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OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEW
PA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

TXR#: 0054098

MEMORANDUM

Date: December 14, 2006

Subject: **Chlorfenapyr:** Review of Developmental Neurotoxicity Study - Rat (MRIDs 46740201, and 46210605)

PC Code.: 129093
DP Barcode No: D326780

From: Guruva B. Reddy, Veterinary Medical Officer
Registration Action Branch 1
Health Effects Division (HED) (7509P)

G. Reddy
12/14/06

To: Richard Gebker/Ann Sibold, RM 03
Registration Division (7505P)

Through: P.V. Shah, Ph.D., Branch Senior Scientist
Registration Action Branch 1
Health Effects Division (HED) (7509P)

P.V. Shah

I CONCLUSIONS

The Health Effects Division has evaluated the developmental neurotoxicity study in rat (MRIDs 46740201, and 46210605) for chlorfenapyr and provided the Data Evaluation Record (DER). The study is classified as **acceptable/non-guideline** and may be used for regulatory purposes. It does not, however, satisfy the guideline requirements for a developmental neurotoxicity study in rats [OPPTS 870.6300, §83-6; OECD 426 (Draft)] due to the pending review of the positive control data. This study satisfies the data gap previously identified.

II ACTION REQUESTED

The Registration Division has requested that the Health Effects Division (HED) review the developmental neurotoxicity study in rat for Chlorfenapyr (MRIDs 46740201, and 46210605) in

support of registration. BASF Corporation submitted this study in response to HIARC recommendations (March 4, 2003, TXR No. 001606)

CITATION: Schneider, S., W. Kaufmann, B. van Ravenzwaay (2006) BAS 306 I, Developmental neurotoxicity study in Wistar rats, oral administration to the dams and pups (gavage). Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen, Germany. Laboratory report number 66R0346/03066, January 11, 2006. MRID 46740201. Unpublished .

Kaufmann, W., S. Schneider, B. van Ravenzwaay (2003) Methylazoxy Methanol Acetate, Positive control – Developmental neurotoxicity study in Wistar rats, single intraperitoneal administration to dams. Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen, Germany. Laboratory report number 03R0076/02004, November 11, 2003. MRID 46210605. Unpublished

EXECUTIVE SUMMARY: In a developmental neurotoxicity study (MRID 46740201) BAS 306 I [Chlorfenapyr (97.8%, batch 2181H88HV)] was administered by gavage to 40 female Wistar rats per dose 0, 5, 10 or 15 mg/kg bw/day from gestation day (GD) 6 through lactation day (LD)10. A Functional Observational Battery (FOB) was performed on 10 dams per group on GDs 7 and 14 and LDs 7 and 14. On postnatal day (PND) 4, litters were culled to yield four males and four females (as closely as possible). The test material was administered by gavage at the same dose levels to pups from PND 11 through PND 21. Offspring were allocated for detailed clinical observations (FOB) and assessment of motor activity, auditory startle reflex habituation, learning and memory (water maze testing) and neuropathology at termination (PND 62). On PND 22, the whole brain was collected from 10 pups/sex/group for histopathologic 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.

No deaths or clinical signs of toxicity were reported in dams during gestation or lactation. Body weight and food consumption were not affected by treatment. Gross necropsy of dams was unremarkable and brain weight and morphometry were similar between treated and control groups.

Pregnancy rate, gestation length, the mean number of delivered pups per dam and percentage of liveborn and stillborn pups were not affected by treatment. Pup survival was decreased in the mid- and high-dose groups as evidenced by an increase in the number of pups cannibalized (7 and 13, respectively, vs 1 each in the control and low-dose groups) and found dead (6 and 12, respectively, vs 3-4 in the control and low-dose groups). Most deaths occurred during lactation days 1-4.

Among surviving pups, no treatment-related effects on sex ratio, clinical signs, pre- and post-weaning body weight, FOB observations, acoustic startle response or learning and memory in offspring were observed. The mean day of achieving sexual maturation in treated animals was comparable to the control group. A dose-related decrease in total movement on PND 13 was

observed in treated males and females; the decrease (53% of control value) was significant at 15 mg/kg/day. During the PND 13 sub-session, the distance moved was generally lower in males and females at 10 and 15 mg/kg/day but the change was significant for only one sub-session in each sex. No treatment-related effects on total distance moved on PNDs 17, 21 or 60 or on the total number of rearings at any of the testing periods were observed.

Brain weight and measurement of the cerebrum and cerebellum were comparable between treated and control groups on PNDs 22, 62 and 111. On microscopic examination at PND 22, treatment-related minimal to moderate vacuolation of the white matter was observed in several areas of the brain, including the frontal lobe, parietal lobe, midbrain, pons, cerebellum and medulla oblongata, in up to 4/10 males and 4/10 females in the high-dose group compared to none in the control group. The low- and mid-dose groups were examined and no lesions were observed. No treatment-related microscopic findings were observed at the PND 62 necropsy. On morphometric examination, size of the left and right hippocampus in females at 15 mg/kg/day was significantly decreased on PND 62. Dimensions of these tissues in females at 5 and 10 mg/kg/day were comparable to the control group.

The maternal LOAEL for BAS 306 I in rats was not established and the maternal NOAEL is 15 mg/kg/day.

The offspring LOAEL for BAS 306 I in rats is 10 mg/kg/day, based on pup deaths on PND 1-4 and cannibalization and decreased motor activity in males and females on PND 13. The offspring NOAEL is 5 mg/kg/day.

This study is classified as **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) due to the pending review of the positive control data. Although, there is no LOAEL observed in dams, the study is acceptable since effects were seen in offspring.

Note: Copy of the DER attached.

DATA EVALUATION RECORD**CHLORFENAPYR
(BAS 306 I)****STUDY TYPE: DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS [OPPTS
870.6300 (§83-6)]
MRID 46740201**

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1801 Bell Street
Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
Life Sciences Division
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This review may have been altered subsequent to the contractor's signatures above.

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Template version 02/06

TXR#: 0054098

DATA EVALUATION RECORD

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

PC CODE: 129093**DP BARCODES:** DP 326780**TEST MATERIAL (PURITY):** BAS 306 I (Chlorfenapyr, 97.8% a.i.)**SYNONYMS:** CL 303,630; AC 303,360; chlorfenapyr, pyrrole technical.

CITATION: Schneider, S., W. Kaufmann, B. van Ravenzwaay (2006) BAS 306 I, Developmental neurotoxicity study in Wistar rats, oral administration to the dams and pups (gavage). Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen, Germany. Laboratory report number 66R0346/03066, January 11, 2006. MRID 46740201. Unpublished.

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SPONSOR: BASF Corporation, Agricultural Products Division, RTP, NC 27709

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

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I. MATERIALS AND METHODS:**A. MATERIALS:**

1. **Test material:** BAS 306 I
Description: Solid/white to light brown
Lot/batch #: 2181H88HV
Purity: 97.8% a.i.
Compound stability: Expiration date: April 8, 2008
CAS # of TGAI: 122453-73-0
Structure: Not available

2. **Vehicle and/or positive control:** Carboxymethylcellulose (0.5%) in double distilled water

3. **Test animals (P):**

Species:	Rat
Strain:	Wistar (CrI:WI(Han)[former:CrIGxBrlHan:WI])
Age at study initiation:	10-12 wks
Wt. at study initiation:	134.1-182.6 g
Source:	Charles River Laboratories, Germany
Housing:	Individually in type DK III stainless steel wire mesh cages, except from day 18 of gestation until day 21 after birth when the pregnant animals, their litters and subset I were housed in Makrolon type M III cages
Diet:	Ground Kliba maintenance diet mouse/rat "GLP" (pregnant animals, their litters and subset I <i>ad libitum</i>); pelleted Kliba maintenance diet mouse/rat "GLP" (subsets after weaning) <i>ad libitum</i>
Water:	Tap water <i>ad libitum</i>
Environmental conditions:	Temperature: 20-24EC Humidity: 30-70% Air changes: Not provided Photoperiod: 12 hrs dark/12 hrs light
Acclimation period:	Six days

B. PROCEDURES AND STUDY DESIGN:

1. **In life dates:** Start: September 19, 2004; End: January 26, 2005
2. **Study schedule:** Maternal animals were time-mated at the supplier. The test substance was administered to the dams from gestation day (GD) 6 through lactation day (LD) 10 and to pups from postnatal day (PND) 11 through PND 21. Pups were weaned on PND 21, after which time maternal animals were killed. F₁ pups remained on study until either PND 22, 62 or 111 (study termination).
3. **Mating procedure:** The animals were paired by the breeder and supplied on day 0 post coitum (equivalent to GD 1). Mating was confirmed by detection of a vaginal plug or sperm in a vaginal smear. Each pregnant female was placed into an individual cage with a solid bottom and bedding, where it was maintained through gestation and lactation.

4. **Animal assignment:** The method for assigning dams to the dose groups was not stated. Dams were assigned to functional observation testing as shown. Offspring were randomly assigned to testing subgroups at the time of litter standardization on PND 4 (Table 1).

