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

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

June 19, 2006
TXR # 0053857

SUBJECT: **Data Evaluation Record (DER) of a developmental neurotoxicity study in rats (MRID no. 46670402) following exposure to zeta-cypermethrin**

PC Code: 129064
DP Barcode: D323552

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I. CONCLUSIONS

This memorandum transmits the evaluation of the definitive developmental neurotoxicity (DNT) study with zeta-cypermethrin (MRID no. 46670402). In this study, female Sprague-Dawley rats were administered zeta-cypermethrin via the diet at nominal concentrations of 0, 50 , 125, or 300 ppm from gestation (GD) 6 through lactation day (LD) 21 [equivalent to 0, 2.9, 7.4 or 17.3 mg/kg/day during gestation]. HED concluded that the maternal NOAEL is 17.4 mg/kg/day (the highest dose tested); a maternal LOAEL was not established. The offspring LOAEL is 300 ppm (17.4 mg/kg/day to dams) based on decreased body weights and body weight gain in females, altered motor activity in males and females, and changes in brain morphometrics. Thus, the offspring NOAEL is 125 ppm (7.4 mg/kg/day to dams).

DATA EVALUATION RECORD

ZETA-CYPERMETHRIN

STUDY TYPE: DEVELOPMENTAL NEUROTOXICITY STUDY - RAT; OPPTS 870.6300

MRID 46670402

Prepared for

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TXR#: 0053857

DATA EVALUATION RECORD

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

PC CODE: 129064 **DP BARCODE**: D317335, D317211, D323552

TEST MATERIAL (PURITY): Zeta-Cypermethrin Technical (81.8% a.i.)

SYNONYMS: (S)-cyano-(3-phenoxyphenyl)methyl (+/-) cis/trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate

CITATION: Nemec, M.D. (2005) A dietary developmental neurotoxicity study of zeta-cypermethrin technical in rats. WIL Research Laboratories, LLC, Ashland, Ohio. Study Number WIL-105018; August 24, 2005. MRID 46670402. Unpublished.

SPONSOR: FMC Corporation, Princeton, NJ

EXECUTIVE SUMMARY: In a developmental neurotoxicity study (MRID 46670402), Zeta-cypermethrin technical (81.8% a.i.; lot # PL03-0427) was administered in the diet to 25 mated female Crl:CD®(SD)IGS BR rats/group at nominal concentrations of 0, 50, 125, or 300 ppm from gestation day (GD) 6 through lactation day (LD) 21. Average doses to the animals, adjusted for purity, were 0, 2.9, 7.4, or 17.3 mg/kg/day, respectively, during gestation and 0, 7.1, 17.5, or 39.8 mg/kg/day, respectively, during lactation. Dietary concentrations were based on the results of preliminary dietary feasibility, range-finding, and placental/lacational transfer studies (MRIDs 46538902, 46670401, and 46670403, respectively [reviewed separately, TXR# 0053857]). Functional Observations (FO) were performed on 25 dams/group on GDs 10 and 15 and on all surviving dams that delivered offspring on LDs 10 and 21. On postnatal day (PND) 4, litters were culled to eight offspring, with at least three males and three females per litter. Offspring were allocated for detailed clinical observations (FO) and assessment of motor activity, auditory startle response, and learning and memory, as well as for neuropathology at study termination (PND 72). On PND 21, the whole brain was collected from 10 pups/sex/dose group, weighed, and subjected to micropathologic examination and morphometric analysis. Pup physical development was evaluated by body weight. The age of sexual maturation (vaginal opening in females and preputial separation in males) was assessed.

One control female was found dead late in gestation; necropsy revealed a ruptured uterus and late resorptions. All remaining animals survived to scheduled sacrifice. No treatment-related clinical signs of toxicity were observed during the daily examinations.

Absolute body weight of dams was similar between the treated and control groups throughout gestation. However, body weight gain by the high-dose group was slightly less (n.s.) than that of controls for each interval, resulting in overall gestational weight gain (GD 0-20) by the high-dose animals that was 90% of the control group level. Food consumption by the high-dose group was significantly less (p # 0.05 or 0.01) than that of the control group during GDs 6-9 (87% of controls) and GDs 6-20 (96% of controls). Throughout lactation, mean body weight of the high-dose group was significantly less (p # 0.05 or 0.01; 92-95% of control value) than that of controls. Food consumption by the high-dose group was significantly less than that of the control group (p # 0.05 or 0.01; 87-92% of controls) throughout lactation. The observed changes in body weight, body weight gain and food consumption were not considered to be adverse, due to the small magnitude of the change. No treatment-related effects were observed in reproductive parameters, and gross necropsy was unremarkable.

No treatment-related effect on the mean number of pups born, mean live litter size, percentage of males per litter, pup survival, or clinical signs was observed. Pup body weights were similar between the treated and control groups on PNDs 1-11. On PNDs 13-21, mean body weight was significantly decreased in the high-dose female offspring (90-92% of control value) and was slightly (n.s.) decreased in the high-dose male offspring (93-94% of control value). Mean body weight gain was significantly decreased in the high-dose females (86-89% of control value) for all intervals during PNDs 7-17 and for PND 4-21 (87% of controls). Mean weight gain was significantly decreased in the high-dose males (86% of control value) during the PND 11-13 interval. Post-weaning body weight and body weight gain were similar between the treated and control groups. The average age and body weight at attainment of sexual maturation was not affected by treatment.

No treatment-related FO changes were observed in males or females on testing days PNDs 4, 11, 45 and 60 or in females on PND 22. On PND 22, high-dose males had significantly reduced fore-limb grip strength (146.8 vs 174.8 for controls; p # 0.05), and four animals were observed with drooping palpebral closure compared with none of the controls.

No significant difference in total motor activity was found between the treated and control groups on any testing day. However, a trend towards increased activity in high-dose males and decreased activity in high-dose females was observed on some testing days. On PND 17, high-dose males had a slight increase in total motor activity (124% of controls), resulting from increased subsession motor activity, particularly during final two 15 minute intervals (150% of controls; n.s. and 281% of controls; p # 0.05). This increased activity in the final subsessions indicates that less habituation occurred in the high dose PND 17 males, compared to controls. In females, decreased motor activity was seen at the high dose on both PNDs 17 and 21 (71% and 70% of controls, respectively; n.s.). On PND 17, this decrease, due to less activity during the first two 15 minute subsessions (47-62% of controls; p # 0.01), was considered to be equivocal in nature. The decreased activity on PND 21 (45-86% of controls; n.s) is considered to a treatment-related effect.

Auditory startle response, learning and memory, and gross and qualitative microscopic findings were not affected by treatment.

A slight, non-dose related increase in male brain weights was noted at the high dose on PND 21 (104% of controls, n.s.). Several slight changes in morphometry measurements were noted, including a statistically significant increase in the vertical thickness of the cortex observed in high dose PND 21 females (106% of controls; p # 0.05). These changes were determined to be marginal and suggestive effect at the high dose and morphometric data for the low and mid dose groups are required to re-affirm the establishment of the mid dose as the NOAEL.

The maternal NOAEL is 300 ppm (17.4 mg/kg/day), the highest dose tested; a LOAEL was not established..

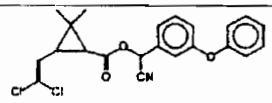
The offspring LOAEL is 300 ppm (17.4 mg/kg/day to dams), based on decreased body weights and body weight gains of females, altered motor activity in males and females, and changes in brain morphometrics. The offspring NOAEL is 125 ppm (7.4 mg/kg/day to dams).

This study is classified **Acceptable/Non-Guideline** and may be used for regulatory purposes, however it does not satisfy the guideline requirement for a developmental neurotoxicity study in rats (OPPTS 870.6300, §83-6); OECD 426 (draft) due to the absence of brain morphometric measurements of the offspring at the mid and low dose groups, and pending the evaluation of available positive control data.

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

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material:	Zeta-Cypermethrin Technical
Description:	dark brown, viscous liquid
Lot #:	PL03-0427
Purity:	81.8 % a.i.
Compound Stability:	Stable in the diet for up to 15 days at room temperature; expiration date 7/30/2005
CAS # of TGAI:	52315-07-8
Structure:	

2. **Vehicle**: The test article was dissolved in acetone and mixed with basal diet.

3. Test animals (P):		
Species:	Rat	
Strain:	Crl:CD®(SD) (formerly known as Crl:CD®(SD)IGS BR)	
Age at mating:	approximately 12 weeks	
Wt. at study initiation:	222-300 g (GD 0)	
Source:	Charles River Laboratories, Inc., Raleigh, NC	
Housing:	Following successful mating, females were individually housed in plastic maternity cages with nesting material. After weaning on PND 21, the offspring were housed with litter mates in plastic cages with nesting material through PND 27. On PND 28, offspring were individually housed in wire-mesh cages and remained in these cages until euthanasia.	
Diet:	PMI Nutrition International, LLC. Certified Rodent LabDiet® 5002, *ad libitum* (basal or test diet)	
Water:	Reverse osmosis drinking water, *ad libitum*	
Environmental conditions:	**Temperature:**	22±3EC
	Humidity:	50±20%
	Air changes:	10/hour
	Photoperiod:	12 hrs dark/12 hrs light
Acclimation period:	11 days	

B. PROCEDURES AND STUDY DESIGN:

1. **In life dates**: Start: August 13, 2004; End: November 13, 2004

2. **Study schedule**: Mated female Sprague-Dawley rats (25/dose group) were administered the test material in the diet from gestation day (GD) 6 through lactation day (LD) 21. Functional Observations (FO) were performed on 25 dams/group on GDs 10 and 15 and on all surviving dams that delivered offspring on LDs 10 and 21. On postnatal day (PND) 4, litters were culled to eight offspring, with at least three males and three females per litter. Pups were weaned from their dam on PND 21 but were not treated with test material. Dams were sacrificed on PND21 after weaning. A subset of 20 pups/sex/group was assigned to FO, auditory startle response, motor and locomotor activity, and learning and memory testing

(PND 62). From this subset, 10 pups/sex/group were selected for neuropathological, morphometric, and brain weight evaluations on PND 72. A second subset of 20 pups/sex/group was selected for learning and memory assessments on PND 25; these animals were not tested for learning and memory at any other time point. A third subset of 10 pups/sex/group was selected for neuropathological, morphometric, and brain weight evaluations on PND 21.

3. **Mating procedure:** One resident sexually mature male and one female were co-housed. The day that a vaginal plug or sperm in a vaginal smear was observed was designated gestation day (GD) 0.

4. **Animal assignment:** Mated females were assigned to groups using a computerized randomization procedure that assigned animals based on stratification of the GD 0 body weights into a block design, as shown in Table 1.

TABLE 1. Study design

Experimental parameter	Dietary concentration (ppm)			
	0	50	125	300
Maternal animals				
	No. of maternal animals assigned			
No. of maternal animals assigned	25	25	25	25
FO (GDs 10 and 15)	25	25	25	25
FO (LDs 10 and 21)	25	25	25	25
Offspring				
	No. of offspring assigned			
Subset A - FO (PNDs 4, 11, 22, 45, and 60); Auditory startle response (PND 20 and 60); Motor activity (PNDs 13, 17, 21 and 61); Learning and memory (PND 62).	20/sex	20/sex	20/sex	20/sex
Subset A - Neuropathological, morphometric and brain weight evaluations (PND 72)	10/sex	10/sex	10/sex	10/sex
Subset B - Learning and memory (PND 25)	20/sex	20/sex	20/sex	20/sex
Subset C - Neuropathological, morphometric and brain weight evaluations (PND 21)	10/sex	10/sex	10/sex	10/sex

5. **Dose selection rationale:** Dose levels were chosen based on the results of a preliminary dietary feasibility study (MRID 46538902), a range-finding study (MRID 46670401), and a placental/lacational transfer study (MRID 46670403). These studies include information regarding levels of pup exposure during lactation, and have been reviewed separately [TXR# 0053857]. The dietary feasibility study demonstrated that the test article was excreted in the milk following dietary administration of 125 or 375 ppm to dams from GD 6 through lactation day 17. Levels of zeta-cypermethrin showed a dose-related and a time-related increase up to lactation day 11. In the range-finding study, dams had lower body weight and

food consumption at dietary concentrations of 350 ppm (24.1 mg/kg/day) and offspring had lower body weight gain at 300 and 350 ppm (20.8 and 24.1 mg/kg/day, respectively). In the reproductive toxicity study, the parental and offspring NOAEL was 100 ppm (7 mg/kg/day) based on clinical signs and hypersensitivity to sound in adults, and decreased body weight gain in pups and adults at 375 ppm (27 mg/kg/day). The executive summary for the reproductive toxicity study was given in MRID 46538901.

