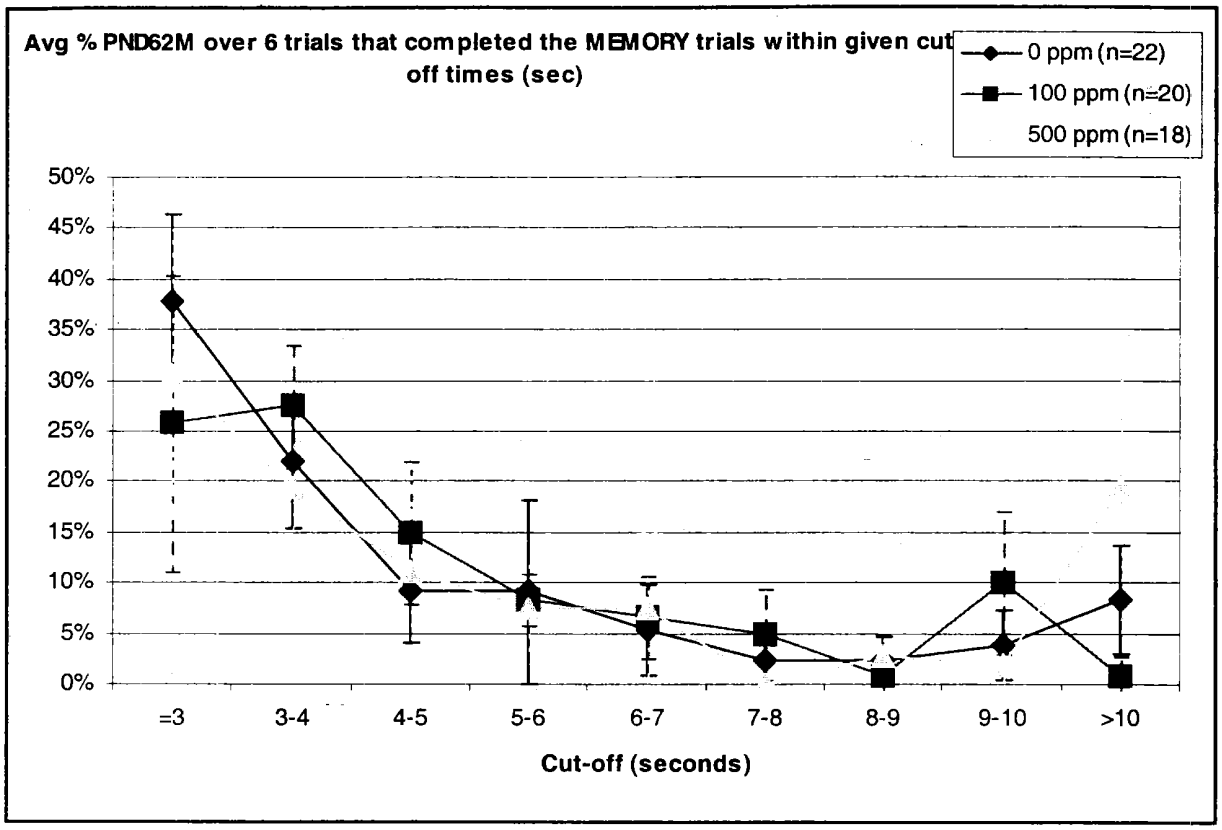
(Analysis of the Learning Assessment by Individual Animal Data)

# of PND59M that completed the LEARNING trials within given cut-off times (sec)								
	0 ppm (n=22)							
Seconds	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Mean %	SD
≤3	0	7	4	9	10	8	28.8%	16.9%
3-4	2	2	6	4	2	6	16.7%	8.9%
4-5	0	2	7	4	1	1	11.4%	11.8%
5-6	3	2	2	3	3	2	11.4%	2.5%
6-7	2	3	1	0	2	0	6.1%	5.5%
7-8	7	3	1	1	0	2	10.6%	11.4%
8-9	2	0	0	0	1	1	3.0%	3.7%
9-10	1	1	1	0	1	2	4.5%	2.9%
>10	5	2	0	1	2	0	7.6%	8.5%
	22	22	22	22	22	22	100.00%	
	100 ppm (n=20)							
Seconds	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Mean %	SD
≤3	0	3	4	6	3	6	18.3%	11.3%
3-4	0	4	3	3	10	6	21.7%	16.9%
4-5	0	5	2	1	4	3	12.5%	9.4%
5-6	1	2	1	4	1	1	8.3%	6.1%
6-7	4	1	4	0	0	1	8.3%	9.3%
7-8	2	0	2	2	1	1	6.7%	4.1%
8-9	3	1	1	1	0	1	5.8%	4.9%
9-10	10	4	3	1	1	1	16.7%	17.5%
>10	0	0	0	2	0	0	1.7%	4.1%
	20	20	20	20	20	20	100.00%	
	500 ppm (n=18)							
Seconds	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Mean %	SD
≤3	0	2	7	7	4	6	24.1%	16.0%
3-4	0	5	2	2	6	3	16.7%	12.2%
4-5	1	0	2	2	5	1	10.2%	9.6%
5-6	3	4	2	3	2	4	16.7%	5.0%
6-7	3	1	1	1	0	1	6.5%	5.5%
7-8	1	3	1	2	0	1	7.4%	5.7%
8-9	2	1	0	0	0	1	3.7%	4.5%
9-10	3	0	0	1	0	1	4.6%	6.5%
>10	5	2	3	0	1	0	10.2%	10.8%
	18	18	18	18	18	18	100.00%	