TABLE 1. Study Design					
Experimental parameter		Dose (mg/kg/day)			
		0	5	10	15
Maternal animals					
No. of maternal animals assigned		40	40	40	40
FOB (GD 7, 14; LD 7, 14)		10	10	10	10
Brain weight, Neuropathology		10	10	10	10
Offspring					
Subset I – PND 22	Perfusion fixation, brain weights, neuropathology	10/sex	10/sex	10/sex	10/sex
Subset II – PND 24, 60	Auditory startle test	10/sex	10/sex	10/sex	10/sex
Subset II – PND 62	Perfusion fixation, brain weight, neuropathology	10/sex	10/sex	10/sex	10/sex
Subset III – PND 111	Perfusion fixation, brain weight, neuropathology	10/sex	10/sex	10/sex	10/sex
Subset IV – PND 4, 11, 21, 35, 45, 60	Open field observation	10/sex	10/sex	10/sex	10/sex
Subset IV – PND 13, 17, 21, 60	Motor activity	10/sex	10/sex	10/sex	10/sex
Subset V – PND 23	Learning and memory test (water maze test)	10/sex	10/sex	10/sex	10/sex
Subset VI – PND 60	Learning and memory test (water maze test)	10/sex	10/sex	10/sex	10/sex

5. **Dose selection rationale:** The basis for the dose levels used in the study was not provided.
6. **Dosage administration:** All doses were administered once daily to maternal animals by gavage, on GD 6 through LD 10, in a volume of 10 mL/kg of body weight/day. The vehicle was 0.5% carboxymethylcellulose in distilled water. Dosing was based on the most recent body weight determination. Pups were dosed by gavage on PND 11 through PND 21.
7. **Dosage preparation and analysis:** Formulations were prepared at the beginning of the administration period and thereafter at 6- or 7-day intervals by mixing appropriate amounts of test substance with 0.5% carboxymethylcellulose solution in double distilled water. Solutions were stored at room temperature. Prior to the start of the study, stability of the test substance in 0.5% carboxymethylcellulose was evaluated for a period of seven days at room temperature. Homogeneity of the test solutions (top, middle, and bottom) was evaluated prior at the beginning of the administration period. During the study, samples of the test substance suspensions were analyzed twice during the study period (at the beginning and near the end) for concentration.

Results:

Homogeneity analysis: The low standard deviations (1.4 and 2.0 for the 0.05 and 0.15 g/100 mL samples, respectively) in the homogeneity analysis demonstrated that the test material was evenly distributed in the formulation.

Stability analysis: The percentage of the nominal value for a 10 mg/mL sample of the test formulation was 100.9%, 103.8%, 96.3% and 100.9% after 0, 48 and 96 hours and 7 days, respectively, when stored at room temperature.

Concentration analysis: The ranges for percent of nominal value were 90.2-93.9%, 92.4-97.7% and 92.2-93.3% for the 0.05, 0.10 and 0.15 g/mL concentrations, respectively.

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:** Twice daily checks for mortality or moribundity and daily cage-side observations were conducted for maternal animals. Clinical observations of the dams were conducted daily. Signs of toxicity were recorded as they were observed, including the time of onset, degree, and duration.

Ten dams per group were observed outside the home cage at least twice during gestation (days 7 and 14) and twice during lactation (days 7 and 14). The following functional observations were recorded.

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 or 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.

The dams tested were selected by lot. For the observations, the animals were removed from their cages by the investigator and placed in a standard arena (50 x 37.5 cm with a lateral border of 25 cm). The findings were graded by intensity. No information was provided on the consistency of technicians performing testing, technician knowledge of treatment group, environmental conditions at the time of testing, or timing of testing with respect to dosing of test substance.

Individual maternal body weight data were recorded on the day of arrival at the testing facility (GD 0) and daily on GDs 6-20. Females with litters were weighed on the day of parturition and on days 10, 14 and 21 post partum. Food consumption was determined on GDs 0, 6, 13 and 20 and on LDs 1, 7, 14 and 21.

b. Offspring:

- 1.) **Litter observations:** The day of completion of parturition was designated as lactation day (postnatal day) 0. The status (sex, liveborn or stillborn) and number of delivered pups was determined at birth. The number and percentage of dead pups were calculated for days 1-4, 5-7, 8-14 and 15-21 of lactation. The number of live pups/litter was determined on the day of birth and on PNDs 4, 7, 14 and 21. Daily throughout lactation, offspring were examined cage-side for gross signs of mortality or morbidity. Any clinical signs of toxicity in the offspring were recorded as they were observed, including the time of onset, degree, and duration. The pups were weighed on the day after birth (PND 1) and on day 4 (before standardization) and daily on PNDs 11-21.

On day 4 postpartum, using random procedures litters were standardized to a maximum of 8 pups/litter; excess pups were killed and discarded. Litters with fewer than eight pups were removed from the study.

- 2.) **Developmental landmarks:** Beginning on PND 40, male offspring were examined daily for balanopreputial separation. Beginning on PND 27, female offspring were examined daily for vaginal patency. The age of onset and body weight at attainment were recorded.
- 3.) **Postweaning observations:** After weaning on postnatal day 21, offspring were examined twice daily for mortality, and cage-side observations were conducted once daily. Individual offspring body weight data were recorded weekly.
- 4.) **Neurobehavioral evaluations:** Observations and the schedule for those observations are summarized as follows from the report.
 - i. **Functional observational battery (FOB):** On PNDs 4, 11, 21, 35, 45, and 60, a total of 10 offspring/sex/group (one male or one female from each litter) (Subset IV) was examined outside the home cage in an FOB assessment, as appropriate for the developmental stage being observed. The same parameters assessed in the maternal FOB were examined for offspring. The same offspring were evaluated at each time point. No information was provided on consistency of technicians performing testing, technician knowledge of treatment group, environmental conditions at the time of testing, and timing of testing with respect to dosing.
 - ii. **Motor activity testing:** Motor activity was evaluated in 10 rats/sex/dose (Subset IV) on days 13, 17, 21, and 60 using Tru Scan Photobeam Linc (Coulbourn Instruments). The animals were measured in 10 activity enclosures which were equipped with 2 sensor rings, each with 16 light beams per cage side. The distance covered and the number of rearings were measured over 12 intervals, each lasting 5 minutes. During the recording, no food or water was provided and the room was darkened. The same offspring were evaluated at each preweaning time point.
 - iii. **Auditory startle reflex habituation:** Auditory startle reflex habituation testing was performed on 10 offspring/sex/dose (Subset II) on postnatal days 24 and 60, using the SR-LAB; STARTLE RESPONSE SYSTEM. The animals were allowed a 5 minute acclimation period in the response chamber with a 70 dBA background noise. The

startle response was recorded in 50 identical trials at a startle sound level of 120 dBA with a 5 second interval between the trials. Maximum amplitude and latency to the peak response were analyzed in 5 blocks of 10 trials each.

- iv. **Learning and memory testing:** Learning and memory testing using a water maze test was performed on 10 offspring/sex/dose on PNDs 23 and 30 (Subset V) and on PNDs 60 and 67 (Subset VI). The test consisted of 3 parts and was performed within 2 weeks, starting with learning ability (learning 1) in the first week, followed by memory and relearning ability (learning 2) in the second week, as discussed below.

Learning ability (learning 1): This test consisted of 6 trials at intervals of 1 hour each for each animal. At each trial, the animals had to find a ladder (escape) on the right side of the M-shaped water maze pool. The maximum swimming time allowed was 6 minutes per trial. If an animal found the way to escape, it was scored positive. If an animal went the wrong way (whole body must be in the indirect alley), it was scored negative but was left in the water until it either found the escape or 6 minutes passed.

Memory: After one week, the animals had to find the ladder (escape) on the right side of the pool again. One trial per animal was performed.

Relearning ability (learning 2): This test started one hour after completion of the memory test. The same procedure was followed as in the learning 1 test, except that the ladder (escape) was placed on the left side of the pool.

The initial trial of either learning 1 or learning 2 was considered an acclimation trial and not included in the evaluation.

2. **Postmortem observations:**

- a. **Maternal animals:** After weaning of pups on PND 21, the dams (except for those intended for neuropathological examination) were anesthetized with isoflurane, sacrificed by cervical dislocation and discarded without examination. The same procedure was used for those dams whose litters were not needed. Animals without a litter were discarded after the uterus was stained to determine the number of implantation sites.

For neuropathological examinations, 10 maternal animals per group were subjected to deep anesthesia and sacrificed by perfusion fixation on PND 21. SOERENSEN phosphate buffer was used as a rinsing solution and neutrally buffered 4% formaldehyde solution was used as a fixative. The cranial vault and the spinal cord were opened and the skin was removed from both extremities. The brain (with olfactory bulb) weight was measured after removal. The length and maximum width of the cerebrum and the cerebellum were measured for all animals selected for neuropathological examinations. The animals were then stored in neutrally buffered, 4% formaldehyde solution for at least 48 hours.

The following organs/tissues were removed and processed histologically: brain with olfactory bulb, pituitary gland, eyes with retina and optical nerve, Gasserian ganglia with

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nerve, spinal cord [cervical swelling (C1-C5), thoracic cord (T5-T8) and lumbar swelling (L1-L4)], gastrocnemius muscle, nose and nasal cavity, dorsal root ganglion [C1-C5 (3x) and L1-L4 (3x)], dorsal root fiber (C3-C6 and L1-L4), ventral root fiber (C3-C6 and L1-L4), proximal sciatic nerve, proximal tibial nerve (at knee) and distal tibial nerve (at lower leg).

The procedures used for examination of the central and peripheral nervous system of dams are described in the tables presented under **Offspring**.

- b. **Offspring:** The offspring selected for brain weight or neuropathological evaluation (Subsets I, and II) were sacrificed on usual postnatal day 22, and 62, respectively. In addition on PND 111 offspring from subgroup III were sacrificed, however there is no explanation in the report why this group was sacrificed so late. Ten offspring/sex/group were subjected to deep anesthesia and sacrificed by perfusion fixation as described under the maternal animals. Brain weight and the length and width of the cerebrum and cerebellum were measured in all three subsets.

At the PND 22 necropsy, the following organs were examined histologically: brain with olfactory bulb, pituitary gland, eyes with retina and optical nerve, Gasserian ganglia with nerve, spinal cord [cervical swelling (C1-C5), thoracic cord (T5-T8) and lumbar swelling (L1-L4)], gastrocnemius muscle and nose and nasal cavity.

At the PND 62 and PND 111 necropsies, the organs examined histologically included those listed under the PND 22 necropsy plus the following: dorsal root ganglion [C1-C5 (3x) and L1-L4 (3x)], dorsal root fiber (C3-C6 and L1-L4), ventral root fiber (C3-C6 and L1-L4), proximal sciatic nerve, proximal tibial nerve (at knee) and distal tibial nerve (at lower leg).