6. **Dosage administration:** Zeta-cypermethrin was administered in the diet to maternal animals on GD 6 through LD 21. After PND 21, untreated food was provided for all offspring.

7. **Dosage preparation and analysis:** For dosage calculations in units of ppm, purity of the test material was assumed to be 100%. The control and test article diets were prepared fresh weekly and stored at room temperature. The appropriate amount of test article for each group was weighed into a tared vessel along with 20 mL of acetone (lot no. SO5352, Spectrum Quality Products, New Brunswick, New Jersey). The test article in acetone was added to an appropriate amount of feed in a Hobart mixing bowl. The preparation was mixed for 10 minutes. This premix, plus enough basal diet to achieve the total batch size of homogeneous diet, was then mixed in a V-blender for 15 minutes. During the first and last 5 minutes of mixing, an intensifier bar was used. The control diet was prepared in the same manner as the test article-treated diets without the addition of test article. The prepared diets were placed in labeled storage bags that remain opened for 24 to 36 hours so that the acetone could dissipate prior to administration.

   Homogeneity and stability of the test article in the diet were analyzed as part of the diet feasibility study (MRID 46538902). Samples for homogeneity were withdrawn from the top, middle and bottom of all the test diets and from the middle of the control diet. Additional samples from these diets were stored for 15 days at room temperature and analyzed for stability. A sample from each diet of each batch was taken throughout the main study for analysis of concentration.

Results:

Homogeneity analysis: Mean concentrations of samples from the top, middle, and bottom of the 50, 125, and 300 ppm nominal dietary mixtures were 46.3 ± 1.2, 119 ± 3.9, and 289 ± 8.4 ppm, respectively.

Stability analysis: After 15 days at room temperature, the mean concentrations of the 50, 125, and 300 ppm nominal dietary mixtures were 98.4%, 99.1%, and 95.8%, respectively, of the initial measured concentration.

Concentration analysis: The mean concentrations of the 50, 125, and 300 ppm nominal dietary mixtures ranged from 84.1-110%, 90.6-114%, and 93.3-106%. The 50 ppm sample that measured 84.1% nominal was re-analyzed, and the mean concentration from both analyses was found to measure 89.4% nominal.

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

C. OBSERVATIONS:

1. In-life observations:

a. **Maternal animals:** Females were observed twice daily for mortality and moribundity. Clinical signs were recorded once daily for each female from GD 0 until necropsy.

Functional Observations (FO) were performed on 25 dams/group on GDs 10 and 15 and on all surviving dams that delivered offspring on LDs 10 and 21. The examiner was unaware of the animal's group assignment. No details were provided on the arena size, examination procedures, or scoring criteria. Animals were evaluated for ease of removal from the cage, ease of in-hand handling, and the following functional observations outside the home cage.

	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 (note: scoring criteria not given) 2) Presence or absence of piloerection and exophthalamus, 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.

Individual maternal body weights were recorded and food consumption was measured on GDs 0, 6, 9, 12, 15, and 20 and on lactation days 1, 4, 7, 11, 14, 17, and 21. Food consumption was reported as g/animal/day and g/kg/day. All females were allowed to deliver naturally.

b. **Offspring:**

1) **Litter observations:** The day of completion of parturition was designated as PND 0. When parturition was complete, the number of stillborn and live pups in each litter was recorded, and the pups were sexed and examined for gross malformations. Pups were also sexed on PND 4, 11 and 21. All pups were observed once daily for survival and clinical signs of toxicity. A detailed physical examination was conducted on PND 4, 11 and 21 and at weekly intervals, thereafter, until necropsy.

On PND 4, litters were standardized to 8 pups/litter (4/sex/litter, when possible). Culled pups were euthanized on PND 4 and discarded. If a litter consisted of less than six pups or did not meet the sex ratio criteria (at least 3/sex), the litter was necropsied on PND 4, and the carcasses were discarded.

Surviving pups were weighed on PNDs 1, 4, 7, 11, 13, 17 and 21 and weekly thereafter until necropsy and whenever they were removed from their cages for behavioral testing.

2) **Developmental landmarks:** Beginning on PND 35, male offspring were examined daily for preputial separation. Beginning on PND 25, female offspring were examined daily for vaginal patency. The age of onset and the offspring body weight at that time were recorded.

3) **Postweaning observations:** After weaning on PND 21, offspring were examined by cage-side observations once daily and detailed weekly observations. Individual offspring body weight data were recorded weekly.

4) **Neurobehavioral evaluations:** Following litter standardization on PND 4, one male and one female from each litter (20 pups/sex/group) were assigned to the following neurobehavioral tests.

i) **Functional observations (FO):** On PNDs 4, 11, 22, 45, and 60, twenty offspring/sex/group were examined outside the home cage in a modified FO assessment. The same animals were observed at each interval, with the exception of animals found dead or sacrificed *in extremis* between PND 4-60, which were replaced with a pup of the same age and sex. The same parameters assessed in the maternal FO were examined in offspring, as appropriate for the developmental stage being observed. Post-weaning assessments on PND 22, 45, and 60 also included fore- and hind-limb grip strength and Rotorod performance. No details were provided on the arena size or examination procedures.

ii) **Motor activity testing:** Motor activity was evaluated in twenty pups/sex/dose on PNDs 13, 17, 21 and 61. The same animals were tested at each interval, with the exception of one 125 ppm female that was found dead and was replaced with a sibling, and were also tested in the FO. Activity was measured using the SDI Photobeam Activity System, which was surrounded by black plastic enclosures to minimize external stimuli. Data were collected in five-minute intervals for a test duration of 60 minutes, but are included in the study report as total activity over 60 minutes and as four 15- minute subsessions. Data for ambulatory and total motor activity were recorded.

iii) **Auditory startle response:** Auditory startle response testing was performed on twenty offspring/sex/dose on PNDs 20 and 60 using the SR-Lab Startle Response System. The same animals were tested at each interval.

Testing was performed in a room equipped with a white-noise generation system set to operate at 70±10 dB. Each test session consisted of a five-minute acclimation period

with a 65-dB broadband background white noise. For each trial, the startle stimulus was a 115-dB mixed-frequency noise burst that lasted approximately 20 milliseconds, and responses were recorded during the first 100 milliseconds after the onset of this stimulus. Each session consisted of 50 trials with an eight-second intertrial interval. Startle response measurements included maximum response amplitude (V_{MAX}), average response amplitude (V_{AVE}) and latency to V_{MAX} (T_{MAX}), which were analyzed in five blocks of 10 trials each.

iv) **Learning and memory testing:** Learning and memory testing was performed in 20 offspring/sex/dose using a water-filled Biel maze. Animals were required to traverse the maze and escape by locating a platform hidden beneath the water surface. The amount of time required (maximum of three minutes) and the number of errors were recorded. An error was defined as any instance when an animal deviated from the correct channel with all four feet.

The testing intervals began on PNDs 25 and 62 and consisted of seven consecutive days; different animals were tested on these two intervals. On day 1 of testing, animals were placed in a straight channel opposite the escape platform, and the time required for each animal to escape was recorded. Each animal was given four trials to assess swimming ability and motivation. On days 2 and 3, animals were allowed two trials per day for two consecutive days to solve the maze in path A. Animals were then allowed two trials per day for three consecutive days (days 4-6) to solve the path B (reverse of path A). On the final day of testing (day 7), each animal was given two trials in path A. The minimum intertrial interval was one hour.

2. **Postmortem observations**:

a. **Maternal animals:** All females were subjected to gross examination. Tissues were saved for histopathological examination, only if necessary based on gross findings. Females that did not deliver by post-mating day 25 were euthanized by carbon dioxide inhalation, and the numbers of implantation sites and corpora lutea were recorded, if macroscopically evident. Uteri without macroscopic evidence of implantation were opened and placed in a 10% ammonium sulfide solution for detection of early implantation loss. Females with premature delivery were euthanized by carbon dioxide inhalation, and intact fetuses were preserved in 10% neutral-buffered formalin. Females with total litter loss were euthanized within 24 hours, and the number of former implantation sites was recorded. In females found dead, those sacrificed moribund, or those whose litter failed to meet the litter size or sex ratio criteria, the number of implantation sites and corpora lutea was recorded. Where appropriate, recognizable fetuses were examined externally, or the offspring were euthanized by intraperitoneal injection of sodium pentobarbital and subjected to gross necropsy. The carcass of each of these dams was discarded.

All females with viable pups on lactation day 21 were euthanized by carbon dioxide inhalation and subjected to gross necropsy. The numbers of former implantation sites

and corpora lutea were recorded. Nongravid uteri were placed in 10% ammonium sulfide. The carcass of each dam was discarded.

b. **Offspring:** Offspring found dead or euthanized *in extremis* between birth and PND 4 were examined externally and sexed, their stomachs were examined for the presence of milk, and their carcasses were then discarded. Offspring found dead or euthanized *in extremis* between PND 4 and study termination were examined grossly, select tissues were saved for histopathological examination based on gross findings, and the carcasses were then discarded. Pups culled on PND 4 were sacrificed by an intraperitoneal injection of sodium pentobarbital and discarded. Offspring not selected for neuropathology or behavioral evaluations were euthanized by carbon dioxide inhalation on PND 21 and subjected to gross necropsy. Tissues of these animals were retained only if deemed necessary by the gross findings, and the carcass was discarded. Pups scheduled for sacrifice on PND 25 after completion of learning and memory testing, as well as pups scheduled for sacrifice on PND 72 that were not allotted for neuropathology/brain weight measurement, were euthanized by carbon dioxide inhalation and subjected to gross necropsy. Tissues were retained only if deemed necessary by the gross findings and the carcasses were discarded.

On PND 21, one male or female offspring from each litter (10/sex/group) was euthanized by carbon dioxide inhalation and perfused *in situ* according to the testing facility's standard operating procedure (T3-034). The whole brain (including olfactory bulbs) was removed, weighed and the size (length and width) recorded. Abnormal coloration or lesions of the brain and spinal cord were recorded. The brain from each animal in all groups was processed and embedded, however, only tissues from control and high-dose animals were examined microscopically. All brains were prepared for histopathological examination by embedding in paraffin, sectioning, and staining with hematoxylin and eosin. Sections from all major brain regions (olfactory bulbs, cerebral cortex, hippocampus, basal ganglia, thalamus, hypothalamus, midbrain, brainstem and cerebellum) were examined. At least two morphometric measurements were made on each of the neocortical, hippocampal, and cerebellar areas of the brain. Level 2, a coronal section of the rostral cerebrum, included height of the hemisphere and the vertical thickness of the cortex. Level 3, a coronal section of mid-cerebrum, included the radial thickness of the cortex, the vertical height between the hippocampal pyramidal neuron layers, the vertical height of the dentate hilus, and the length of the ventral limb of the dentate hilus. Level 5, a mid-saggital section of the cerebellum and pons, included the vertical thickness of the pons and the base of lobule 9. For level 5, measurements were not paired because half of the tissues were sectioned transversely for visualization of cerebellar nuclei. Additional details of these procedures were not given in the protocol.