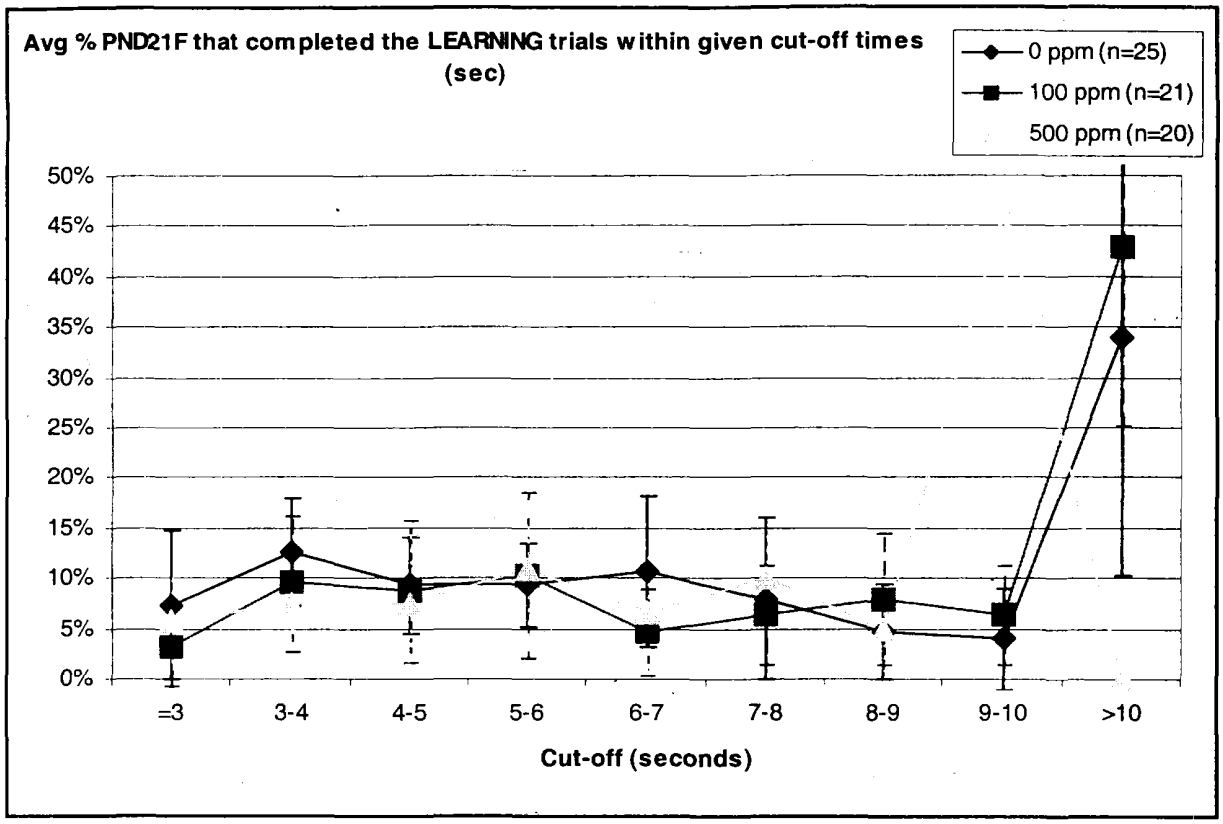
Note: "=3" refers to values less than or equal to 3 seconds