The following specimens from **dams and PND 62 offspring** were processed histotechnically according to the table below. The semithin sections were examined by light microscopy.

Organ samples from:	Dose (mg/kg/day)			
	0	5	10	15
Peripheral nervous system:				
Dorsal root ganglion (C3-C6), 3x	T10	P10	P10	T10
Dorsal root fiber (C3-C6)	T10	P10	P10	T10
Ventral root fiber (C3-C6)	T10	P10	P10	T10
Dorsal root ganglion (L1-L4), 3x	T10	P10	P10	T10
Dorsal root fiber (L1-L4)	T10	P10	P10	T10
Ventral root fiber (L1-L4)	T10	P10	P10	T10
Proximal sciatic nerve	T10	P10	P10	T10
Proximal tibial nerve (at knee)	T10	P10	P10	T10
Distal tibial nerve (at lower leg)	T10	P10	P10	T10

T = Secondary fixation in 5% glutaraldehyde solution, plastic embedding (epoxy resin), semithin sectioning and staining with Azure II-Methylene blue-basic Fuchsin (AMbF).

P = Secondary fixation in 5% glutaraldehyde solution and storage of fixed specimen in buffer solution.

10 = All perfused animals per group and sex.

The following specimens from **dams and PND 22 and PND 62 offspring** were processed histotechnically according to the table below. The HE-stained sections were examined by light microscopy. The EPA commented on the registrant's protocol for developmental neurotoxicity study and recommended that they use a myelin stain, such as Luxol Fast Blue, in addition to H&E (November 4, 2004), since chlorphenapyr is known to cause myeloneuropathy in several species. The registrant on August 09, 2006 (Daniel J O'Byrne to Ann Sibold, Registration Division) by email informed the Agency that Luxol Fast Blue stain was not used since the study pathologist considered the stain was unnecessary. The note explained that neurological and neurohistomorphological evaluations did not justify using the special stains as there was no suggestive of hypomyelination or impact on the myelination gliosis, based on microscopic morphometry of the major brain areas, including white matter cords like corpus collosum which showed no significant difference compared to the controls. Furthermore, standard stains provided adequate sensitivity for detecting white matter effects evidenced by white matter changes in high dose pups on PD 22 which was not present following a 6-week recovery period in PD 62 animals.

Organ samples from:	Dose (mg/kg/day)			
	0	5	10	15
Brain (cross section):				
– Olfactory bulb	A10	B10	B10	A10
– Prosencephalon with frontal lobe	A10	B, C10	B, C10	A10
– Diencephalon with parietal lobe	A10	B, C, D10	B, C, D10	A10
– Mesencephalon with occipital lobe and temporal lobe	A10	B, C10	B, C10	A10
– Pons	A10	B, C10	B, C10	A10
– Cerebellum (2 planes of section)	A10	B, C10	B, C10	A10
– Medulla oblongata	A10	B, C10	B, C10	A10
Spinal cord (longitudinal and cross sections):				
– Cervical swelling I (C1-C3): C1)	A10	F10	F10	A10
– Cervical swelling II (C3-C5:C5)	A10	F10	F10	A10
– Thoracic cord (T5-T8: T8)	A10	F10	F10	A10
– Lumbar swelling (L1-L4: L4)	A10	F10	F10	A10
Brain-associated organs/tissues:				
– Eyes with retina and optical nerve	A10	F10	F10	A10
– Pituitary gland	A10	F10	F10	A10
– Olfactory epithelium (nose cavity, level III)	A10	F10	F10	A10
Peripheral nervous system				
– Gasserian ganglia with nerve	A10	F10	F10	A10
– Gastrocnemius muscle (longitudinal and cross sections)	A10	F10	F10	A10

A = Paraplast embedding, sectioning and staining with hematoxylin-eosin (HE).

B = Paraplast embedding

C = Paraplast embedding, sectioning and staining with hematoxylin-eosin (HE) – male and female animals of PND 22 subset only.

D = Sectioning and staining with hematoxylin-eosin (HE) – female animals of PD 62 subset only.

F = Preservation in neutrally buffered, 4% formaldehyde solution.

10 = All perfused animals per group and sex.

Morphometry of major brain areas was performed on the control and high dose groups of offspring sacrificed on PNDs 22 and 62. Due to significant findings in the left and right hippocampus of the high dose females on PND 62, linear measurements of this organ were taken in the low and intermediate dose groups of females. The following thickness measurements were made:

Neocortex (frontal and parietal cortices): The width of the total cortical mantle (layers I-VI from the surface of the pia mater to the white substance) was measured vertically to a tangent over a region of the frontal and parietal cortices determined beforehand.

Caudate nucleus/putamen: The largest lateral extension of the left and right part was determined.

Corpus collosum: The width was measured at the middle line of the cross section.

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Hippocampus: The largest dorsoventral extension was measured.

Cerebellum: The width of a select folium (e.g. folium pyramis) was measured in the middle of a line which runs vertically to a tangent from the tip to the base of the folium.

D. DATA ANALYSIS:

1. **Statistical analyses:** The following parameters were analyzed using the Dunnett test (two-sided) for the hypothesis of equal means: food consumption (dams), body weight and body weight change (dams and pups; for the pup weights, the litter means were used), duration of gestation, number of pups delivered per litter, duration of sexual maturation (days to preputial separation, days to vaginal opening).

The following parameters were analyzed using the Fisher's Exact test of the hypothesis of equal proportions: female fertility index, gestation index, females with liveborn pups, females with stillborn pups, females with all stillborn pups, live birth index, pups stillborn, pups died, pups cannibalized, pups sacrificed moribund, water maze evaluation and sexual maturation data (preputial separation and vaginal opening).

Water maze evaluation, motor activity and startle response data were evaluated by a non-parametric one-way analysis using Kruskal-Wallis test (two-sided). If the resulting p-value was equal to or less than 0.05, a pairwise comparison of each dose group with the control group was performed using the Wilcoxon test (two-sided) for the hypothesis of equal medians.

For the neuropathology data, weight parameters were analyzed as described in the paragraph above. The morphometric parameters were analyzed by a pairwise comparison of each dose group with the control group using the Wilcoxon test (one-sided) for the hypothesis of equal medians.

2. Indices:

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

$$\text{Female fertility index (\%)} = \frac{\text{number of females pregnant}^*}{\text{number of females mated}^{**}} \times 100$$

* defined as the number of females that gave birth to a litter or with implants *in utero*

** defined as the number of females with vaginal sperm or that gave birth to a litter or with implants *in utero*

$$\text{Gestation index (\%)} = \frac{\text{number of females with live pups on the day of birth}}{\text{number of females pregnant}^*} \times 100$$

* defined as the number of females that gave birth to a litter or with implants *in utero*

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

$$\text{Live birth index (\%)} = \frac{\text{number of liveborn pups at birth}}{\text{total number of pups born}} \times 100$$

3. **Positive and historical control data:** Positive control data on methylazoxy methanol acetate (MRID 46210605) were submitted to demonstrate positive findings and the ability of laboratory to identify such changes. The positive control data was generated during November of 2003 and is under review. Historical control data for motor activity and auditory startle response were included with the study report.

II. RESULTS:

A. PARENTAL ANIMALS:

1. **Mortality and clinical and functional observations:** No deaths or clinical signs of toxicity were reported in dams during gestation and lactation. No treatment-related effects were observed during the open field observations on GDs 7 and 14 or on LDs 7 and 14.
2. **Body weight and food consumption:** Selected group mean body weights and food consumption values for pregnant and nursing dams were summarized in Table 2. No treatment-related changes in body weight or food consumption were observed.

TABLE 2. Mean (\pm SD) maternal body weight and food consumption ^a				
Observations/study week	Dose (mg/kg/day)			
	0	5	10	15
Gestation				
Mean body weight (g) Gestation day 0	161.9 \pm 9.6	161.1 \pm 10.6	164.4 \pm 11.2	162.0 \pm 10.1
Mean body weight (g) Gestation day 6	191.5 \pm 10.5	189.9 \pm 11.9	193.7 \pm 12.6	191.8 \pm 11.6
Mean body weight (g) Gestation day 20	273.3 \pm 19.4	269.7 \pm 16.7	278.1 \pm 18.9	275.1 \pm 18.2
Mean weight gain (g) Gestation days 6-20	81.8 \pm 11.9	79.8 \pm 7.7	84.4 \pm 9.4	83.3 \pm 10.0
Mean food consumption (g/animal/day) ^b Gestation days 6-20	19.5 \pm 1.3	19.7 \pm 1.0	20.1 \pm 1.2	20.1 \pm 1.3
Lactation				
Mean body weight (g) Lactation day 0	218.8 \pm 13.7	213.6 \pm 13.3	219.0 \pm 17.9	218.9 \pm 14.6
Mean body weight (g) Lactation day 21	247.9 \pm 13.7	242.4 \pm 17.7	251.1 \pm 19.3	248.1 \pm 16.6
Mean weight gain (g) Lactation days 1-21	35.5 \pm 8.0	30.2 \pm 12.0	36.0 \pm 8.7	34.7 \pm 9.7
Mean food consumption (g/animal/day) ^b Lactation days 1-21	45.1 \pm 11.9	45.5 \pm 11.9	46.1 \pm 12.3	46.1 \pm 12.6

^a Data obtained from pages 104-113, MRID 46740201.

^b Calculated as mean of means

N = 22-30

3. **Reproductive performance:** Table 3 presents reproductive performance of maternal animals. Of the 40 females/group, two of the control group, four at 5 mg/kg/day, two at 10 mg/kg/day and one at 15 mg/kg/day were not pregnant. The fertility index was 95%, 90%, 95% and 98% in the control, low-dose, mid-dose and high-dose groups, respectively. The mean duration of gestation was 21.5, 21.7, 21.5 and 21.6 days for the respective groups. One control female was euthanized because she was unable to deliver. The gestation index was 97% in the control group and 100% in each of the treated groups. Two dams at 15 mg/kg/day had no pups alive during lactation; one dam had one pup which died one day after delivery and the other cannibalized its eight pups on LD 1. Six male and one female offspring from different litters at 10 mg/kg/day were cannibalized.