On PND 72, one male and one female from each litter (10/sex/group) was randomly selected from the 20/sex/group pups involved in neurobehavioral testing, was euthanized by carbon dioxide inhalation, and was perfused *in situ* according to the testing facility's standard operating procedure (T3-034). The whole brain (including olfactory bulb) was removed, weighed and the size (width and length) recorded. The central and peripheral nervous tissues were preserved as described in the testing facility's standard operating

procedure (T3-035) and embedded in paraffin or plastic, respectively. Tissues for all groups were processed and embedded; however, only control and high-dose tissues were examined microscopically. Tissues were prepared for histopathological examination by sectioning and staining with hematoxylin and eosin. Morphometric measurements were made on Levels 2, 3 and 5 of the brain, as described for PND 21. The following tissues from control and high-dose animals perfused *in situ* at study termination (PND 72) were examined microscopically:

X	**CENTRAL NERVOUS SYSTEM**			X	**PERIPHERAL NERVOUS SYSTEM**
	BRAIN				**SCIATIC NERVE**
X	Olfactory bulbs	X	Hippocampus	X	Cross section
X	Cerebral cortex	X	Basal ganglia	X	Longitudinal section
X	Central gray matter	X	Thalamus		**OTHER**
X	Cerebellum	X	Hypothalamus	X	Sural Nerve
X	Tectum	X	Cerebral peduncles	X	Tibial Nerve
X	Pons	X	*Tegmenta*	X	*Peroneal Nerve*
X	Medulla oblongata			X	Lumbar dorsal root ganglion (T_{13} - L_4)
	SPINAL CORD			X	Lumbar dorsal root fibers (T_{13} - L_4)
X	Cervical swelling (C_3 - C_7)			X	Lumbar ventral root fibers (T_{13} - L_4)
X	Lumbar swelling (T_{13} - L_4)			X	Cervical dorsal root ganglion (C_3 - C_7)
	OTHER			X	Cervical dorsal root fibers (C_3 - C_7)
	Gasserian ganglion			X	Cervical ventral root fibers (C_3 - C_7)
X	Trigeminal ganglion/nerves				
X	Optic nerve				
X	Eyes			X	Skeletal muscle (gastrocnemius)

D. DATA ANALYSIS:

1. **Statistical analyses:** Maternal and offspring body weight and body weight gain, maternal food consumption, gestation length, implantation sites, number of pups and litter sizes, day and body weight at attainment of sexual maturation, brain weight and dimensions, morphometric data, and continuous FO and Biel Maze data were analyzed by a parametric one-way Analysis of Variance (ANOVA) to determine intergroup differences. If the ANOVA was significant, Dunnett's test was applied to compare the treated and control groups. FO data which yielded scalar and descriptive data, as well as qualitative histopathological data, were analyzed using the Fisher's Exact Test. The Kruskal-Wallis nonparametric ANOVA test with the Mann-Whitney U test was used to analyze mean litter proportions of pup viability and sex ratio.

   Locomotor activity and auditory startle data were analyzed with a repeated measures ANOVA (RANOVA). For locomotor activity, factors in the model included treatment group, time interval, and the interaction of time and treatment. For auditory startle response, factors in the model included treatment group, trial block, and the interaction of block and treatment. The monotonic dose response relationship was evaluated using sequential linear

trend tests based on ordinal spacing of dose levels. If the linear dose by time or trial interaction was significant at p#0.05, trend tests on treatment means were performed for each time interval; if not significant, the trend test was conducted across the pooled time intervals for the entire session only. Nonmonotonic dose responses were evaluated when no significant linear trends were detected, but the treatment and/or the interaction was significant at p#0.01. If the interaction was significant, the comparisons were conducted for each time interval or block; if only the treatment effect was significant, the comparisons were conducted across the pooled intervals or blocks for the entire session.

2. **Indices**:

   a. **Reproductive indices**: No reproductive indices were calculated.

   b. **Offspring viability indices**: The following litter and offspring indices were calculated from parturition and pup survival records.

Mean live litter size =
(Total no. viable offspring on PND 0)/(No. litters with viable offspring on PND 0)

Postnatal survival between birth and PND 0 or PND 4 (% per litter) =
[3(Viable offspring per litter on PND 0 or PND 4/No. offspring born per litter) / No. litters per group] H 100

Postnatal survival for all other intervals (% per litter) =
[3(Viable offspring per litter at end of interval N/Viable offspring per litter at start of interval N) / No. litters per group] H 100

Where N = PND 0-1, 1-4 (pre-selection), 4-7 (post-selection), 7-14, 14-21, or 4-21 (post-selection)

3. **Positive and historical control data**: Positive and historical control data submitted for neurobehavioral testing conducted at WIL Research Laboratories, LLC are under review.

II. RESULTS:

A. PARENTAL ANIMALS:

1. **Mortality and clinical and functional observations**: One control female was found dead on GD 24; necropsy revealed a ruptured uterus and late resorptions. All remaining animals survived to scheduled sacrifice. No clinical signs of toxicity were observed during the daily examinations. Hair loss was a common finding in both treated and control animals.

During the FOB, slight increases in incidence of several parameters were observed in high dose animals. On GDs 10 and 15 and on lactation day 10, two or three high-dose animals (n=25) were asleep in the cage, compared with all controls sitting or standing normally. On GD 10, 22/25 animals in the high-dose group scored very easy for removal from the cage, compared with 18/25 control animals. A slightly drooping or shut palpebral closure was noted in 1/25 high-dose animal compared with none of the controls on lactation day 10, as

well as in 4/25 high-dose animals versus 1/23 controls on lactation day 21. These findings are considered to be within the range of normal variability for this type of observations.

2. **Body weight and food consumption:** Selected group mean body weight, body weight gain and food consumption values for pregnant or nursing dams are summarized in Table 2. Absolute body weight was similar between the treated and control groups throughout gestation. However, body weight gain by the high-dose group was slightly less (n.s.) than that of controls for each interval, resulting in a significant decrease in overall gestational weight gain (GD 0-20) by the high-dose animals (90% of controls; p # 0.05). Food consumption by the high-dose group was significantly less (p # 0.05 or 0.01) than that of the control group during GDs 6-9 (87% of controls) and GDs 6-20 (96% of controls).
Mean body weight of the high-dose group was significantly less (p # 0.05 or 0.01; 92-95% of control value) than that of controls throughout lactation. Body weight gains were slightly lower in the high-dose group, compared to controls, but these differences were not statistically significant. Food consumption by the high-dose group was significantly less (p # 0.05 or 0.01; 87-92% of controls) than that of the control group throughout lactation when expressed as g/animal/day. No significant differences were noted between the treated and control groups when food consumption was expressed as g/kg/day, indicating that reduced food consumption per animal by the high-dose group was a result of lower body weight.

TABLE 2. Selected mean (±SD) maternal body weight (g), body weight gain (g), and food consumption (g/animal/day)				
Observations/study interval	Dietary concentration (ppm)			
	0	50	125	300
Gestation (n=24-25)				
Body wt. gestation day 0	262 ± 14.8	262 ± 13.5	260 ± 15.7	259 ± 13.2
Body wt. gestation day 6	292 ± 14.7	290 ± 15.2	290 ± 19.0	286 ± 15.2
Body wt. gestation day 12	322 ± 17.4	321 ± 17.3	320 ± 23.2	314 ± 18.6
Body wt. gestation day 20	406 ± 22.1	401 ± 24.5	399 ± 35.5	389 ± 21.3
Wt. gain gestation days 0-6	31 ± 5.1	28 ± 6.6	30 ± 8.8	26 ± 7.3 (84)[a]
Wt. gain gestation days 6-20	114 ± 14.1	112 ± 13.8	109 ± 22.4	103 ± 12.2 (90)
Wt. gain gestation days 0-20	145 ± 14.5	139 ± 15.6	139 ± 25.3	130* ± 15.9 (90)
Food consumption gestation days 6-9	23 ± 2.0	22 ± 2.3	22 ± 2.3	20** ± 2.0 (87)
Food consumption gestation days 6-20	24 ± 1.8	24 ± 1.9	24 ± 2.0	23* ± 1.7 (96)
Lactation (n=24-25)				
Body wt. lactation day 1	311 ± 20.4	306 ± 17.2	305 ± 23.4	296* ± 16.2 (95)
Body wt. lactation day 4	329 ± 20.9	323 ± 20.2	323 ± 22.5	308** ± 19.1 (94)
Body wt. lactation day 7	338 ± 21.1	331 ± 19.8	333 ± 26.6	315** ± 19.1 (93)
Body wt. lactation day 14	352 ± 19.1	349 ± 20.5	355 ±28.3	324**± 22.8 (92)
Body wt. lactation day 21	344 ± 20.4	342 ± 23.9	345 ± 27.3	324** ± 18.6 (94)
Wt. gain lactation days 1-4	18 ± 13.4	17 ± 12.3	19 ± 10.5	12 ± 9.1 (67)
Wt. gain lactation days 1-21	33 ± 20.6	35 ± 20.2	41 ± 20.2	28 ± 15.9 (85)
Food consumption lactation days 1-4	38 ± 7.0	40 ± 4.6	39 ± 8.6	33* ± 5.4 (87)
Food consumption lactation days 1-21	57 ± 4.4	58 ± 4.1	58 ± 5.1	51** ± 3.5 (89)

Data taken from Tables 5-7 and 10-12, pp. 180-184 and 188-191, MRID 46670402.
[a]Numbers in parentheses are percent of control; calculated by reviewer.
Significant different from control: *p # 0.05; **p # 0.01.

3. **Test substance intake**: Maternal test article intake values are shown in Table 3. Based on maternal food consumption and body weight and nominal dietary concentrations, the overall doses to the 0, 50, 125, and 300 ppm groups, adjusted for purity, were 0, 2.9, 7.4, and 17.3 mg/kg/day, respectively, during gestation and 0, 7.1, 17.5, and 39.8 mg/kg/day, respectively, during lactation.

TABLE 3. Mean (±SD) maternal test substance intake (mg/kg body weight/day)			
Period	Dietary concentration (ppm)		
	50	125	300
Gestation			
Gestation days 6-9, not adjusted for purity	3.8 ± 0.31	9.3 ± 0.51	20.3 ± 1.40
Gestation days 9-12, not adjusted for purity	3.6 ± 0.27	9.0 ± 0.59	22.1 ± 3.21
Gestation days 15-20, not adjusted for purity	3.5 ± 0.20	8.6 ± 0.53	20.4 ± 1.08
Gestation days 6-20, not adjusted for purity	3.6 ± 0.21	9.0 ± 0.37	21.1 ± 1.17
Gestation days 6-20, adjusted for purity [a]	2.9	7.4	17.3
Lactation			
Lactation days 1-4, not adjusted for purity	6.3 ± 0.73	15.6 ± 3.00	32.7 ± 4.60
Lactation days 7-11, not adjusted for purity	7.9 ± 0.66	19.6 ± 1.23	44.5 ± 3.26
Lactation days 17-21, not adjusted for purity	10.7 ± 1.04	25.5 ± 2.67	59.8 ± 6.45
Lactation days 1-21, not adjusted for purity	8.7 ± 0.65	21.4 ± 1.33	48.7 ± 2.92
Lactation days 1-21, adjusted for purity [a]	7.1	17.5	39.8

Data taken Tables 9 and 14, pp. 187 and 194, respectively, MRID 46670402.
[a] Adjusted for purity of the test compound (81.8% a.i.) by the reviewer.

4. **Reproductive performance:** Results for the maternal animals are summarized in Table 4. The number of animals pregnant, mean gestation length, implantations/dam, and number of live litters were similar between the treated and control groups. One mid-dose dam failed to deliver and had complete early resorption of one implantation site.

TABLE 4. Reproductive performance				
Observation	Dietary concentration (ppm)			
	0	50	125	300
Number mated (pregnant)	25 (25)	25 (25)	25 (24)	25 (25)
Pregnancy rate (%)	100.0	100.0	96.0	100.0
Intercurrent deaths	1	0	0	0
Number of live litters	24	25	23	25
Implantation sites/dam (mean±SD)	15.0 ± 2.26	15.4 ± 2.29	15.0 ± 3.20	14.6 ± 1.98
Mean (±SD) gestation length (days)	21.6 ± 0.58	21.7 ± 0.46	21.7 ± 0.57	21.7 ± 0.46

Data taken from Tables 1, 15, and 16, pp. 157, 195, and 197, respectively, MRID 46670402.

5. **Maternal postmortem results:** No treatment-related gross lesions were observed in any animal.

B. OFFSPRING:

1. **Viability and clinical signs:** Litter size and viability (survival) of pups during lactation are summarized in Table 5. No treatment-related effect on the mean number of pups born, mean live litter size, percentage of males per litter, or pup survival was observed. Additionally, one dam plus litter in each of the control and mid-dose groups was sacrificed because the litter failed to meet the sex ratio criteria.

   During lactation, a total of 2, 5, 2, and 8 pups from the control, low-, mid-, and high-dose groups, respectively, were noted to be small in size. The incidence of other clinical signs was comparable between the treated and control groups.