# of PND62M that completed the MEMORY trials within given cut-off times (sec)								
	0 ppm (n=22)							
Seconds	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Mean %	SD
≤3	11	10	7	8	8	6	37.9%	8.5%
3-4	4	6	7	5	4	3	22.0%	6.7%
4-5	2	3	2	2	0	3	9.1%	5.0%
5-6	0	1	1	5	1	4	9.1%	9.1%
6-7	1	0	2	0	2	2	5.3%	4.5%
7-8	0	0	0	0	2	1	2.3%	3.8%
8-9	1	0	1	0	0	1	2.3%	2.5%
9-10	2	1	0	1	1	0	3.8%	3.4%
>10	1	1	2	1	4	2	8.3%	5.3%
	22	22	22	22	22	22	100.00%	
	100 ppm (n=20)							
Seconds	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Mean %	SD
≤3	4	11	5	4	4	3	25.8%	14.6%
3-4	7	4	6	4	6	6	27.5%	6.1%
4-5	5	2	3	4	1	3	15.0%	7.1%
5-6	1	2	2	2	1	2	8.3%	2.6%
6-7	1	0	2	2	2	1	6.7%	4.1%
7-8	0	1	0	1	2	2	5.0%	4.5%
8-9	0	0	0	1	0	0	0.8%	2.0%
9-10	1	0	2	2	4	3	10.0%	7.1%
>10	1	0	0	0	0	0	0.8%	2.0%
	20	20	20	20	20	20	100.00%	
	500 ppm (n=18)							
Seconds	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Mean %	SD
≤3	3	10	7	4	4	5	30.6%	14.4%
3-4	4	2	4	4	4	3	19.4%	4.6%
4-5	4	0	2	4	2	0	11.1%	9.9%
5-6	2	2	2	0	1	1	7.4%	4.5%
6-7	4	0	1	1	1	1	7.4%	7.6%
7-8	0	0	0	0	0	0	0.0%	0.0%
8-9	1	0	0	1	0	1	2.8%	3.0%
9-10	0	1	1	0	0	0	1.9%	2.9%
>10	0	3	1	4	6	7	19.4%	15.2%
	18	18	18	18	18	18	100.00%	



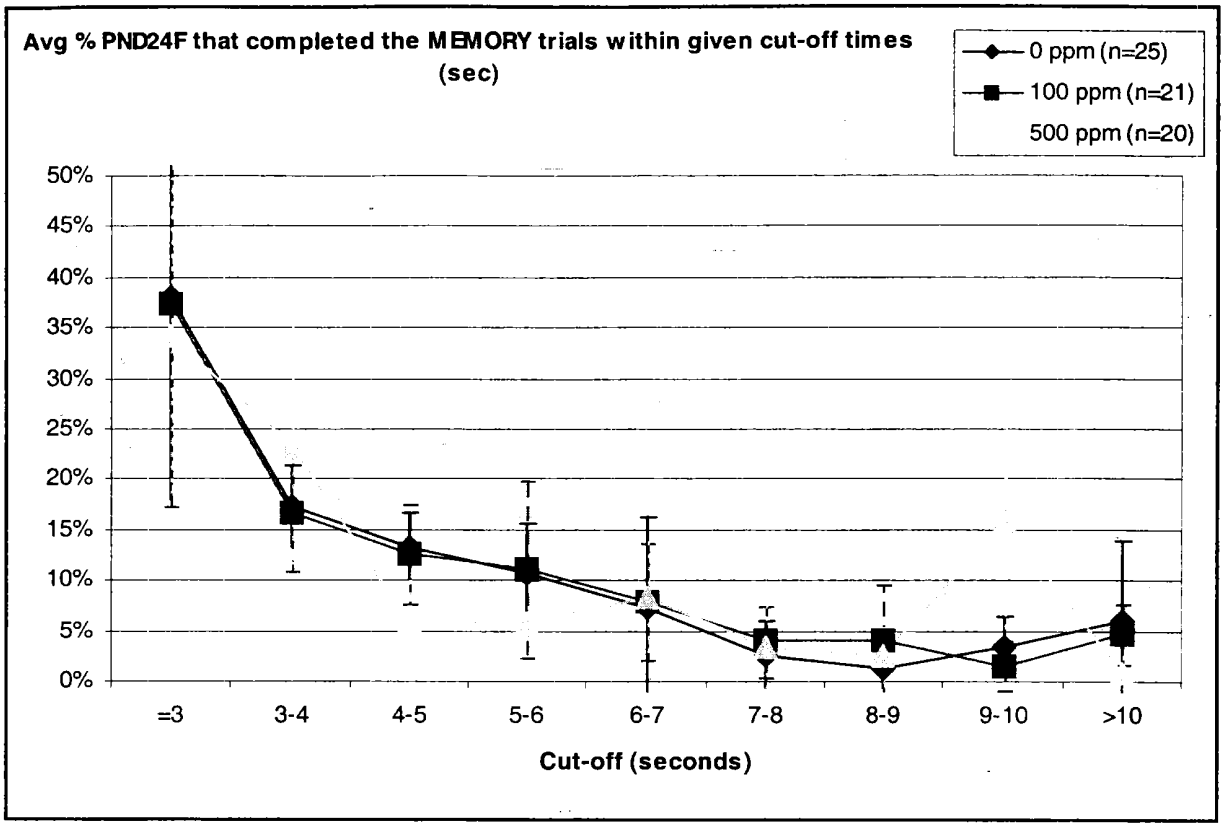
Note: "=3" refers to values less than or equal to 3 seconds