TABLE 3. Reproductive performance ^a				
Observation	Dose (mg/kg/day)			
	0	5	10	15
Number mated	40	40	40	40
Number of litters	37	36	38	39
Intercurrent deaths	1 ^b	0	0	0
Fertility index (%)	95	90	95	98
Gestation index (%)	97	100	100	100
Mean (VSD) gestation duration (days)	21.5 ± 0.6	21.7 ± 0.5	21.5 ± 0.6	21.6 ± 0.6
Incidence of dystocia	1	0	0	0

^a Data obtained from page 114, MRID 46740201.

^b Dam sacrificed due to dystocia.

4. **Maternal postmortem results:** No treatment-related changes were observed in absolute and relative brain weight, length and width of the cerebrum and cerebellum, gross lesions or histopathology. Brain weight and measurement data are presented in Table 4.

TABLE 4. Mean (±SD) brain weight and measurement data in dams ^a				
Parameter	Dose (mg/kg/day)			
	0	5	10	15
Terminal body weight (g)	246.74 ± 17.49	246.61 ± 12.93	251.20 ± 13.98	251.80 ± 13.23
Brain weight (g)	1.89 ± 0.08	1.87 ± 0.10	1.87 ± 0.05	1.85 ± 0.04
Brain-to-body weight ratio (%)	0.77 ± 0.04	0.76 ± 0.03	0.75 ± 0.04	0.74 ± 0.04
Cerebrum				
– Length (cm)	1.45 ± 0.03	1.43 ± 0.04	1.48 ± 0.03	1.44 ± 0.04
– Width (cm)	1.48 ± 0.03	1.48 ± 0.04	1.50 ± 0.03	1.47 ± 0.03
Cerebellum				
– Length (cm)	0.66 ± 0.03	0.69 ± 0.04	0.67 ± 0.04	0.65 ± 0.04
– Width (cm)	1.18 ± 0.03	1.19 ± 0.02	1.20 ± 0.03	1.18 ± 0.03

^a Data obtained from pages 300-301 and 324, MRID 46740201.
N = 10

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B. OFFSPRING:

1. **Viability and clinical signs:** Litter size and viability (survival) results from pups during lactation are summarized in Table 5. The mean number of delivered pups per dam and the percentage of liveborn and stillborn pups were not affected by treatment. There was no treatment-related effect on sex ratio on the day of birth or PND 21. The number of cannibalized pups was significantly increased at 10 and 15 mg/kg/day. The offspring cannibalized at 10 mg/kg/day were single individuals from different litters. In contrast at 15 mg/kg/day, two dams cannibalized all or most of their litter by PND 2. The total number of pups at 10 and 15 mg/kg/day that died or were cannibalized was increased during PNDs 1-4 (2, 2, 7 and 22 in the 0, 5, 10 and 15 mg/kg/day groups, respectively) but the increase was not statistically significant. No treatment-related clinical signs of toxicity were observed in the surviving pups during lactation.

TABLE 5. Litter size and viability ^a				
Observation	Dose (mg/kg/day)			
	0	5	10	15
Number of Litters	37	36	38	39
Total number born	320	299	323	349
Number born live	318	296	321	344
Number born dead	2	3	2	5
Number cannibalized	1	1	7*	13**
Sex Ratio Day 0 (% %)	47.2	48.0	49.2	55.2
# Deaths Days 1-4 (%)	2 (0.6)	2 (0.7)	7 (2.2)	22 (6.4)
# Deaths Days 5-7 (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
# Deaths Days 8-14 (%)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
# Deaths Days 15-21 (%)	3 (0.9)	2 (0.7)	2 (0.6)	0 (0.0)
Mean litter size ^c				
Day 0	8.6 ± 2.0	8.2 ± 1.6	8.4 ± 2.1	8.8 ± 1.9
Day 4 ^b	7.5 ± 3.8	6.7 ± 4.0	6.9 ± 4.0	7.4 ± 3.7
Day 4 ^c	6.3 ± 3.3	5.5 ± 3.7	5.5 ± 3.8	5.9 ± 3.5
Day 7	6.3 ± 3.3	4.9 ± 3.9	5.1 ± 3.9	5.1 ± 3.9
Day 14	6.3 ± 3.3	4.9 ± 3.9	5.0 ± 3.9	5.1 ± 3.9
Day 21	6.1 ± 3.3	4.7 ± 3.8	5.0 ± 3.9	5.1 ± 3.9
Live birth index	99	99	99	99

^a Data obtained from pages 114-117, MRID 46740201.

^b Before standardization (culling).

^c After standardization (culling).

* Statistically different from control, p<0.05

** Statistically different from control, p<0.01

2. **Body weight:** No treatment-related effects on offspring body weight during lactation were observed. Selected mean preweaning pup body weight data are presented in Table 6.

TABLE 6. Mean (\pm SD) pre-weaning pup body weights (g) ^a								
Postnatal day	Dose (mg/kg/day)							
	0	5	10	15	0	5	10	15
Number of pups	29	25	26	29	29	25	26	29
1	6.4 \pm 0.5	6.5 \pm 0.6	6.2 \pm 0.7	6.2 \pm 0.5	6.1 \pm 0.5	6.1 \pm 0.5	5.9 \pm 0.7	6.0 \pm 0.5
4 b	9.8 \pm 0.9	10.2 \pm 1.2	9.6 \pm 1.3	9.6 \pm 0.9	9.5 \pm 0.9	9.7 \pm 1.1	9.3 \pm 1.3	9.4 \pm 1.0
4 c	9.9 \pm 0.9	10.2 \pm 1.2	9.6 \pm 1.2	9.6 \pm 0.9	9.5 \pm 0.9	9.7 \pm 1.1	9.3 \pm 1.3	9.5 \pm 1.0
11	23.4 \pm 1.8	23.4 \pm 2.2	22.8 \pm 2.4	22.3 \pm 1.9	22.5 \pm 1.8	22.6 \pm 2.3	22.3 \pm 2.4	21.8 \pm 1.9
17	35.7 \pm 2.4	35.5 \pm 3.1	35.4 \pm 3.2	34.7 \pm 2.1	34.8 \pm 2.3	34.2 \pm 3.7	34.7 \pm 2.9	33.7 \pm 2.3
21	46.3 \pm 3.1	46.7 \pm 4.2	45.7 \pm 4.1	45.7 \pm 3.3	44.8 \pm 2.8	44.9 \pm 4.7	44.9 \pm 3.7	44.1 \pm 3.3

^a Data obtained from pages 118-122, MRID 46740201.

^b Before standardization (culling).

^c After standardization (culling).

Offspring postweaning body weight was measured in Subsets II, III and IV. No treatment-related effects were observed in any of the subsets. Selected mean postweaning offspring body weight data are presented in Table 7.

TABLE 7. Mean (\pm SD) post-weaning pup body weight (g) ^a								
Postnatal week	Dose (mg/kg/day)							
	0	5	10	15	0	5	10	15
Subset II								
Week 4	232.1 \pm 17.4	226.0 \pm 20.5	221.2 \pm 20.9	225.3 \pm 15.2	158.6 \pm 13.9	152.2 \pm 10.7	159.4 \pm 14.2	161.9 \pm 9.3
Week 5	276.3 \pm 15.9	268.7 \pm 24.1	261.8 \pm 25.7	265.7 \pm 15.7	171.0 \pm 18.5	167.8 \pm 12.9	172.9 \pm 16.6	177.3 \pm 11.4
Subset III								
Week 4	227.9 \pm 9.5	220.7 \pm 20.8	223.2 \pm 11.5	220.2 \pm 17.2	159.8 \pm 11.9	157.3 \pm 11.4	155.0 \pm 11.6	161.4 \pm 6.1
Week 5	268.6 \pm 10.6	256.3 \pm 24.9	264.5 \pm 14.8	260.6 \pm 19.0	176.5 \pm 13.8	172.0 \pm 12.0	171.4 \pm 14.1	177.5 \pm 5.9
Week 12	385.7 \pm 23.4	368.1 \pm 32.6	385.0 \pm 32.4	382.3 \pm 19.9	226.6 \pm 13.1	223.5 \pm 21.0	220.7 \pm 17.1	233.1 \pm 12.8
Subset IV								
Week 4	217.5 \pm 11.4	217.9 \pm 19.9	222.3 \pm 17.1	221.7 \pm 12.3	155.3 \pm 9.2	150.1 \pm 11.8	151.5 \pm 11.6	152.6 \pm 6.6
Week 5	255.3 \pm 14.2	256.6 \pm 24.8	261.9 \pm 20.8	260.4 \pm 13.9	168.5 \pm 11.9	164.0 \pm 13.4	168.2 \pm 12.8	167.3 \pm 9.8

^a Data obtained from pages 140-153 in the study report.

N = 10

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3. Developmental landmarks/Sexual maturation: No treatment-related effects on vaginal opening or balanopreputial separation were observed. The mean number of days to reach vaginal opening was 33.3, 32.9, 32.8 and 32.7 days for the 0, 5, 10 and 15 mg/kg/day female groups, respectively. The mean number of days to balanopreputial separation was 43.8, 43.5, 44.0 and 43.3 days for the respective male groups. Mean body weight on the day criteria were reached was similar in the control and treated groups. The data are presented in Table 8. No other measures of developmental landmarks were reported.