TABLE 5. Mean (±SD) litter size and viability

Observation	Dietary concentration (ppm)			
	0	50	125	300
Number of live litters	24	25	23	25
Mean no. pups born	14.5 ± 2.23	14.2 ± 2.06	14.5 ± 3.03	14.0 ± 1.96
Mean live litter size (PND 0)	14.5 ± 2.23	14.1 ± 2.07	14.4 ± 3.01	13.9 ± 2.00
Total litter loss/sacrificed [a]	1	0	1	0
Sex ratio (% males/litter)	51.1 ± 16.52	47.1 ± 13.50	53.7 ± 11.62	47.9 ± 11.28
Live Birth Index (PND 0; % per litter)	100 ± 0.00	99.4 ± 1.94	99.7 ± 1.30	99.4 ± 2.06
Viability Index [PNDs 0-4(precull); % per litter]	98.5 ± 3.23	98.9 ± 2.57	97.7 ± 3.82	97.7 ± 4.17
Lactation Index [PNDs 4(post-cull)-21; % per litter]	100 ± 0.00	98.0 ± 5.91	98.3 ± 5.84	100 ± 0.00

Data taken from Tables 21 and 22, pp. 201 and 202-203, respectively, MRID 46670402.

[a] One control dam failed to deliver and was found dead on GD 24. One 125 ppm dam failed to deliver by GD 25 and was sacrificed.

2. **Body weight:** Selected mean pre-weaning pup body weight and body weight gain data are presented in Table 6. Pup body weight was similar between the treated and control groups on PNDs 1-11. On PNDs 13-21, mean body weight was slightly (n.s.) decreased in the high-dose male offspring (93-94% of control value) and was significantly decreased in the high-dose female offspring (90-92% of control value). Mean body weight gain was significantly decreased in the high-dose males (86% of control value) only during the PND 11-13 interval. Mean body weight gain was significantly decreased in the high-dose females (86-89% of control value) for all intervals during PNDs 7-17 and for PND 4-21 (87% of controls).

Selected mean post-weaning body weight and body weight gain data for offspring assigned to the F0 are presented in Table 7. No differences were seen between the treated and control groups at any time during the post-weaning interval.

TABLE 6. Selected mean (±SD) pup body weight and body weight gain				
PND	Dietary concentration (ppm)			
	0	50	125	300
Males				
Body weight (g)				
1	7.1 ± 0.89	7.1 ± 0.68	7.0 ± 0.77	6.7 ± 0.62 (94)
4 (pre-cull)	9.8 ± 1.57	9.8 ± 1.20	9.8 ± 1.36	9.2 ± 1.23 (94)
7	14.8 ± 2.50	15.8 ± 1.99	15.5 ± 1.59	14.5 ± 1.76 (98)
11	23.5 ± 4.40	24.9 ± 2.84	24.9 ± 2.70	22.6 ± 2.43 (96)
13	28.6 ± 4.26	29.8 ± 3.11	29.8 ± 3.08	27.0 ± 2.59 (94)
17	38.1 ± 4.42	39.3 ± 3.89	39.9 ± 4.04	35.6 ± 3.23 (93)
21	49.3 ± 6.77	51.0 ± 5.30	51.4 ± 5.54	45.8 ± 4.79 (93)
Body weight gain (g)				
1-4	2.7 ± 0.76	2.7 ± 0.62	2.8 ± 0.69	2.4 ± 0.77 (89)
4-7	5.3 ± 1.74	5.9 ± 1.04	5.9 ± 0.89	5.3 ± 0.87 (100)
7-11	8.7 ± 2.19	9.2 ± 1.36	9.4 ± 1.58	8.1 ± 1.05 (93)
11-13	5.1 ± 0.82	4.9 ± 0.71	5.0 ± 0.81	4.4** ± 0.68 (86)[a]
13-17	9.5 ± 1.16	9.3 ± 1.76	10.0 ± 1.46	8.6 ± 1.01 (91)
17-21	11.2 ± 3.35	11.7 ± 2.47	11.6 ± 2.67	10.2 ± 2.20 (91)
4-21	39.7 ± 5.78	41.1 ± 4.47	41.9 ± 4.96	36.6 ± 4.01 (92)
Females				
Body weight (g)				
1	6.7 ± 0.80	6.8 ± 0.58	6.6 ± 0.69	6.4 ± 0.61 (96)
4 (pre-cull)	9.4 ± 1.43	9.4 ± 1.14	9.2 ± 1.29	8.7 ± 1.11 (93)
7	14.6 ± 2.46	14.9 ± 2.10	14.6 ± 1.54	13.9 ± 1.80 (95)
11	23.5 ± 3.84	23.8 ± 2.85	23.6 ± 2.77	21.8 ± 2.55 (93)
13	28.5 ± 3.62	28.6 ± 3.03	28.2 ± 3.28	26.1* ± 2.78 (92)
17	37.8 ± 3.82	37.4 ± 3.62	38.0 ± 3.77	34.2** ± 3.19 (90)
21	48.7 ± 5.96	48.3 ± 5.38	48.7 ± 4.80	43.8** ± 4.71 (90)
Body weight gain (g)				
1-4	2.7 ± 0.72	2.6 ± 0.68	2.7 ± 0.68	2.3 ± 0.67 (85)
4-7	5.4 ± 1.49	5.6 ± 1.15	5.6 ± 0.83	5.2 ± 0.82 (96)
7-11	8.9 ± 1.67	8.9 ± 1.22	8.9 ± 1.64	7.9* ± 1.11 (89)

TABLE 6. Selected mean (±SD) pup body weight and body weight gain				
PND	Dietary concentration (ppm)			
	0	50	125	300
11-13	5.0 ± 0.76	4.9 ± 0.76	4.7 ± 0.81	4.3** ± 0.66 (86)
13-17	9.4 ± 1.13	8.8 ± 1.61	9.6 ± 1.48	8.1** ± 0.80 (86)
17-21	10.9 ± 3.16	10.9 ± 2.50	10.7 ± 2.34	9.6 ± 2.14 (88)
4-21	39.5 ± 4.97	38.9 ± 4.56	39.7 ± 4.16	35.0** ± 3.93 (87)

Data taken from Tables 24 and 25, pp. 205-207 and 208-210, respectively, MRID 46670402.
[a]Number in parentheses is percent of control; calculated by reviewer.
Significantly different from control: *p # 0.05; **p # 0.01.
n = 23, 25, 22, or 25 litters in the 0, 50, 125, or 300 ppm groups, respectively.

TABLE 7. Selected mean (±SD) post-weaning pup body weight and body weight gain				
PND	Dietary concentration (ppm)			
	0	50	125	300
Males				
Body weight (g)				
28	84.5 ± 12.08	85.8 ± 5.88	88.3 ± 9.35	80.6 ± 8.67
35	145.4 ± 18.22	147.1 ± 9.68	151.1 ± 12.70	139.9 ± 12.59
49	268.8 ± 27.79	271.9 ± 15.97	278.1 ± 19.75	263.2 ± 21.46
72	405.3 ± 33.22	411.9 ± 25.00	414.9 ± 36.21	393.8 ± 33.40
Body weight gain (g)				
28-35	60.8 ± 6.61	61.3 ± 5.49	62.8 ± 4.25	59.3 ± 5.89
42-49	55.1 ± 7.25	59.1 ± 7.03	58.3 ± 6.30	57.7 ± 8.60
70-72	9.9 ± 3.52	11.6 ± 4.89	7.5 ± 8.24	9.9 ± 6.31
Females				
Body weight (g)				
28	80.0 ± 9.68	79.6 ± 10.71	82.2 ± 8.21	72.9 ± 9.16
35	127.9 ± 12.14	128.4 ± 15.19	131.6 ± 13.64	119.0 ± 11.38
49	191.1 ± 14.08	195.8 ± 22.05	192.6 ± 16.20	183.2 ± 14.31
72	256.7 ± 20.23	266.8 ± 29.46	253.9 ± 20.83	243.8 ± 17.51
Body weight gain (g)				
28-35	47.9 ± 4.02	48.7 ± 5.66	49.4 ± 6.56	46.1 ± 4.14
42-49	24.7 ± 6.05	26.5 ± 8.86	24.2 ± 6.04	25.6 ± 5.76
70-72	4.3 ± 7.84	7.6 ± 7.05	2.5 ± 8.18	3.0 ± 8.25

Data taken from Tables 31 and 32, pp. 218-221 and 222-225, respectively, MRID 46670402.
n = 20/sex/group

3. **Developmental landmarks**:

a. **Sexual maturation**: Age and body weight at sexual maturation are given in Table 8. The average age of onset of preputial separation in males was 44.0-44.9 days for the control and treated groups. The average age of onset of vaginal opening was 32.5-32.7 days for the control and treated groups. Body weight in the treated animals was similar to the control group at the time of acquisition. These data indicate no delays in sexual maturation of offspring from treated dams compared with controls.

b. **Developmental landmarks**: Other endpoints of offspring development (eye opening, pinna unfolding, hair growth, etc.) were not monitored in this study.

TABLE 8. Mean (±SD) age and body weight at sexual maturation

Parameter	Dietary concentration (ppm)			
	0	50	125	300
N (M/F)	20/20	20/20	20/20	20/20
Preputial separation				
mean age (days)	44.1 ± 1.96	44.8 ± 1.83	44.0 ± 1.95	44.9 ± 1.92
mean body weight (g)	228.3 ±22.44	235.5 ± 19.94	236.0 ± 25.86	228.0 ± 21.71
Vaginal opening				
mean age (days)	32.7 ± 1.42	32.5 ± 1.36	32.6 ± 1.05	32.6 ± 1.28
mean body weight (g)	111.6 ± 12.05	110.3 ± 13.71	113.8 ± 10.67	103.3 ± 10.59

Data taken from Tables 28 and 29, pp. 213 and 214, respectively, MRID 46670402.

4. **Behavioral assessment**:

a. **Functional observations**: No treatment-related FO changes were observed in males or females on testing days PNDs 4, 11, 45 and 60 or in females on PND 22. However, on PND 22, high-dose males had significantly reduced fore-limb grip strength (146.8 ± 30.9 vs 174.8 ±35.6 for controls; p # 0.05). Hind-limb grip strength was also reduced in PND 22 high-dose males, although not significantly (89.3 ± 23.4 vs 97.8 ± 24.0 for controls). Red deposits were present in the nose of 4/20 high-dose males on PND22, compared to only 1/20 of each of the control, low-dose, and mid-dose groups. Also on PND 22, drooping or completely shut palpebral closure was observed in 4/20 or 1/20 of the high-dose males, respectively, compared to only 0/20 or 2/20 of the controls.

b. **Motor/locomotor activity**: Total motor and ambulatory activity data are presented in Table 9. Interval data for total counts are presented in Tables 10 (males) and 11 (females); habituation was evident in all groups by PND 17. No significant difference in total activity was found between the treated and control groups on any testing day, although a trend toward increased activity by high-dose males and decreased activity by high-dose females was observed on some testing days.

Although highly variable, the combined total motor activity count over the 60 minute session appears increased in the 300 ppm males on PND 13 (126% of controls, NS). When motor counts from the individual 15 minute intervals of this group were examined, however, no significant increases were observed.

In PND 17 males, habituation occurred to a lesser extent at the high-dose, compared to controls. At 300 ppm, the 31-45 minute subsession motor activity count was slightly increased to 150% of controls (NS), and the 46-60 minute count was significantly increased to 281% of controls ($p \# 0.05$). Combined, these increases resulted in a higher motor activity count for the total session (124% of controls; NS). A significant increase in ambulatory counts over the 46-60 minute interval was also noted (362% of controls; $p \# 0.05$).

In PND 13 males the increased activity (total and subsession) was determined to be equivocal in nature. In PND 13 females, an indication of increasing total motor activity counts was observed. Additionally, the 16-30, 31-45, and 46-60 minute subsession counts were elevated in the high dose PND 13 males and females. Additional statistical analyses (ANOVA) showed essentially no statistically significant difference among the treated groups; we note, however, that variance was generally high, and was increased in treated females.