# of PND21F that completed the LEARNING trials within given cut-off times (sec)								
	0 ppm (n=25)							
Seconds	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Mean %	SD
≤3	0	0	2	2	2	5	7.3%	7.3%
3-4	1	4	4	4	4	2	12.7%	5.3%
4-5	1	3	3	1	2	4	9.3%	4.8%
5-6	2	1	3	4	2	2	9.3%	4.1%
6-7	1	5	0	3	4	3	10.7%	7.4%
7-8	0	0	3	1	3	5	8.0%	8.0%
8-9	1	2	0	0	3	1	4.7%	4.7%
9-10	0	1	0	3	2	0	4.0%	5.1%
>10	19	9	10	7	3	3	34.0%	23.7%
	25	25	25	25	25	25	100.00%	
	100 ppm (n=21)							
Seconds	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Mean %	SD
≤3	0	2	0	0	1	1	3.2%	3.9%
3-4	0	1	2	4	2	3	9.5%	6.7%
4-5	0	1	2	3	1	4	8.7%	7.0%
5-6	2	3	1	2	0	5	10.3%	8.2%
6-7	0	1	2	1	2	0	4.8%	4.3%
7-8	1	3	0	1	2	1	6.3%	4.9%
8-9	1	0	4	2	2	1	7.9%	6.5%
9-10	1	2	1	0	3	1	6.3%	4.9%
>10	16	8	9	8	8	5	42.9%	17.6%
	21	21	21	21	21	21	100.00%	
	500 ppm (n=20)							
Seconds	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Mean %	SD
≤3	0	2	1	2	2	0	5.8%	4.9%
3-4	0	0	3	1	2	3	7.5%	6.9%
4-5	1	1	1	4	0	2	7.5%	6.9%
5-6	1	4	0	2	4	2	10.8%	8.0%
6-7	2	0	1	3	2	0	6.7%	6.1%
7-8	1	3	3	1	2	2	10.0%	4.5%
8-9	1	2	2	0	0	1	5.0%	4.5%
9-10	14	8	9	7	8	10	46.7%	12.5%
>10	0	0	0	0	0	0	0.0%	0.0%
	20	20	20	20	20	20	100.00%	



Note: "=3" refers to values less than or equal to 3 seconds

# of PND24F that completed the MEMORY trials within given cut-off times (sec)								
	0 ppm (n=25)							
Seconds	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Mean %	SD
≤3	1	13	14	11	12	6	38.0%	20.0%
3-4	4	5	4	6	4	3	17.3%	4.1%
4-5	4	2	3	4	3	4	13.3%	3.3%
5-6	3	2	1	2	4	4	10.7%	4.8%
6-7	5	0	0	0	2	4	7.3%	8.9%
7-8	0	0	1	2	0	1	2.7%	3.3%
8-9	1	0	1	0	0	0	1.3%	2.1%
9-10	2	1	1	0	0	1	3.3%	3.0%
>10	5	2	0	0	0	2	6.0%	7.9%
	25	25	25	25	25	25	100.00%	
	100 ppm (n=21)							
Seconds	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Mean %	SD
≤3	1	5	10	13	9	9	37.3%	20.1%
3-4	2	5	4	2	4	4	16.7%	5.8%
4-5	2	4	3	1	3	3	12.7%	4.9%
5-6	5	2	2	4	0	1	11.1%	8.9%
6-7	3	3	0	1	1	2	7.9%	5.8%
7-8	2	0	1	0	1	1	4.0%	3.6%
8-9	3	1	0	0	1	0	4.0%	5.6%
9-10	1	0	0	0	1	0	1.6%	2.5%
>10	2	1	1	0	1	1	4.8%	3.0%
	21	21	21	21	21	21	100.00%	
	500 ppm (n=20)							
Seconds	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Mean %	SD
≤3	1	9	9	7	6	9	34.2%	15.6%
3-4	1	5	3	5	7	7	23.3%	11.7%
4-5	2	0	2	1	2	0	5.8%	4.9%
5-6	2	1	1	1	1	1	5.8%	2.0%
6-7	4	2	1	1	1	1	8.3%	6.1%
7-8	1	0	0	0	2	1	3.3%	4.1%
8-9	1	0	1	1	0	0	2.5%	2.7%
9-10	8	3	2	4	1	1	15.8%	13.2%
>10	0	0	1	0	0	0	0.8%	2.0%
	20	20	20	20	20	20	100.00%	



Note: "=3" refers to values less than or equal to 3 seconds