TABLE 8. Mean (\pm SD) age and body weight at sexual maturation ^a				
Parameter	Dose (mg/kg/day)			
	0	5	10	15
N (M/F)	40/40	40/40	39/39	40/39
Males				
Preputial separation (days)	43.8 \pm 1.6	43.5 \pm 1.4	44.0 \pm 1.3	43.3 \pm 1.4
Body weight (g)	184.2 \pm 13.2	180.3 \pm 11.6	180.6 \pm 12.0	179.8 \pm 10.4
Females				
Vaginal opening (days)	33.3 \pm 2.1	32.9 \pm 2.1	32.8 \pm 2.4	32.7 \pm 2.7
Body weight (g)	102.2 \pm 10.4	98.0 \pm 8.4	98.7 \pm 11.1	98.9 \pm 11.7

^a Data obtained from pages 128-129, MRID 46740201.

4. Behavioral assessments:

- a. **Functional observational battery:** No treatment-related findings were observed in the Subset IV animals.
- b. **Motor activity:** Total movement activity data are presented in Table 9a. A dose-related decrease in total movement on PND 13 was observed in males and females; the decrease (53% of control value) was statistically significant in females at 15 mg/kg/day. No treatment-related effects were observed on total movement on PNDs 17, 21 or 60. During the sub-sessions on PND 13, the distance moved was lower in males and females at 15 mg/kg/day but significance was achieved at only one interval in each sex. Other significant changes during the sub-sessions were incidental since they were sporadic and not dose-related. Sub-session data are presented in Table 9b (males) and 9c (females). Habituation was clearly demonstrated in treated and control animals of both sexes by PND 17.

No treatment-related effects on the total number of rearings were observed. Data are presented in Table 9d. Significant changes during the sub-sessions are considered incidental since they were sporadic and not dose-related. Sub-session data are included in Tables 9e (males) and 9f (females). Habituation was demonstrated in treated and control animals of both sexes on all testing days.

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TABLE 9a. Mean (\pm S.D.) motor activity data [total movement distance (cm) per session] ^a				
Test Day	Dose (mg/kg/day)			
	0	5	10	15
Males				
PND 13	4090.7 \pm 3097.1	4777.3 \pm 6113.5	3228.9 \pm 2108.5 (79)	2944.1 \pm 1556.4 (72) ^b
PND 17	5473.9 \pm 3503.7	6779.1 \pm 4485.6	7617.9 \pm 4250.7	5388.6 \pm 3116.7
PND 21	3722.0 \pm 2180.3	2472.1 \pm 750.5	3535.8 \pm 933.4	3258.1 \pm 1657.0
PND 60	8138.4 \pm 766.9	7601.4 \pm 2061.1	6845.0 \pm 1628.5	7238.5 \pm 1516.1
Females				
PND 13	4321.3 \pm 2133.8	3369.8 \pm 1529.2	2761.3 \pm 1546.4 (64)	2272.5* \pm 1559.8 (53)
PND 17	6801.0 \pm 4703.4	5046.8 \pm 2435.0	7268.9 \pm 3985.3	6142.8 \pm 3895.7
PND 21	3644.7 \pm 1547.8	3340.3 \pm 973.1	3573.3 \pm 1569.8	2857.5 \pm 1180.2
PND 60	10154.0 \pm 1977.8	7906.0 \pm 1463.6	9075.4 \pm 1565.0	8506.3 \pm 1442.0

^a Data obtained from pages 236-251, MRID 46740201.

^b Number in parentheses is percent of control; calculated by reviewer.

N = 10

* Statistically different from control, $p < 0.05$

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TABLE 9b. Motor activity sub-sessions - males [mean movement distance (cm) \pm S.D.] ^a					
Sub-session		Dose (mg/kg/day)			
		0	5	10	15
PND 13	1	343.6 \pm 296.8	428.9 \pm 333.5	410.3 \pm 215.5	385.6 \pm 109.8
	2	429.1 \pm 380.2	513.0 \pm 636.3	342.4 \pm 211.4	284.2 \pm 242.0
	3	428.2 \pm 599.0	494.1 \pm 649.4	208.6 \pm 127.0	332.1 \pm 299.6
	4	458.9 \pm 458.5	337.9 \pm 413.5	195.8 \pm 185.2	353.9 \pm 320.9
	5	404.3 \pm 484.6	519.8 \pm 692.8	288.6 \pm 272.6	329.0 \pm 337.5
	6	501.9 \pm 435.6	216.4 \pm 211.1	449.5 \pm 434.3	288.3 \pm 232.2
	7	461.6 \pm 493.8	278.8 \pm 445.8	284.9 \pm 382.7	226.9 \pm 285.3
	8	363.1 \pm 332.3	393.2 \pm 575.0	311.4 \pm 355.2	59.9** \pm 60.4
	9	161.5 \pm 113.1	548.6 \pm 738.3	223.2 \pm 240.0	91.9 \pm 87.8
	10	89.6 \pm 64.1	413.8 \pm 652.5	193.0 \pm 236.7	136.4 \pm 157.4
	11	188.9 \pm 275.7	360.3 \pm 695.6	165.7 \pm 167.5	280.3 \pm 353.6
	12	259.9 \pm 494.4	272.6 \pm 548.4	155.8 \pm 122.3	175.6 \pm 247.8
PND 17	1	893.7 \pm 539.6	978.7 \pm 521.8	785.8 \pm 234.3	761.6 \pm 408.3
	2	724.6 \pm 365.1	968.7 \pm 487.7	933.3 \pm 436.3	672.6 \pm 356.6
	3	443.3 \pm 448.2	862.8 \pm 538.2	669.3 \pm 287.1	511.5 \pm 315.4
	4	407.5 \pm 486.5	631.7 \pm 448.7	773.3 \pm 500.6	594.5 \pm 380.8
	5	252.1 \pm 303.3	617.4 \pm 521.5	623.5 \pm 505.9	346.3 \pm 308.3
	6	222.7 \pm 256.2	428.1 \pm 482.0	355.8 \pm 323.9	307.0 \pm 410.4
	7	250.5 \pm 489.3	432.0 \pm 426.6	525.5 \pm 462.8	297.9 \pm 354.0
	8	356.7 \pm 510.6	468.7 \pm 500.6	589.2 \pm 617.3	362.3 \pm 367.3
	9	510.7 \pm 515.8	248.8 \pm 253.5	847.4 \pm 715.5	418.6 \pm 532.7
	10	477.1 \pm 433.3	159.9* \pm 281.6	570.6 \pm 441.6	302.8 \pm 343.1
	11	550.4 \pm 549.7	370.5 \pm 479.6	418.2 \pm 510.4	370.4 \pm 393.6
	12	384.6 \pm 368.4	611.8 \pm 748.3	525.8 \pm 608.0	443.1 \pm 448.5
PND 21	1	1024.1 \pm 326.9	938.8 \pm 195.3	1106.9 \pm 137.8	1068.9 \pm 353.0
	2	505.6 \pm 290.3	464.6 \pm 229.1	561.8 \pm 120.5	527.8 \pm 219.0
	3	397.0 \pm 216.6	274.0 \pm 180.0	488.6 \pm 201.5	240.8 \pm 242.0
	4	353.6 \pm 264.9	159.8 \pm 168.6	164.3 \pm 133.1	168.6 \pm 188.3
	5	228.2 \pm 234.2	123.1 \pm 139.0	370.0 \pm 250.2	228.0 \pm 216.8
	6	216.9 \pm 295.4	106.1 \pm 164.4	295.3 \pm 323.2	189.2 \pm 191.5
	7	90.6 \pm 130.9	75.6 \pm 110.3	106.7 \pm 136.0	103.9 \pm 191.3
	8	124.3 \pm 177.0	94.7 \pm 168.9	74.1 \pm 86.4	70.6 \pm 163.5
	9	278.9 \pm 389.7	63.1 \pm 133.3	127.7 \pm 177.8	133.6 \pm 195.6
	10	199.3 \pm 245.7	61.9 \pm 123.0	124.1 \pm 219.6	165.7 \pm 243.4
	11	171.3 \pm 209.0	40.2 \pm 55.1	73.9 \pm 107.4	215.0 \pm 270.5
	12	132.1 \pm 169.6	70.3 \pm 101.8	42.3 \pm 37.5	146.0 \pm 184.6
PND 60	1	1262.6 \pm 145.1	1209.2 \pm 193.4	1277.0 \pm 173.0	1273.4 \pm 194.5
	2	1034.6 \pm 167.3	1037.4 \pm 248.4	1019.4 \pm 146.4	1041.4 \pm 194.2
	3	916.2 \pm 148.9	890.7 \pm 235.5	759.3 \pm 312.1	904.4 \pm 184.6
	4	823.4 \pm 103.4	779.6 \pm 171.8	614.2 \pm 191.9	797.6 \pm 246.4
	5	767.4 \pm 91.9	650.2 \pm 223.3	615.7 \pm 205.6	618.0 \pm 178.0
	6	684.2 \pm 293.5	634.8 \pm 276.8	523.8 \pm 219.0	564.6 \pm 137.0
	7	627.6 \pm 238.5	566.3 \pm 167.4	527.8 \pm 166.9	541.0 \pm 201.7
	8	521.9 \pm 217.8	542.5 \pm 353.0	399.4 \pm 207.5	448.7 \pm 226.6
	9	431.7 \pm 245.8	345.3 \pm 267.4	394.5 \pm 323.5	469.2 \pm 297.2
	10	448.9 \pm 226.4	308.4 \pm 302.4	371.9 \pm 241.2	302.6 \pm 218.1
	11	373.4 \pm 216.3	360.0 \pm 389.7	162.4 \pm 202.7	147.4 \pm 137.7
	12	246.6 \pm 198.6	277.2 \pm 251.2	179.8 \pm 264.5	130.4 \pm 217.7