In PND 17 females, a clear dose-response was not seen; total motor activity counts were 71% of controls (NS) at both the mid and high doses. Compared to all controls, significant decreases were observed in the high-dose females at both the 0-15 minute interval (62% of all controls; $p \# 0.01$) and the 16-30 minute interval (47% of all controls; $p \# 0.01$). At the mid-dose, only the activity counts during the 16-30 minute interval were significantly decreased (31% of all controls; $p \# 0.01$). However, control female #62442-11 had particularly high total and subsession motor activity counts on PND17. The total motor activity count for this animal was 4285, whereas the range for the remaining controls was 661-2745 (1307 ± 601). During the 16-30 minute subsession specifically, this female's motor count was 1728, while counts for the remaining controls were between 37-876.

On PND 21, total activity in high-dose females was 70% of the control level due to a reduction in activity during minutes 16-30 (45% of controls), 31-45 (45% of controls), and 46-60 (74% of controls). Statistical significance was not attained for the intervals due to large variability in the data. However, repeated measures analysis for each session found significant differences ($p \# 0.05$) from the control group in total and ambulatory activity of high-dose females on PND 21.

TABLE 9. Mean (±SD) total and ambulatory motor activity counts

Test day	Dietary concentration (ppm)			
	0	50	125	300
Males				
PND 13				
Total	580 ± 561.8	490 ± 390.2	582 ± 316.9	730 ± 596.0 (126) [a]
Ambulatory	195 ± 291.3	152 ± 202.6	131 ± 105.7	252 ± 278.9 (129)
PND 17				
Total	1241 ± 985.3	1067 ± 862.9	826 ± 572.1	1533 ± 967.8 (124)
Ambulatory	439 ± 456.9	361 ± 313.2	270 ± 210.6	543 ± 398.6 (124)
PND 21				
Total	1074 ± 475.3	928 ± 373.5	885 ± 393.8	914 ± 412.0
Ambulatory	332 ± 171.0	270 ± 120.3	265 ± 132.4	275 ± 150.2
PND 61				
Total	2208 ± 545.6	2081 ± 808.3	2562 ± 501.7	2492 ± 527.3
Ambulatory	776 ± 214.2	708 ± 338.0	866 ± 224.0	891 ± 234.2
Females				
PND 13				
Total	503 ± 395.9	532 ± 458.4	700 ± 674.3	761 ± 868.1 (151)
Ambulatory	140 ± 169.3	149 ± 206.4	223 ± 356.6	276 ± 409.4 (197)
PND 17				
Total	1456 ± 886.2	1239 ± 994.9	1030 ± 555.0 (71)	1041 ± 659.0 (71)
Ambulatory	533 ± 443.3	452 ± 438.8	371 ± 233.7 (70)	356 ± 263.9 (67)
PND 21				
Total	1091 ± 437.3	941± 385.6	1037 ± 430.5	769 ± 385.9 (70)
Ambulatory	335 ± 192.7	300 ± 142.7	310 ± 150.7	221 ± 127.6 (66)
PND 61				
Total	2138 ± 595.3	2028 ± 606.2	2193 ± 593.0	2194 ± 571.0
Ambulatory	867 ± 267.5	796 ± 274.1	884 ± 233.9	880 ± 270.0

Data taken from Tables 37 and 86, pp. 277-292 and 1413-1444, respectively, MRID 46670402.
N=20/sex/group.
[a]Number in parentheses is percent of control; calculated by reviewer.

TABLE 10. Mean (± SD) sub-session motor activity count for males				
Interval (min)	Dietary concentration (ppm)			
	0	50	125	300
PND 13				
0-15	183 ± 140.9	162 ± 137.6	157 ± 87.9	177 ± 162.6
16-30	149 ± 236.6	147 ± 202.3	153 ± 151.4	173 ± 184.8
31-45	99 ± 109.7	89 ± 155.2	111 ± 98.5	191 ± 211.6
46-60	149 ± 221.4	91 ± 100.4	161 ± 125.0	190 ± 204.3
PND 17				
0-15	614 ± 310.8	552 ± 210.1	447 ± 209.0	538 ± 303.0
16-30	294 ± 346.3	232 ± 313.7	155 ± 175.4	340 ± 293.2 (116)[a]
31-45	211 ± 262.7	159 ± 267.7	115 ± 171.4	316 ± 271.7 (150)
46-60	121 ± 183.4	124 ± 220.8	109 ± 164.2	340* ± 309.8 (281)
PND 21				
0-15	566 ± 146.5	571 ± 175.9	549 ± 162.0	535 ± 157.3
16-30	192 ± 153.1	165 ± 161.7	180 ± 164.1	160 ± 122.2
31-45	177 ± 168.9	84 ± 93.5	83 ± 110.5	97 ± 136.4
46-60	138 ± 150.3	108 ± 127.1	73 ± 114.8	122 ± 149.9
PND 61				
0-15	1104 ± 216.1	1016 ± 307.2	1207 ± 215.2	1239 ± 201.3
16-30	478 ± 216.4	478 ± 297.5	578 ± 206.2	548 ± 140.2
31-45	289 ± 143.6	330 ± 199.9	403 ± 238.2	427 ± 245.3
46-60	338 ± 306.6	257 ± 233.5	374 ± 184.0	278 ± 210.6

Data taken from Tables 37 and 86, pp. 277-292 and 1413-1444, respectively, MRID 46670402.
N = 20.
[a]Number in parentheses is percent of control; calculated by reviewer.
Significantly different from control: *p # 0.05

TABLE 11. Mean (± SD) sub-session motor activity count for females				
Interval (min)	Dietary concentration (ppm)			
	0	50	125	300
PND 13				
0-15	184 ± 196.2	148 ± 131.6	169 ± 120.6	164 ± 167.5
16-30	116 ± 104.0	137 ± 199.5	188 ± 231.1	208 ± 328.1
31-45	105 ± 120.2	128 ± 140.6	182 ± 272.1	221 ± 275.1
46-60	99 ± 144.4	118 ± 182.0	160 ± 183.4	169 ± 164.4
PND 17				
0-15	652 ± 244.0	560 ± 261.1	572 ± 246.0	405** ± 176.6 (62)[a]
16-30	406 ± 376.9	252 ± 268.2	124** ± 145.5 (31)	191** ± 190.5 (47)
31-45	230 ± 346.6	207 ± 271.7	151 ± 184.8	199 ± 210.1
46-60	168 ± 228.2	220 ± 293.2	182 ± 205.6	245 ± 263.4
PND 21				
0-15	591 ± 174.1	547 ± 149.7	585 ± 158.1	509 ± 140.1
16-30	217 ± 174.7	167 ± 152.5	229 ± 155.4	97 ± 101.1 (45)
31-45	154 ± 179.8	125 ± 142.2	136 ± 154.8	69 ± 95.3 (45)
46-60	128 ± 157.4	102 ± 149.6	87 ± 114.9	95 ± 155.7 (74)
PND 61				
0-15	1051 ± 199.3	1024 ± 200.6	1087 ± 152.0	1082 ± 169.4
16-30	516 ± 199.1	474 ± 235.0	517 ± 241.9	516 ± 252.8
31-45	311 ± 222.2	328 ± 214.8	349 ± 231.3	325 ± 240.2
46-60	261 ± 214.7	202 ± 222.6	240 ± 206.5	272 ± 196.9

Data taken from Tables 37 and 86, pp. 277-292 and 1413-1444, respectively, MRID 46670402.
N = 20.
[a]Number in parentheses is percent of control; calculated by reviewer.
Significantly different from control: **p # 0.01.

c. **Auditory startle reflex habituation:** Overall maximum response amplitude (V_{MAX}), latency to V_{MAX} (T_{MAX}), and average response amplitude (V_{AVE}) data in male and female rats are presented in Table 12. Mean interval data are presented in Table 13. Habituation was apparent on both testing days. No statistically significant differences between treated and control groups were observed, however the data were highly variable (for example, on PND 60 the standard deviation exceeded the mean values for some blocks of trials). Given the high variability, the sensitivity of this measure to detect treatment-related changes is not clear.

TABLE 12. Mean (±SD) overall acoustic startle peak amplitude (V_{MAX}), latency to peak (T_{MAX}) and average response amplitude (V_{AVE})

Dietary conc. (ppm)	Males		Females	
	PND 20	PND 60	PND 20	PND 60
		V_{MAX} (mv)		
0	138.9 ± 70.79	92.7 ± 72.16	124.4 ± 59.27	55.5 ± 52.63
50	135.0 ± 55.84	97.6 ± 95.86	141.2 ± 52.96	66.1 ± 69.14
125	161.4 ± 63.41	133.4 ± 93.27	114.3 ± 44.15	49.8 ± 39.61
300	129.8 ± 43.18	102.7 ± 79.49	115.4 ± 46.60	47.1 ± 23.89
		T_{MAX} (msec)		
0	24.8 ± 4.03	31.8 ± 6.88	24.9 ± 3.24	32.8 ± 4.57
50	23.8 ± 2.28	31.8 ± 4.25	23.3 ± 2.36	31.4 ± 6.70
125	25.4 ± 2.99	31.0 ± 4.28	24.3 ± 2.74	33.1 ± 4.37
300	25.0 ± 2.23	34.1 ± 6.02	26.5 ± 3.36	31.5 ± 4.78
		V_{AVE} (mv)		
0	26.4 ± 13.10	16.6 ± 14.19	24.0 ± 12.02	8.6 ± 9.21
50	26.2 ± 11.16	18.9 ± 20.23	28.3 ± 11.98	10.7 ± 11.94
125	33.0 ± 13.76	26.0 ± 20.89	22.3 ± 9.81	7.4 ± 6.56
300	25.9 ± 9.46	19.3 ± 15.38	22.4 ± 9.32	7.0 ± 3.91

Data taken from Table 38, pp. 293-304, MRID 46670402.
N = 20/sex/group

TABLE 13. Interval data for acoustic startle peak amplitude (V_{MAX}), latency to peak (T_{MAX}) and average response amplitude (V_{AVE})					
Dietary conc. (ppm)	**Trials 1-10**	**Trials 11-20**	**Trials 21-30**	**Trials 31-40**	**Trials 41-50**
Males - PND 20					
V_{MAX} (mv)					
0	162.6 ± 79.33	144.5 ± 83.81	131.3 ± 65.68	133.3 ± 80.24	123.0 ± 76.97
50	161.2 ± 64.38	143.6 ± 68.10	142.2 ± 61.34	117.3 ± 79.92	110.8 ± 63.76
125	215.5 ± 97.07	166.9 ± 59.71	142.7 ± 62.65	141.9 ± 82.23	140.2 ± 68.16
300	166.8 ± 63.62	137.2 ± 49.08	123.6 ± 53.59	116.3 ± 51.08	105.4 ± 59.08
T_{MAX} (msec)					
0	26.7 ± 4.95	24.4 ± 4.15	25.2 ± 7.22	23.9 ± 7.71	23.7 ± 4.11
50	25.2 ± 3.81	22.3 ± 2.55	23.3 ± 4.21	23.7 ± 4.22	24.6 ± 4.42
125	27.6 ± 5.20	24.6 ± 3.89	24.7 ± 3.46	24.5 ± 4.90	25.8 ± 4.96
300	27.0 ± 2.91	25.0 ± 3.48	24.4 ± 3.78	23.8 ± 3.37	24.6 ± 4.00
V_{AVE} (mv)					
0	30.3 ± 15.12	26.4 ± 15.36	25.2 ± 12.82	25.6 ± 15.60	24.3 ± 14.69
50	31.6 ± 12.78	26.0 ± 12.62	27.9 ± 12.82	22.4 ± 15.78	23.1 ± 13.23
125	44.2 ± 21.76	33.7 ± 12.56	28.6 ± 12.61	29.4 ± 18.44	29.3 ± 15.59
300	32.1 ± 12.74	27.2 ± 9.42	24.9 ± 11.74	23.8 ± 11.59	21.4 ± 13.61
Males - PND 60					
V_{MAX} (mv)					
0	150.6 ± 135.45	102.4 ± 99.34	70.3 ± 63.05	66.9 ± 52.83	73.3 ± 53.12
50	131.7 ± 113.25	98.5 ± 92.79	93.4 ± 112.48	93.4 ± 129.47	70.9 ± 79.74
125	193.0 ± 149.01	144.9 ± 136.16	132.1 ± 98.21	98.5 ± 75.53	98.5 ± 84.67
300	154.0 ± 122.47	86.6 ± 101.41	96.1 ± 88.33	80.9 ± 87.79	96.1 ± 99.43
T_{MAX} (msec)					
0	32.5 ± 7.40	30.1 ± 6.73	33.1 ± 9.82	31.9 ± 10.90	31.5 ± 7.62
50	30.8 ± 5.86	32.4 ± 8.28	33.1 ± 8.86	29.9 ± 7.84	32.5 ± 6.82
125	30.1 ± 6.27	30.6 ± 7.39	30.7 ± 5.75	31.1 ± 6.65	32.3 ± 8.39
300	33.4 ± 9.74	34.3 ± 6.99	35.4 ± 7.90	35.5 ± 10.88	32.0 ± 8.33
V_{AVE} (mv)					
0	29.8 ± 30.23	18.3 ± 18.96	11.4 ± 10.67	10.9 ± 9.84	12.5 ± 9.91
50	25.2 ± 22.60	18.9 ± 19.92	18.4 ± 23.51	18.8 ± 28.05	13.1 ± 16.38
125	40.1 ± 36.43	28.0 ± 31.64	26.4 ± 21.88	17.8 ± 17.56	17.8 ± 16.97
300	31.1 ± 24.40	14.9 ± 17.14	17.3 ± 16.72	14.6 ± 17.60	18.5 ± 21.11
Females - PND 20					
V_{MAX} (mv)					

TABLE 13. Interval data for acoustic startle peak amplitude (V_{MAX}), latency to peak (T_{MAX}) and average response amplitude (V_{AVE})					
0	149.1 ± 65.74	123.3 ± 70.60	118.7 ± 84.97	112.0 ± 79.15	118.9 ± 61.30
50	186.4 ± 76.58	143.3 ± 65.75	136.9 ± 63.45	124.7 ± 57.30	114.6 ± 66.59
125	150.8 ± 111.17	120.4 ± 51.86	97.3 ± 59.23	99.0 ± 61.80	104.1 ± 49.58
300	144.1 ± 54.45	111.1 ± 53.72	101.2 ± 59.07	105.9 ± 54.99	114.9 ± 45.30
T_{MAX} (msec)					
0	25.9 ± 3.99	24.4 ± 3.80	24.4 ± 5.74	26.3 ± 5.12	23.7 ± 4.65
50	25.6 ± 4.53	23.1 ± 3.80	23.1 ± 3.62	22.0 ± 2.97	22.8 ± 3.46
125	26.7 ± 5.59	24.7 ± 4.74	22.6 ± 3.83	23.0 ± 4.57	24.4 ± 4.30
300	30.1 ± 7.85	26.3 ± 5.08	24.5 ± 5.48	25.5 ± 5.58	26.3 ± 6.32
V_{AVE} (mv)					
0	28.6 ± 13.72	24.0 ± 15.29	23.6 ± 18.92	21.3 ± 16.01	22.8 ± 12.18
50	37.7 ± 16.76	29.1 ± 15.24	27.3 ± 14.84	24.7 ± 12.60	22.9 ± 13.47
125	27.4 ± 16.52	23.1 ± 11.94	19.4 ± 14.13	20.3 ± 15.31	21.2 ± 12.11
300	28.4 ± 10.79	20.2 ± 9.59	19.3 ± 11.96	21.5 ± 11.50	22.8 ± 9.68
Females - PND 60					
V_{MAX} (mv)					
0	83.3 ± 96.49	66.8 ± 65.43	39.7 ± 26.81	47.7 ± 52.94	40.0 ± 37.95
50	73.7 ± 48.42	77.9 ± 84.57	59.7 ± 101.33	49.8 ± 61.68	69.2 ± 103.51
125	77.4 ± 53.53	43.3 ± 31.28	43.6 ± 30.63	46.0 ± 59.10	38.7 ± 42.64
300	64.4 ± 31.02	39.0 ± 27.16	38.3 ± 17.94	44.6 ± 37.11	49.0 ± 43.77
T_{MAX} (msec)					
0	34.2 ± 6.86	30.5 ± 6.74	34.2 ± 8.42	33.1 ± 7.52	32.2 ± 6.61
50	32.5 ± 8.72	31.1 ± 8.10	29.5 ± 7.66	31.6 ± 8.13	32.2 ± 9.26
125	35.7 ± 7.31	34.8 ± 8.20	33.1 ± 8.17	29.9 ± 8.96	31.7 ± 6.72
300	31.8 ± 6.60	31.2 ± 8.04	33.5 ± 6.17	30.9 ± 8.36	29.8 ± 7.59
V_{AVE} (mv)					
0	13.4 ± 15.49	10.2 ± 10.85	5.7 ± 4.55	7.3 ± 10.59	6.2 ± 7.71
50	12.3 ± 9.19	12.7 ± 15.07	9.5 ± 18.09	7.9 ± 10.11	11.0 ± 18.02
125	12.6 ± 9.21	6.3 ± 4.81	6.3 ± 5.18	6.6 ± 10.39	5.4 ± 7.25
300	10.3 ± 5.29	5.6 ± 4.84	5.1 ± 2.89	6.4 ± 5.22	7.4 ± 7.94

Data taken from Table 38, pp. 293-304, MRID 46670402.
N = 20/sex/group

d. Learning and memory testing:

Watermaze performance: The watermaze performance data for PNDs 25 and 62 are presented in Tables 14 and 15, respectively. Data for both swimming time and number of errors were highly variable on both testing perods in both sexes. No treatment-related effects on learning and memory were found at either testing interval. At both time points, learning was evident for all groups as a decrease in both time and number of errors with successive trials through both paths of the maze. Memory was also demonstrated for all groups on PND 62 as a decrease in both endpoints in trial 12 compared with trial 11.

TABLE 14. Water maze performance in offspring on PND 25 (mean±SD)

Day/Trial	Dietary concentration (ppm)			
	0	50	125	300
Males				
Day 1 - Swimming Ability Mean Time (secs)	8.91 ± 2.491	8.94 ± 3.066	8.17 ± 1.416	9.18 ± 2.379
Trial 1 (Day 2) - Path A Mean Time (secs) Mean No. Errors	103.56 ± 60.462 24 ± 15.4	84.94 ± 55.938 20 ± 15.3	67.16 ± 56.178 14 ± 14.2	52.15 ± 29.118 11 ± 8.3
Trial 2 (Day 2) - Path A Mean Time (secs) Mean No. Errors	84.90 ± 55.785 19 ± 12.1	68.57 ± 49.383 15 ± 13.0	60.43 ± 45.896 14 ± 11.5	61.38 ± 48.357 14 ± 13.9
Trial 3 (Day 3) - Path A Mean Time (secs) Mean No. Errors	57.86 ± 44.933 15 ± 15.0	45.47 ± 40.510 10 ± 10.6	58.56 ± 46.711 15 ± 16.2	66.09 ± 62.68 17 ± 19.1
Trial 4 (Day 3) - Path A Mean Time (secs) Mean No. Errors	53.55 ± 49.408 12 ± 13.7	47.67 ± 49.786 9 ± 11.5	36.69 ± 21.445 8 ± 7.5	29.68 ± 21.093 6 ± 6.5
Trial 5 (Day 4) - Path B Mean Time (secs) Mean No. Errors	154.61 ± 44.330 37 ± 12.8	119.25 ± 57.794 29 ± 17.1	150.18 ± 46.204 40 ± 13.7	122.26 ± 60.162 31 ± 16.4
Trial 6 (Day 4) - Path B Mean Time (secs) Mean No. Errors	117.74 ± 57.783 27 ± 15.2	130.16 ± 60.611 30 ± 16.9	103.66 ± 60.762 26 ± 16.9	104.99 ± 62.962 25 ± 18.0
Trial 7 (Day 5) - Path B Mean Time (secs) Mean No. Errors	102.55 ± 69.667 21 ± 18.1	84.17 ± 56.837 18 ± 14.3	75.37 ± 59.353 16 ± 12.7	96.35 ± 67.367 20 ± 17.0
Trial 8 (Day 5) - Path B Mean Time (secs) Mean No. Errors	88.75 ± 70.953 18 ± 16.4	70.65 ± 56.390 13 ± 12.2	86.71 ± 67.311 18 ± 15.3	99.45 ± 59.882 20 ± 13.6
Trial 9 (Day 6) - Path B Mean Time (secs) Mean No. Errors	90.43 ± 64.048 19 ± 15.0	72.98 ± 60.041 16 ± 14.2	84.35 ± 65.667 18 ± 16.6	76.52 ± 62.017 16 ± 15.9
Trial 10 (Day 6) - Path B Mean Time (secs) Mean No. Errors	85.73 ± 62.055 19 ± 15.3	56.97 ± 52.213 11 ± 11.5	49.39 ± 44.278 10 ±10.1	73.85 ± 47.528 16 ± 12.8

TABLE 14. Water maze performance in offspring on PND 25 (mean±SD)				
	Dietary concentration (ppm)			
Trial 11 (Day 7) - Path A (Probe) Mean Time (secs) Mean No. Errors	79.98 ± 41.551 19 ± 11.6	82.81 ± 43.067 21 ± 15.0	91.16 ± 51.586 24 ± 13.6	85.67 ± 51.157 24 ± 16.2
Trial 12 (Day 7) - Path A (Probe) Mean Time (secs) Mean No. Errors	46.75 ± 22.173 11 ± 7.0	64.64 ± 48.283 15 ± 14.5	62.52 ± 48.554 16 ± 14.3	87.24 ± 56.689 24 ± 17.2
Overall Biel (Trials 1-10) Mean Time (secs) Mean No. Errors	93.97 ± 30.456 21 ± 6.9	78.08 ± 22.205 17 ± 5.5	77.25 ± 28.814 18 ± 7.2	78.27 ± 24.995 18 ± 6.3
Overall Probe (Trials 11-12) Mean Time (secs) Mean No. Errors	63.37 ± 24.545 15 ± 7.3	73.72 ± 32.340 18 ± 10.5	76.84 ± 47.608 20 ± 12.9	86.45 ± 43.911 24 ± 13.8
Females				
Day 1 - Swimming Ability Mean Time (secs)	8.91 ± 2.146	7.69 ± 2.357	8.09 ± 1.502	9.01 ± 2.749
Trial 1 (Day 2) - Path A Mean Time (secs) Mean No. Errors	83.27 ± 51.886 19 ± 12.0	72.45 ± 45.740 17 ± 10.7	70.08 ± 40.883 16 ± 9.9	81.84 ± 57.070 19 ± 15.4
Trial 2 (Day 2) - Path A Mean Time (secs) Mean No. Errors	63.67 ± 45.444 15 ± 12.6	48.14 ± 38.643 11 ± 10.5	59.67 ± 46.387 13 ± 12.4	72.11 ± 54.018 17 ± 14.8
Trial 3 (Day 3) - Path A Mean Time (secs) Mean No. Errors	52.45 ± 45.362 13 ± 13.4	53.05 ± 43.233 14 ± 13.4	61.15 ± 39.875 16 ± 11.7	65.59 ± 55.704 16 ± 15.9
Trial 4 (Day 3) - Path A Mean Time (secs) Mean No. Errors	38.07 ± 35.195 8 ± 10.6	43.91 ± 44.515 10 ± 13.2	43.28 ± 29.819 10 ± 8.3	35.30 ± 28.161 8 ± 9.1
Trial 5 (Day 4) - Path B Mean Time (secs) Mean No. Errors	132.90 ± 53.343 31 ± 13.6	150.58 ± 38.555 36 ± 12.3	136.49 ± 56.244 34 ± 16.7	133.24 ± 56.606 34 ± 15.8
Trial 6 (Day 4) - Path B Mean Time (secs) Mean No. Errors	87.27 ± 60.980 19 ± 13.9	111.01 ± 64.046 24 ± 14.3	111.54 ± 57.497 25 ± 14.1	113.62 ± 61.294 29 ± 16.4
Trial 7 (Day 5) - Path B Mean Time (secs) Mean No. Errors	91.05 ± 64.805 16 ± 14.4	93.97 ± 61.125 18 ± 11.6	100.09 ± 63.311 23 ± 14.6	105.59 ± 57.145 25 ± 13.8
Trial 8 (Day 5) - Path B Mean Time (secs) Mean No. Errors	94.25 ± 62.738 20 ± 17.2	76.03 ± 68.769 16 ± 16.4	87.46 ± 67.742 17 ± 12.9	80.51 ± 64.976 16 ± 14.5
Trial 9 (Day 6) - Path B Mean Time (secs) Mean No. Errors	83.26 ± 58.683 18 ± 15.9	82.03 ± 67.128 18 ± 15.3	94.32 ± 68.542 21 ± 16.2	85.37 ± 58.406 19 ± 14.9
Trial 10 (Day 6) - Path B Mean Time (secs) Mean No. Errors	50.70 ± 42.761 9 ± 10.3	78.18 ± 67.426 15 ± 15.2	73.79 ± 57.397 15 ± 14.4	76.05 ± 60.604 15 ± 13.6
Trial 11 (Day 7) - Path A (Probe) Mean Time (secs) Mean No. Errors	82.94 ± 40.241 22 ± 13.6	88.27 ± 47.157 23 ± 14.2	86.26 ± 54.601 21 ± 13.8	81.08 ± 52.562 19 ± 13.6