^a Data obtained from pages 236-243, MRJD 46470201.
N = 9-10

* Statistically different from control, $p < 0.05$

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TABLE 9c. Motor activity sub-sessions - females [mean movement distance (cm) \pm S.D.] ^a					
Sub-session		Dose (mg/kg/day)			
		0	5	10	15
PND 13	1	449.1 \pm 178.2	352.0 \pm 119.2	366.3 \pm 161.7	294.9 \pm 122.0
	2	365.0 \pm 264.6	234.5 \pm 134.3	242.6 \pm 170.5	232.9 \pm 226.8
	3	444.1 \pm 341.0	255.4 \pm 173.2	300.3 \pm 249.5	281.1 \pm 304.1
	4	557.4 \pm 307.8	270.7* \pm 196.7	341.9 \pm 226.5	163.2** \pm 126.5
	5	461.8 \pm 403.1	330.8 \pm 303.6	263.9 \pm 254.7	254.7 \pm 372.1
	6	471.5 \pm 463.3	340.5 \pm 322.5	280.7 \pm 233.2	259.8 \pm 330.7
	7	420.0 \pm 425.0	195.5 \pm 170.3	214.0 \pm 165.8	206.2 \pm 212.9
	8	220.5 \pm 222.8	360.0 \pm 515.0	202.9 \pm 225.5	78.5 \pm 61.4
	9	248.3 \pm 367.0	332.9 \pm 461.9	129.6 \pm 176.6	133.9 \pm 168.3
	10	228.9 \pm 305.6	184.9 \pm 225.1	131.8 \pm 131.2	82.2 \pm 55.9
	11	255.7 \pm 312.9	206.4 \pm 221.8	128.8 \pm 156.7	142.1 \pm 165.3
	12	199.2 \pm 221.8	306.4 \pm 426.0	158.6 \pm 307.1	143.0 \pm 174.8
PND 17	1	1068.9 \pm 427.8	948.5 \pm 412.4	947.4 \pm 393.0	836.7 \pm 354.7
	2	863.4 \pm 505.8	725.8 \pm 469.8	880.8 \pm 400.6	773.0 \pm 311.5
	3	655.4 \pm 618.0	648.5 \pm 257.6	786.8 \pm 447.4	681.0 \pm 530.1
	4	500.8 \pm 351.1	389.9 \pm 603.3	596.4 \pm 501.0	567.8 \pm 402.1
	5	522.3 \pm 539.9	367.0 \pm 312.9	589.7 \pm 511.5	539.7 \pm 406.3
	6	444.6 \pm 457.9	274.7 \pm 291.2	710.9 \pm 487.6	411.2 \pm 357.7
	7	361.2 \pm 391.5	106.6* \pm 173.5	448.0 \pm 421.2	331.1 \pm 379.8
	8	404.7 \pm 608.8	266.7 \pm 398.5	460.2 \pm 456.3	279.9 \pm 407.4
	9	548.5 \pm 574.2	279.1 \pm 310.3	509.8 \pm 511.2	457.7 \pm 546.5
	10	505.1 \pm 596.1	390.4 \pm 436.2	506.2 \pm 541.5	494.9 \pm 533.3
	11	510.0 \pm 540.9	391.7 \pm 417.8	393.1 \pm 411.1	317.6 \pm 515.8
	12	416.0 \pm 457.4	258.1 \pm 314.1	439.8 \pm 450.5	452.3 \pm 554.8
PND 21	1	1177.5 \pm 241.0	1183.9 \pm 214.1	1121.3 \pm 298.3	1122.0 \pm 242.9
	2	541.0 \pm 188.4	557.9 \pm 131.6	545.0 \pm 121.6	444.9 \pm 299.0
	3	380.5 \pm 194.6	382.0 \pm 179.7	255.9 \pm 207.7	154.0** \pm 166.1
	4	247.0 \pm 171.7	302.8 \pm 202.9	162.2 \pm 182.3	219.4 \pm 302.3
	5	272.2 \pm 272.8	210.2 \pm 196.9	200.9 \pm 274.8	97.7 \pm 183.9
	6	202.0 \pm 217.8	135.2 \pm 201.0	182.0 \pm 259.9	67.0 \pm 87.9
	7	105.1 \pm 151.7	56.2 \pm 106.5	186.6 \pm 220.7	47.6 \pm 62.4
	8	84.5 \pm 65.7	144.3 \pm 263.5	155.2 \pm 186.6	134.5 \pm 178.4
	9	92.7 \pm 167.1	80.0 \pm 123.1	213.3 \pm 248.4	141.4 \pm 208.6
	10	200.0 \pm 348.1	38.5 \pm 23.6	216.5 \pm 212.9	74.7 \pm 119.9
	11	139.7 \pm 269.5	102.1 \pm 122.0	157.2 \pm 165.0	151.4 \pm 222.4
	12	202.5 \pm 298.3	147.4 \pm 213.3	177.3 \pm 228.6	202.9 \pm 272.2
PND 60	1	1364.6 \pm 256.5	1290.5 \pm 265.3	1453.8 \pm 177.5	1443.1 \pm 192.9
	2	1137.9 \pm 255.1	1079.0 \pm 177.3	1209.8 \pm 185.6	1200.2 \pm 209.4
	3	1131.2 \pm 311.3	922.9 \pm 187.9	1007.1 \pm 221.8	1061.9 \pm 319.2
	4	937.2 \pm 346.5	818.9 \pm 219.2	881.1 \pm 201.3	973.4 \pm 241.2
	5	992.3 \pm 303.9	768.8 \pm 287.1	654.6 \pm 270.1	830.6 \pm 322.4
	6	930.1 \pm 250.7	575.3* \pm 213.6	705.1 \pm 316.5	790.2 \pm 178.8
	7	730.9 \pm 309.9	488.6 \pm 304.4	662.7 \pm 222.7	621.9 \pm 185.9
	8	602.7 \pm 422.0	297.7 \pm 318.9	521.8 \pm 226.9	491.8 \pm 331.1
	9	736.8 \pm 270.4	298.9** \pm 290.0	521.6 \pm 196.3	310.5** \pm 316.1
	10	535.5 \pm 291.1	510.6 \pm 429.7	542.2 \pm 263.7	159.1** \pm 234.9
	11	538.2 \pm 361.7	486.8 \pm 383.8	509.7 \pm 221.8	192.6* \pm 237.0
	12	516.2 \pm 359.5	368.0 \pm 298.8	405.9 \pm 398.6	431.0 \pm 315.7

^a Data obtained from pages 244-251, MRID 46470201.

N = 10

* Statistically different from control, p<0.05.

** Statistically different from control, p<0.01.

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TABLE 9d. Motor activity data –mean (\pm S.D.) number of total rearings per session ^a				
Test Day	Dose (mg/kg/day)			
	0	5	10	15
Males				
PND 13	128.8 \pm 94.2	75.6 \pm 41.5	106.1 \pm 72.2	65.4 \pm 64.2
PND 17	201.4 \pm 119.3	218.2 \pm 113.4	277.8 \pm 101.6	193.9 \pm 142.2
PND 21	128.9 \pm 68.8	90.5 \pm 28.0	142.4 \pm 48.4	126.5 \pm 68.1
PND 60	205.3 \pm 24.6	165.7 \pm 47.8	158.4 \pm 48.0	173.0 \pm 45.0
Females				
PND 13	122.0 \pm 59.5	109.2 \pm 55.4	75.3 \pm 60.3	60.7 \pm 57.3
PND 17	181.0 \pm 65.8	181.5 \pm 83.1	235.8 \pm 141.2	202.7 \pm 92.6
PND 21	124.5 \pm 40.9	113.1 \pm 36.8	114.8 \pm 57.0	84.5 \pm 25.4
PND 60	261.2 \pm 69.9	193.7 \pm 41.3	219.1 \pm 38.6	233.0 \pm 65.2

^a Data obtained from pages 252-267, MRID 46470201.

N = 10

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TABLE 9e. Motor activity sub-sessions - males [mean number of rearings \pm S.D.]^a