TABLE 14. Water maze performance in offspring on PND 25 (mean±SD)				
	Dietary concentration (ppm)			
Trial 12 (Day 7) - Path A (Probe) Mean Time (secs) Mean No. Errors	44.02 ± 22.812 10 ± 7.2	60.90 ± 41.243 15 ± 12.7	58.50 ± 46.654 12 ± 8.3	64.33 ± 46.079 16 ± 13.1
Overall Biel (Trials 1-10) Mean Time (secs) Mean No. Errors	77.69 ± 25.372 17 ± 5.6	80.93 ± 26.872 18 ± 5.8	83.79 ± 28.795 19 ± 6.1	84.50 ± 25.327 20 ± 5.8
Overall Probe (Trials 11-12) Mean Time (secs) Mean No. Errors	63.48 ± 23.010 16 ± 7.6	74.59 ± 36.066 19 ± 12.0	72.38 ± 46.375 16 ± 9.3	72.71 ± 44.374 18 ± 12.2

Data taken from Table 39, pp. 305-314, MRID 46670402.
N=19-20

TABLE 15. Water maze performance in offspring on PND 62 (mean±SD)

Day/Trial	Dietary concentration (ppm)			
	0	50	125	300
Males				
Day 1 - Swimming Ability Mean Time (secs)	6.37 ± 3.059	5.75 ± 1.467	6.57 ± 1.772	6.67 ± 2.414
Trial 1 (Day 2) - Path A Mean Time (secs) Mean No. Errors	71.25 ± 50.901 15 ± 8.8	90.07 ± 57.224 19 ± 11.4	58.69 ± 35.348 12 ± 8.1	78.91 ± 47.039 18 ± 11.1
Trial 2 (Day2) - Path A Mean Time (secs) Mean No. Errors	57.08 ± 42.650 12 ± 8.0	52.52 ± 41.174 10 ± 7.0	43.49 ± 27.727 9 ± 7.1	54.63 ± 40.991 11 ± 8.6
Trial 3 (Day 3) - Path A Mean Time (secs) Mean No. Errors	28.66 ± 30.346 6 ± 7.9	45.18 ± 33.990 9 ± 7.2	32.82 ± 22.820 7 ± 6.2	42.63 ± 32.263 9 ± 7.8
Trial 4 (Day 3) - Path A Mean Time (secs) Mean No. Errors	37.66 ± 36.899 9 ± 9.1	33.57 ± 25.748 9 ± 9.7	30.47 ± 23.776 7 ± 5.5	36.73 ± 38.314 9 ± 10.5
Trial 5 (Day 4) - Path B Mean Time (secs) Mean No. Errors	104.17 ± 53.515 24 ± 10.2	132.25 ± 59.376 31 ± 15.4	107.89 ± 69.124 23 ± 16.4	117.71 ± 59.619 30 ± 15.4
Trial 6 (Day 4) - Path B Mean Time (secs) Mean No. Errors	74.36 ± 69.355 16 ± 16.0	88.42 ± 65.400 18 ± 13.6	94.81 ± 65.258 17 ± 13.0	90.26 ± 66.255 19 ± 14.8
Trial 7 (Day 5) - Path B Mean Time (secs) Mean No. Errors	81.99 ± 64.086 19 ± 16.1	58.16 ± 44.892 14 ± 11.8	55.61 ± 52.394 11 ± 10.0	62.10 ± 61.005 16 ± 18.0
Trial 8 (Day 5) - Path B Mean Time (secs) Mean No. Errors	40.98 ± 51.672 8 ± 11.2	49.98 ± 52.174 12 ± 13.1	44.87 ± 55.772 7 ± 10.0	43.61 ± 45.898 11 ± 12.9
Trial 9 (Day 6) - Path B Mean Time (secs) Mean No. Errors	40.74 ± 42.737 9 ± 11.0	42.54 ± 28.383 9 ± 8.2	35.80 ± 39.591 6 ± 7.2	31.29 ± 41.598 6 ± 9.3
Trial 10 (Day 6) - Path B Mean Time (secs) Mean No. Errors	21.53 ± 13.641 5 ± 4.3	29.42 ± 21.398 6 ± 6.0	22.36 ± 14.945 3 ± 3.4	32.64 ± 40.578 6 ± 8.8
Trial 11 (Day 7) -Path A (Probe) Mean Time (secs) Mean No. Errors	81.15 ± 54.849 21 ± 15.5	62.31 ± 32.863 16 ± 9.4	64.03 ± 46.565 15 ± 10.4	83.13 ± 51.642 24 ± 15.5
Trial 12 (Day 7) -Path A (Probe) Mean Time (secs) Mean No. Errors	48.62 ± 37.415 12 ± 11.3	55.30 ± 46.820 13 ± 10.6	42.35 ± 26.574 9 ± 6.0	46.61 ± 31.049 13 ± 10.8

TABLE 15. Water maze performance in offspring on PND 62 (mean±SD)				
Day/Trial	Dietary concentration (ppm)			
	0	50	125	300
Overall Biel (Trials 1-10) Mean Time (secs) Mean No. Errors	55.50 ± 27.001 12 ± 4.6	62.21 ± 22.086 14 ± 4.7	52.55 ± 21.838 10 ± 3.7	59.05 ± 23.955 14 ± 5.9
Overall Probe (Trials 11-12) Mean Time (secs) Mean No. Errors	64.88 ± 37.358 17 ± 10.2	61.19 ± 36.514 14 ± 8.5	53.19 ± 29.629 12 ± 6.1	64.87 ± 34.293 19 ± 10.9
Females				
Day 1 - Swimming Ability Mean Time (secs)	6.85 ± 2.770	6.22 ± 2.513	5.69 ± 0.935	6.81 ± 2.423
Trial 1 (Day 2) - Path A Mean Time (secs) Mean No. Errors	78.28 ± 44.981 16 ± 10.4	76.45 ± 44.259 16 ± 10.4	67.12 ± 33.522 15 ± 7.6	70.16 ± 45.525 15 ± 10.1
Trial 2 (Day 2) - Path A Mean Time (secs) Mean No. Errors	67.85 ± 45.137 15 ± 10.5	65.41 ± 48.501 13 ± 10.2	57.54 ± 44.796 14 ± 11.1	49.49 ± 36.057 11 ± 8.0
Trial 3 (Day 3) - Path A Mean Time (secs) Mean No. Errors	33.63 ± 18.250 7 ± 5.2	34.56 ± 35.964 7 ± 9.8	30.03 ± 23.068 7 ± 6.8	54.94 ± 47.986 12 ± 11.0
Trial 4 (Day 3) - Path A Mean Time (secs) Mean No. Errors	24.86 ± 13.789 5 ± 5.2	32.65 ± 15.992 8 ± 6.4	19.61 ± 8.217 3 ± 2.8	25.32 ± 14.019 5 ± 4.3
Trial 5 (Day 4) - Path B Mean Time (secs) Mean No. Errors	130.78 ± 60.645 33 ± 17.6	112.18 ± 58.362 27 ± 16.0	119.53 ± 53.063 30 ± 13.8	116.11 ± 55.542 29 ± 15.7
Trial 6 (Day 4) - Path B Mean Time (secs) Mean No. Errors	76.06 ± 63.097 16 ± 14.5	84.46 ± 56.248 19 ± 14.9	68.59 ± 61.959 16 ± 16.5	63.71 ± 57.566 15 ± 15.1
Trial 7 (Day 5) - Path B Mean Time (secs) Mean No. Errors	44.95 ± 50.558 10 ± 13.0	47.57 ± 41.157 11 ± 11.0	62.57 ± 56.591 15 ± 13.9	66.29 ± 46.906 16 ± 13.8
Trial 8 (Day 5) - Path B Mean Time (secs) Mean No. Errors	70.30 ± 66.617 17 ± 19.8	36.55 ± 28.269 7 ± 9.3	26.17 ± 11.373 6 ± 8.2	42.20 ± 36.958 11 ± 13.1
Trial 9 (Day 6) - Path B Mean Time (secs) Mean No. Errors	24.46 ± 32.299 4 ± 8.0	32.12 ± 25.387 6 ± 7.5	27.60 ± 20.887 5 ± 6.0	32.90 ± 27.706 7 ± 8.7
Trial 10 (Day 6) - Path B Mean Time (secs) Mean No. Errors	23.34 ± 15.142 4 ± 3.9	30.43 ± 30.926 5 ± 6.5	24.29 ± 25.219 4 ± 6.2	22.44 ± 14.748 3 ± 4.1
Trial 11 (Day 7) -Path A (Probe) Mean Time (secs) Mean No. Errors	49.97 ± 19.275 12 ± 6.8	66.80 ± 36.212 18 ± 11.0	63.42 ± 28.033 18 ± 10.8	82.22 ± 53.227 22 ± 16.2
Trial 12 (Day 7) -Path A (Probe) Mean Time (secs) Mean No. Errors	45.14 ± 33.648 10 ± 7.6	48.77 ± 24.772 12 ± 8.3	32.51 ± 13.627 6 ± 4.8	44.20 ± 38.027 10 ± 9.9

TABLE 15. Water maze performance in offspring on PND 62 (mean±SD)				
Day/Trial	Dietary concentration (ppm)			
	0	50	125	300
Overall Biel (Trials 1-10) Mean Time (secs) Mean No. Errors	 57.45 ± 20.684 13 ± 5.0	 55.24 ± 14.690 12 ± 3.6	 50.31 ± 16.225 12 ± 3.8	 54.36 ± 13.559 12 ± 3.6
Overall Probe (Trials 11-12) Mean Time (secs) Mean No. Errors	 47.55 ± 17.544 11 ± 4.3	 57.78 ± 24.128 15 ± 7.6	 47.97 ± 12.250 12 ± 5.2	 63.21 ± 39.845 16 ± 10.8

Data taken from Table 40, 315-324, MRID 46670402
N=19-20

7. Postmortem results:

a. **Brain weight:** Mean absolute brain weight data are presented in Table 16. A slight increase (not statistically significant) in male brain weights was noted at the high dose on PND 21; this increase was not considered to be treatment-related.

TABLE 16. Brain weight data (mean g±SD) from offspring				
Sex and age	Dietary concentration (ppm)			
	0	50	125	300
Males - PND 21	1.6390 ± 0.13900	1.6704 ± 0.11398	1.6377 ± 0.10386	1.7069 ± 0.06248 (104)[a]
Females - PND 21	1.5895 ± 0.09126	1.5913 ± 0.08290	1.5730 ± 0.13457	1.5758 ± 0.05151 (99)
Males - PND 72	1.97 ± 0.123	1.94 ± 0.067	1.99 ± 0.046	1.92 ± 0.049 (97)
Females - PND 72	1.84 ± 0.076	1.84 ± 0.125	1.81 ± 0.158	1.79 ± 0.129 (97)

Data taken from Tables 42 and 47, pp. 327-328 and 343-344, respectively, MRID 46670402.
N=10
[a]Number in parentheses is percent of control; calculated by reviewer.

b. **Macroscopic examination:** No remarkable changes were seen in pups found dead during lactation, culled pups, or pups selected for neuropathology on PNDs 21 and 72.

c. **Neuropathology**:

1) **Microscopic examination:** No treatment-related microscopic lesions were observed on PNDs 21 or 72. Similar, low incidences of minimal degeneration of several nerves, retinal dysplasia, and corneal mineralization were observed in both control and high-dose animals on PND 72.