Sub-session		Dose (mg/kg/day)			
		0	5	10	15
PND 13	1	19.2 \pm 10.8	9.5 \pm 8.7	17.8 \pm 13.9	11.5 \pm 6.7
	2	18.0 \pm 15.9	7.9 \pm 7.7	15.6 \pm 14.1	7.3 \pm 6.5
	3	8.4 \pm 10.0	8.1 \pm 8.0	9.0 \pm 8.3	7.2 \pm 9.6
	4	14.4 \pm 13.9	7.6 \pm 8.7	8.9 \pm 12.0	5.4 \pm 6.2
	5	10.7 \pm 15.3	6.0 \pm 5.7	9.6 \pm 8.4	6.7 \pm 10.3
	6	16.9 \pm 17.0	4.7 \pm 8.9	12.9 \pm 11.6	5.0 \pm 6.0
	7	13.7 \pm 12.4	5.3 \pm 9.7	5.8 \pm 6.8	5.6 \pm 10.1
	8	9.0 \pm 9.9	3.5 \pm 5.3	6.0 \pm 6.5	2.1 \pm 4.3
	9	4.9 \pm 5.0	10.6 \pm 12.9	9.5 \pm 11.3	1.8 \pm 2.8
	10	1.7 \pm 2.3	5.0 \pm 6.4	3.1 \pm 5.4	2.7 \pm 4.9
	11	4.6 \pm 9.6	5.2 \pm 10.2	3.0 \pm 4.1	5.4 \pm 7.8
	12	7.3 \pm 12.6	2.2 \pm 4.4	4.9 \pm 5.2	4.7 \pm 10.1
PND 17	1	33.8 \pm 16.8	33.9 \pm 8.1	35.3 \pm 11.7	31.2 \pm 11.2
	2	31.0 \pm 16.4	34.1 \pm 9.6	38.9 \pm 13.5	28.6 \pm 9.1
	3	16.1 \pm 15.9	28.6 \pm 17.5	31.0 \pm 10.7	22.0 \pm 12.0
	4	16.8 \pm 20.0	24.3 \pm 15.7	27.7 \pm 17.3	19.8 \pm 13.7
	5	9.1 \pm 13.9	17.6 \pm 15.5	23.5 \pm 18.5	12.6 \pm 15.0
	6	10.8 \pm 14.3	12.8 \pm 15.3	16.9 \pm 17.0	9.4 \pm 15.7
	7	7.8 \pm 11.5	15.0 \pm 15.3	15.8 \pm 16.2	7.0 \pm 10.7
	8	11.1 \pm 14.2	15.4 \pm 16.0	16.8 \pm 16.1	12.4 \pm 14.3
	9	17.9 \pm 17.0	10.9 \pm 12.0	21.9 \pm 15.5	11.2 \pm 15.9
	10	17.3 \pm 16.4	5.2 \pm 9.8	20.6 \pm 13.3	10.6 \pm 16.5
	11	16.6 \pm 16.9	8.0 \pm 12.4	12.1 \pm 14.9	11.6 \pm 16.3
	12	13.1 \pm 15.2	12.4 \pm 16.6	17.3 \pm 17.7	17.5 \pm 21.7
PND 21	1	40.0 \pm 13.6	36.2 \pm 8.9	49.0 \pm 8.7	42.0 \pm 14.3
	2	23.1 \pm 13.9	19.3 \pm 10.2	30.0 \pm 10.6	26.6 \pm 10.6
	3	17.5 \pm 10.8	13.6 \pm 8.3	18.9 \pm 11.7	10.2 \pm 12.6
	4	11.9 \pm 8.7	5.5 \pm 6.6	5.6 \pm 5.7	7.0 \pm 8.0
	5	8.0 \pm 7.9	4.4 \pm 5.3	14.0 \pm 11.7	10.8 \pm 11.7
	6	5.9 \pm 9.5	3.1 \pm 6.7	10.9 \pm 11.6	7.3 \pm 8.7
	7	2.5 \pm 4.8	1.6 \pm 3.1	2.3 \pm 3.0	4.0 \pm 8.7
	8	2.6 \pm 4.8	1.7 \pm 3.8	2.3 \pm 3.6	1.9 \pm 6.0
	9	7.2 \pm 13.0	1.9 \pm 5.7	3.4 \pm 5.3	3.4 \pm 6.4
	10	4.2 \pm 6.4	1.1 \pm 3.5	3.7 \pm 7.8	4.7 \pm 8.5
	11	3.3 \pm 4.7	0.4 \pm 1.3	1.8 \pm 3.6	5.0 \pm 7.7
	12	2.7 \pm 5.0	1.7 \pm 3.6	0.6 \pm 1.7	3.6 \pm 5.6
PND 60	1	34.4 \pm 5.3	28.9 \pm 6.1	30.5 \pm 4.3	33.7 \pm 8.4
	2	27.1 \pm 8.0	24.0 \pm 5.6	26.3 \pm 7.7	25.4 \pm 7.6
	3	22.2 \pm 5.2	21.2 \pm 6.6	18.6 \pm 7.1	22.6 \pm 7.3
	4	22.1 \pm 7.4	19.7 \pm 9.8	14.0 \pm 6.7	21.8 \pm 8.7
	5	20.5 \pm 4.6	14.2 \pm 5.6	16.9 \pm 9.1	14.2 \pm 6.1
	6	15.5 \pm 6.0	12.6 \pm 7.3	9.8 \pm 5.7	11.8 \pm 7.1
	7	16.0 \pm 9.0	11.0 \pm 4.2	12.3 \pm 4.1	11.7 \pm 5.9
	8	14.3 \pm 5.6	10.6 \pm 11.1	8.6 \pm 7.1	9.6 \pm 6.5
	9	9.5 \pm 6.6	6.7 \pm 6.3	8.8 \pm 7.7	10.6 \pm 8.0
	10	10.2 \pm 6.7	5.6 \pm 6.8	6.7 \pm 4.6	5.9 \pm 5.9
	11	8.2 \pm 5.7	6.7 \pm 8.8	2.7 \pm 5.5	2.2 \pm 3.2
	12	5.3 \pm 5.7	4.5 \pm 4.4	3.2 \pm 6.3	3.5 \pm 6.7

^a Data obtained from pages 252-259, MRID 46470201
N = 10

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TABLE 9f. Motor activity sub-sessions - females [mean number of rearings \pm S.D.] ^a					
Sub-session		Dose (mg/kg/day)			
		0	5	10	15
PND 13	1	18.4 \pm 12.1	17.5 \pm 12.9	14.1 \pm 11.5	7.0 \pm 5.0
	2	18.9 \pm 16.2	17.4 \pm 15.2	7.6 \pm 9.3	8.9 \pm 10.0
	3	16.7 \pm 10.1	13.8 \pm 14.6	10.7 \pm 13.6	5.9 \pm 5.7
	4	17.4 \pm 8.4	13.2 \pm 10.8	9.5 \pm 9.6	5.9** \pm 11.0
	5	10.7 \pm 10.2	9.6 \pm 6.3	7.7 \pm 9.4	5.9 \pm 8.1
	6	7.9 \pm 7.7	9.6 \pm 12.6	6.4 \pm 7.3	6.0 \pm 6.9
	7	10.3 \pm 9.6	5.6 \pm 5.2	5.0 \pm 5.7	7.9 \pm 11.3
	8	5.2 \pm 6.8	5.5 \pm 6.4	3.6 \pm 4.6	1.7 \pm 2.9
	9	4.4 \pm 6.8	7.5 \pm 11.2	2.5 \pm 3.6	3.7 \pm 7.8
	10	4.8 \pm 6.6	2.7 \pm 3.8	2.9 \pm 4.8	2.1 \pm 3.4
	11	3.8 \pm 4.7	3.6 \pm 5.0	3.0 \pm 4.9	3.5 \pm 4.7
	12	3.5 \pm 4.9	3.2 \pm 6.1	2.3 \pm 6.3	2.2 \pm 3.9
PND 17	1	36.4 \pm 8.8	36.9 \pm 13.4	31.4 \pm 11.4	34.6 \pm 7.0
	2	28.1 \pm 6.4	30.7 \pm 14.5	30.7 \pm 12.2	32.5 \pm 13.1
	3	18.2 \pm 15.0	26.2 \pm 9.6	26.8 \pm 17.3	26.3 \pm 18.5
	4	14.6 \pm 11.4	11.8 \pm 15.1	19.2 \pm 18.3	21.0 \pm 12.1
	5	15.1 \pm 13.1	14.5 \pm 16.2	19.3 \pm 14.8	21.0 \pm 16.9
	6	10.9 \pm 9.6	11.9 \pm 14.2	23.6 \pm 17.8	16.8 \pm 14.8
	7	10.5 \pm 11.5	4.0 \pm 9.4	17.5 \pm 19.2	10.3 \pm 10.7
	8	4.0 \pm 7.8	7.9 \pm 14.3	14.1 \pm 14.5	6.7 \pm 7.3
	9	9.9 \pm 9.2	8.4 \pm 9.6	14.4 \pm 14.1	7.9 \pm 10.4
	10	8.7 \pm 10.2	9.6 \pm 11.1	14.0 \pm 16.3	11.3 \pm 10.0
	11	15.7 \pm 17.0	11.0 \pm 12.0	11.6 \pm 12.9	6.4 \pm 11.4
	12	8.9 \pm 11.4	8.6 \pm 12.7	13.2 \pm 15.2	7.9 \pm 12.8
PND 21	1	45.8 \pm 12.3	42.5 \pm 10.3	37.0 \pm 9.3	38.4 \pm 10.9
	2	28.2 \pm 12.0	21.4 \pm 7.3	22.1 \pm 9.5	18.5 \pm 11.1
	3	13.1 \pm 8.0	17.4 \pm 9.5	9.3 \pm 7.4	4.9* \pm 5.9
	4	7.1 \pm 8.6	10.8 \pm 9.2	5.7 \pm 6.7	7.3 \pm 12.0
	5	8.5 \pm 7.5	6.5 \pm 6.5	6.3 \pm 10.5	1.6 \pm 4.1
	6	5.1 \pm 7.0	3.3 \pm 6.3	5.9 \pm 10.9	0.9 \pm 2.5
	7	2.1 \pm 3.6	0.5 \pm 1.3	4.3 \pm 6.2	0.5 \pm 1.6
	8	1.4 \pm 2.9	2.6 \pm 5.8	4.2 \pm 6.6	2.4 \pm 3.9
	9	1.1 \pm 2.5	1.3 \pm 4.1	6.8 \pm 10.4	3.0 \pm 5.1
	10	4.4 \pm 10.4	0.1 \pm 0.3	5.9 \pm 7.0	0.6 \pm 1.3
	11	2.6 \pm 5.3	3.0 \pm 5.8	3.9 \pm 6.5	2.7 \pm 6.2
	12	5.1 \pm 9.0	3.7 \pm 6.4	3.4 \pm 4.3	3.7 \pm 6.6
PND 60	1	45.3 \pm 9.9	36.5 \pm 6.4	38.8 \pm 6.6	39.4 \pm 7.4
	2	31.9 \pm 6.6	31.3 \pm 9.6	30.9 \pm 7.8	35.4 \pm 13.0
	3	34.5 \pm 7.8	24.2 \pm 7.2	27.7 \pm 8.2	31.6 \pm 14.1
	4	26.0 \pm 9.9	19.8 \pm 9.5	23.5 \pm 7.1	30.7 \pm 10.9
	5	24.4 \pm 10.3	20.3 \pm 12.7	19.4 \pm 8.0	24.3 \pm 11.0
	6	22.1 \pm 11.6	10.2** \pm 5.2	18.4 \pm 10.3	23.0 \pm 9.0
	7	17.3 \pm 8.7	11.4 \pm 9.8	13.9 \pm 5.3	15.3 \pm 8.9
	8	12.5 \pm 12.2	5.9 \pm 8.1	10.9 \pm 6.1	11.3 \pm 10.5
	9	17.3 \pm 9.1	7.7* \pm 9.6	10.6 \pm 6.8	6.8* \pm 9.3
	10	10.6 \pm 7.0	10.4 \pm 9.5	10.0 \pm 8.1	4.1 \pm 7.4
	11	10.4 \pm 10.2	8.7 \pm 7.0	8.0 \pm 6.9	3.7 \pm 5.7
	12	8.9 \pm 9.3	7.3 \pm 9.9	7.0 \pm 8.3	7.4 \pm 6.7

^a Data obtained from pages 260-267, MRID 46470201

N = 10

* Statistically different from control, p<0.05

** Statistically different from control, p<0.01

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- c. **Auditory startle reflex habituation:** The overall amplitude and latency data are presented in Table 10a. On PND 24, a significant increase in latency was observed in males at 15 mg/kg/day but there was no dose response. Interval amplitude and latency data are included in Tables 10b (males) and 10c (females). The only significant change in latency interval data was an increase in block 2 in high-dose males on PND 24; however, the values at all intervals were higher than control values resulting in an overall increase. No treatment-related changes were observed on PND 60. Habituation was apparent in control and treated animals on both testing days but was more pronounced on PND 60.