2) **Brain Morphometry:** Brain length and width measurements are given in Table 17 and data from morphometric measurements are presented in Table 18. Several slight increases and decreases were noted in various morphometric measurements in both PND 21 and 72 males and females. A statistically significant increase (105.6% of controls; p # 0.05) in the vertical thickness of the cortex was observed in high dose PND 21 females, compared to controls. These changes were determined to be marginal and suggestive of effects limited to the high dose. However, data for this measurement should be submitted for the low- and mid-dose to confirm these findings.

TABLE 17. Brain length and width measurements (mean mm±SD) from rats on PNDs 21 and 72

Endpoint	Dietary concentration (ppm)			
	0	50	125	300
PND 21				
Males				
length	17.9 ± 0.59	18.1 ± 0.41	18.0 ± 0.44	18.0 ± 0.44
width	14.6 ± 0.49	14.8 ± 0.59	14.5 ± 0.47	14.7 ± 0.42
Females				
length	17.8 ± 0.63	17.9 ± 0.39	17.9 ± 0.66	17.7 ± 0.58
width	14.4 ± 0.39	14.2 ± 0.49	14.3 ± 0.50	14.4 ± 0.49
PND 72				
Males				
length	20.3 ± 0.43	20.9 ± 0.79	20.8 ± 0.90	20.5 ± 0.80
width	14.8 ± 0.52	15.0 ± 0.50	15.3 ± 0.71	14.9 ± 0.49
Females				
length	19.7 ± 0.71	20.1 ± 0.70	19.8 ± 0.70	20.0 ± 0.56
width	14.8 ± 0.45	14.6 ± 0.34	14.8 ± 0.41	14.4 ± 0.49

Data taken from Tables 42 and 47, pp. 327-328 and 343-344, respectively, MRID 46670402.
N=10

TABLE 18. Brain morphometric measurements (mean cm±SD) from rat offspring on PNDs 21 and 72

Parameter	Dietary concentration (ppm)			
	0	300	0	300
	Males		Females	
PND 21				
Height hemisphere	0.7564 ± 0.03462	0.7791 ± 0.03393	0.7354 ± 0.03196	0.7568 ± 0.03370
Vertical thickness cortex	0.1896 ± 0.01449	0.1879 ± 0.01355	0.1849 ± 0.00893	0.1953 * ± 0.01134 (105.6)
Radial thickness cortex	0.1564 ± 0.01284	0.1612 ± 0.00667	0.1670 ± 0.01586	0.1659 ± 0.01244
Vertical height between hippocampal pyramidal neuron layers	0.0926 ± 0.00794	0.0946 ± 0.00955	0.0878 ± 0.00652	0.0910 ± 0.00776
Vertical height of dentate hilus	0.0479 ± 0.00526	0.0501 ± 0.00519 (104.6)	0.0474 ± 0.00345	0.0490 ± 0.00366
Length ventral limb dentate hilus	0.1251 ± 0.01695	0.1324 ± 0.00915 (105.8)	0.1228 ± 0.01818	0.1306 ± 0.01057 (106.4)
Vertical thickness of pons	0.2487 ± 0.02557	0.2453 ± 0.02368	0.2414 ± 0.02784	0.2568 ± 0.03397 (106.4)
Base of lobule 9	0.0616 ± 0.01260	0.0608 ± 0.00760	0.0617 ± 0.00654	0.0578 ± 0.00511
PND 72				
Height hemisphere	0.6665 ± 0.16634	0.6580 ± 0.14812	0.6433 ± 0.14379	0.5590 ± 0.23526 (86.9)
Vertical thickness cortex	0.1849 ± 0.01528	0.1672 ± 0.03060 (90.4)	0.1645 ± 0.03672	0.1630 ± 0.05514
Radial thickness cortex	0.1611 ± 0.00529	0.1611 ± 0.00984	0.1536 ± 0.02744	0.1339 ± 0.04933 (87.2)
Vertical height between hippocampal pyramidal neuron layers	0.0953 ± 0.00832	0.0935 ± 0.00839	0.0897 ± 0.00732	0.0905 ± 0.00746
Vertical height of dentate hilus	0.0377 ± 0.01718	0.0323 ± 0.01804 (85.7)	0.0404 ± 0.01598	0.0391 ± 0.01615
Length ventral limb dentate hilus	0.1356 ± 0.01271	0.1319 ± 0.01245	0.1329 ± 0.00850	0.1266 ± 0.01705 (95.3)
Vertical thickness of pons	0.2810 ± 0.03371	0.2728 ± 0.02660	0.2557 ± 0.01390	0.2634 ± 0.02543
Base of lobule 9	0.0684 ± 0.00683	0.0727 ± 0.00349 (106.3)	0.0669 ± 0.00315	0.0668 ± 0.00601

Data taken from Table 45 and 50, pp. 337-340 and 361-364, respectively, MRID 46670402.
N = 9-10
Significantly different from control: *p # 0.05.

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS:

Maternal toxicity was evident at 300 ppm as reduced body weight gains during gestation and lactation, reduced body weights during lactation, and reduced food consumption during gestation and lactation.

Offspring toxicity also occurred at 300 ppm as reduced body weight gain and body weight during lactation. No evidence of developmental neurotoxicity was found. The Sponsor attributed the increased motor activity on PND 13 and decreased motor activity on PND 21 to a "slight shift in the timing of the normal U-shaped developmental activity pattern", rather than to treatment. They did not attribute changes in motor activity during the individual subsessions on PND 17 to treatment. The PND 61 motor activity counts were stated to fall within the WIL historical control range. Finally, the increase in the mean height of the vertical thickness of the cerebral cortex in 300 ppm females on PND 21 was considered spurious and unrelated to treatment.

The Sponsor concluded that the maternal and offspring LOAELs are 300 ppm, and the maternal and offspring NOAELs are 125 ppm.

B. REVIEWER COMMENTS: In a developmental neurotoxicity study (MRID 46670402), Zeta-cypermethrin technical (81.8% a.i.; lot # PL03-0427) was administered in the diet to 25 mated female Crl:CD®(SD)IGS BR rats/group at nominal concentrations of 0, 50, 125, or 300 ppm from gestation day (GD) 6 through lactation day (LD) 21. Average doses to the dams, adjusted for purity, were 0, 2.9, 7.4, or 17.3 mg/kg/day, respectively, during gestation and 0, 7.1, 17.5, or 39.8 mg/kg/day, respectively, during lactation. Dietary concentrations were based on the results of preliminary dietary feasibility, range-finding, and placental/lacational transfer studies (MRIDs 46538902, 46670401, and 46670403, respectively); lactional exposure to the pups was determined in these supplementary studies, reviewed separately [TXR# 0053857]. Functional Observations (FO) were performed on 25 dams/group on GDs 10 and 15 and on all surviving dams that delivered offspring on LDs 10 and 21. On postnatal day (PND) 4, litters were culled to eight offspring, with at least three males and three females per litter. Offspring were allocated for detailed clinical observations (FO) and assessment of motor activity, auditory startle response, and learning and memory, as well as for neuropathology at study termination (PND 72). On PND 21, the whole brain was collected from 10 pups/sex/dose group, weighed, and subjected to micropathologic examination and morphometric analysis. Pup physical development was evaluated by body weight. The age of sexual maturation (vaginal opening in females and preputial separation in males) was assessed.

One control female was found dead late in gestation; necropsy revealed a ruptured uterus and late resorptions. All remaining animals survived to scheduled sacrifice. No treatment-related clinical signs of toxicity were observed during the daily examinations. During the FO on GDs 10 and 15 and on lactation day 10, two or three high-dose animals were asleep in the cage, compared with

all controls sitting or standing normally. On GD 10, 22 animals in the high-dose group were scored very easy for removal from the cage, compared with 18 control animals. A slightly drooping or shut palpebral closure was noted on one high-dose animal compared with none of the controls on lactation day 10 and on four high-dose animals verses one control on lactation day 21.

Absolute body weight was similar between the treated and control dams throughout gestation. However, body weight gain by the high-dose group was slightly less (n.s.) than that of controls for each interval, resulting in overall gestational weight gain (GD 0-20) by the high-dose animals that was 90% of the control group level. Food consumption by the high-dose group was significantly less (p # 0.05 or 0.01) than that of the control group during GDs 6-9 (87% of controls) and GDs 6-20 (96% of controls). Throughout lactation, mean body weight of the high-dose group was significantly less (p # 0.05 or 0.01; 92-95% of control value) than that of controls. Food consumption by the high-dose group was significantly less than that of the control group (p # 0.05 or 0.01; 87-92% of controls) throughout lactation. The observed changes in body weight, body weight gain and food consumption were not considered to be adverse. No treatment-related effects were observed in reproductive parameters, and gross necropsy was unremarkable.

No treatment-related effect on the mean number of pups born, mean live litter size, percentage of males per litter, pup survival, or clinical signs was observed. Pup body weights were similar between the treated and control groups on PNDs 1-11. On PNDs 13-21, mean body weight was significantly decreased in the high-dose female offspring (90-92% of control value) and was slightly (n.s.) decreased in the high-dose male offspring (93-94% of control value). Mean body weight gain was significantly decreased in the high-dose females (86-89% of control value) for all intervals during PNDs 7-17 and for PND 4-21 (87% of controls). Mean weight gain was significantly decreased in the high-dose males (86% of control value) during the PND 11-13 interval. Post-weaning body weight and body weight gain were similar between the treated and control groups. The average age and body weight at attainment of sexual maturation was not affected by treatment.

No treatment-related FO changes were observed in males or females on testing days PNDs 4, 11, 45 and 60 or in females on PND 22. On PND 22, high-dose males had significantly reduced fore-limb grip strength (146.8 vs 174.8 for controls; p # 0.05), and four animals were observed with drooping palpebral closure compared with none of the controls.

No significant difference in total motor activity was found between the treated and control groups on any testing day. However, a trend towards increased activity in high-dose males and decreased activity in high-dose females was observed on some testing days. On PND 17, high-dose males had a slight increase in total motor activity (124% of controls), resulting from increased subsession motor activity, particularly during final two 15 minute intervals (150% of controls; n.s. and 281% of controls; p # 0.05). This increased activity in the final subsessions indicates that less habituation occurred in the high dose PND 17 males, compared to controls. In females, decreased motor activity was seen at the high dose on both PNDs 17 and 21 (71% and 70% of controls, respectively; n.s.). On PND 17, this decrease is was considered to be equivocal in nature due to

less activity during the first two 15 minute subsessions (47-62% of controls; p # 0.01). The decreased activity on PND 21 (45-86% of controls; n.s) is considered to a treatment-related effect.

Auditory startle response, learning and memory, and gross and microscopic findings were not affected by treatment.

A slight increase in male brain weights was noted at the high dose on PND 21 (104% of controls, n.s.). Several slight changes in morphometry measurements were noted, including a statistically significant increase in the vertical thickness of the cortex observed in high dose PND 21 females (106% of controls; p # 0.05). These changes were determined to be marginal and suggestive effect at the high dose and morphometric data for the low and mid dose groups are required to re-affirm the establishment of the mid dose as the NOAEL.

The maternal NOAEL is 300 ppm (17.4 mg/kg/day), the highest dose tested; a LOAEL was not established.

The offspring LOAEL is 300 ppm (17.4 mg/kg/day to dams), based on decreased body weights and body weight gains of females, altered motor activity in males and females, and changes in brain morphometrics. The offspring NOAEL is 125 ppm (7.4 mg/kg/day to dams).

This study is classified **Acceptable/Non-Guideline** and may be used for regulatory purposes, however it does not satisfy the guideline requirement for a developmental neurotoxicity study in rats (OPPTS 870.6300, §83-6); OECD 426 (draft) due to the absence of brain morphometric measurements of the offspring at the mid and low dose groups, and pending the evaluation of available positive control data.

C. **STUDY DEFICIENCIES:** Data for the vertical thickness of the cortex in the low- and mid-dose PND 21 female groups should be submitted.