TABLE 10a. Mean (\pm SD) overall (Blocks 1-5) acoustic startle peak amplitude (g) and latency to peak (msec) ^a					
Dose (mg/kg/day)	Parameter	Males		Females	
		PND 24	PND 60	PND 24	PND 60
0	Peak Amp.	345.3 \pm 178.3	1918.8 \pm 771.5	442.3 \pm 250.5	1455.9 \pm 828.2
	Latency	25.9 \pm 6.6	32.8 \pm 5.4	31.1 \pm 7.7	34.2 \pm 10.3
5	Peak Amp.	444.7 \pm 171.5	1781.4 \pm 805.6	349.4 \pm 226.7	1026.9 \pm 349.9
	Latency	29.3 \pm 8.3	34.7 \pm 6.6	23.3 \pm 7.4	28.0 \pm 4.5
10	Peak Amp.	285.1 \pm 96.1	1409.8 \pm 779.1	458.4 \pm 202.8	1323.9 \pm 672.5
	Latency	24.6 \pm 3.6	31.2 \pm 5.1	30.4 \pm 8.2	29.6 \pm 7.9
15	Peak Amp.	562.8 \pm 456.4	2044.6 \pm 1118.5	421.5 \pm 148.4	1765.3 \pm 996.2
	Latency	33.6* \pm 7.8	36.8 \pm 9.8	28.9 \pm 7.7	31.9 \pm 8.1

^a Data were obtained from pages 268-275, MRID 46740201.

n= 9-10

* Significantly different from controls at p#0.05

TABLE 10b. Mean (\pm SD) interval acoustic startle peak amplitude (g) and latency to peak (msec) in F ₁ male rats ^a						
Dose (mg/kg/day)	Parameter	Block 1	Block 2	Block 3	Block 4	Block 5
PND 24						
0	Peak Amp.	406.9 \pm 193.8	352.1 \pm 203.5	307.6 \pm 165.6	302.3 \pm 144.3	357.7 \pm 226.7
	Latency	34.5 \pm 9.7	24.6 \pm 8.2	24.1 \pm 8.0	23.6 \pm 7.4	22.6 \pm 8.2
5	Peak Amp.	489.5 \pm 251.3	585.1* \pm 371.1	396.6 \pm 132.7	340.9 \pm 111.1	411.5 \pm 180.5
	Latency	34.3 \pm 11.9	33.2* \pm 10.6	26.2 \pm 8.8	26.1 \pm 7.4	26.6 \pm 9.7
10	Peak Amp.	371.5 \pm 171.3	257.9 \pm 94.6	257.8 \pm 89.6	248.7 \pm 110.6	289.6 \pm 105.1
	Latency	31.4 \pm 8.3	26.4 \pm 4.2	21.0 \pm 3.7	22.2 \pm 4.8	21.9 \pm 3.2
15	Peak Amp.	587.0 \pm 231.3	614.9 \pm 562.0	525.1 \pm 478.1	538.4 \pm 509.5	548.8 \pm 696.5
	Latency	41.7 \pm 9.4	36.3* \pm 10.8	34.5 \pm 10.2	29.6 \pm 8.8	26.2 \pm 9.2
PND 60						
0	Peak Amp.	3187.2 \pm 1364.3	1758.0 \pm 748.3	1568.8 \pm 694.7	1629.8 \pm 694.0	1450.3 \pm 762.7
	Latency	48.9 \pm 15.6	30.2 \pm 7.2	28.8 \pm 6.1	27.4 \pm 6.1	28.5 \pm 3.8
5	Peak Amp.	2826.1 \pm 1831.8	1671.1 \pm 953.7	1355.6 \pm 587.0	1397.2 \pm 898.0	1656.9 \pm 767.0
	Latency	47.9 \pm 15.6	36.2 \pm 9.6	29.7 \pm 4.7	31.3 \pm 6.9	28.5 \pm 5.0
10	Peak Amp.	2576.4 \pm 1808.8	1244.9 \pm 865.4	1105.6 \pm 664.8	1041.0 \pm 584.4	1080.9 \pm 399.0
	Latency	43.9 \pm 16.7	28.8 \pm 7.5	28.1 \pm 6.8	27.0 \pm 5.2	28.4 \pm 4.7
15	Peak Amp.	3184.8 \pm 2046.0	1928.8 \pm 1258.9	1775.6 \pm 1123.5	1772.8 \pm 1254.8	1560.8 \pm 1244.8
	Latency	46.7 \pm 18.9	32.8 \pm 9.8	35.3 \pm 11.8	36.0 \pm 15.1	33.2 \pm 12.7

^a Data were obtained from pages 268-269 and 272-273, MRID 46740201.

* Significantly different from controls at p#0.05

N = 10

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TABLE 10c. Mean (\pm SD) interval acoustic startle peak amplitude (g) and latency to peak (msec) in F ₁ female rats ^a						
Dose (mg/kg/day)	Parameter	Block 1	Block 2	Block 3	Block 4	Block 5
PND 24						
0	Peak Amp.	466.7 \pm 180.5	507.0 \pm 430.4	421.3 \pm 283.4	416.7 \pm 251.5	399.7 \pm 283.2
	Latency	33.9 \pm 10.7	35.5 \pm 14.2	30.7 \pm 12.8	31.0 \pm 10.3	24.7 \pm 9.0
5	Peak Amp.	420.2 \pm 337.0	347.1 \pm 261.2	322.7 \pm 204.0	349.3 \pm 275.8	307.7 \pm 91.7
	Latency	25.9 \pm 12.6	24.8 \pm 9.7	22.3 \pm 6.8	21.7 \pm 6.3	21.9 \pm 5.0
10	Peak Amp.	569.4 \pm 453.1	499.5 \pm 222.0	430.3 \pm 179.3	378.2 \pm 180.2	414.5 \pm 244.2
	Latency	37.1 \pm 14.7	34.5 \pm 10.8	29.4 \pm 7.9	24.6 \pm 8.4	26.7 \pm 10.0
15	Peak Amp.	548.9 \pm 313.5	451.1 \pm 246.8	373.8 \pm 166.1	377.7 \pm 128.5	356.1 \pm 95.9
	Latency	35.9 \pm 9.6	31.8 \pm 11.1	25.7 \pm 8.3	25.8 \pm 8.7	25.5 \pm 7.6
PND 60						
0	Peak Amp.	2253.6 \pm 1622.7	1688.9 \pm 946.7	1219.8 \pm 763.8	1120.0 \pm 715.8	997.4 \pm 656.7
	Latency	41.7 \pm 17.2	38.5 \pm 13.9	31.3 \pm 7.1	31.5 \pm 13.3	28.3 \pm 6.8
5	Peak Amp.	1435.9 \pm 545.7	991.1 \pm 298.0	912.3 \pm 481.9	878.8 \pm 290.5	916.6 \pm 325.1
	Latency	29.0 \pm 7.6	27.1 \pm 6.9	28.5 \pm 6.3	25.9 \pm 4.8	29.7 \pm 7.9
10	Peak Amp.	1943.0 \pm 1090.5	1415.5 \pm 789.1	1138.8 \pm 679.0	988.7 \pm 395.9	1133.7 \pm 719.1
	Latency	35.7 \pm 15.2	31.2 \pm 12.3	28.9 \pm 8.6	24.7 \pm 2.6	27.4 \pm 5.2
15	Peak Amp.	2413.1 \pm 1511.9	2128.9 \pm 1546.1	1829.8 \pm 1211.7	1335.5 \pm 695.0	1119.3 \pm 397.3
	Latency	40.3 \pm 14.8	35.0 \pm 11.6	35.0 \pm 12.0	25.8 \pm 5.7	23.6 \pm 2.1

^a Data were obtained from pages 270-271 and 274-275, MRID 46740201.
N = 10

- d) **Learning and memory testing:** No treatment-related changes were observed in overall learning, memory or relearning or in time to success. The number (%) of animals reaching criterion during learning 1, memory and learning 2 phases on PNDs 23 and 60 are presented in Tables 11a and 11c, respectively. The time to criterion for PNDs 23 and 60 are included in Tables 11b and 11d, respectively.

TABLE 11a. Water Maze Performance in PND 23 Offspring – Number (Percent) of Animals Reaching Criteria ^a					
Session/Parameter		Dose (mg/kg/day)			
		0	5	10	15
Males					
Learning 1	Trial 2	5 (50)	3 (30)	4 (40)	3 (30)
	Trial 3	8 (80)	4 (40)	6 (60)	7 (70)
	Trial 4	8 (80)	7 (70)	9 (90)	7 (70)
	Trial 5	9 (90)	8 (80)	10 (100)	9 (90)
	Trial 6	8 (80)	8 (80)	7 (70)	10 (100)
Memory		9 (90)	7 (70)	8 (80)	9 (90)
Learning 2	Trial 2	3 (30)	3 (30)	1 (10)	1 (10)
	Trial 3	6 (60)	6 (60)	2 (20)	2 (20)
	Trial 4	6 (60)	7 (70)	5 (50)	3 (30)
	Trial 5	7 (70)	7 (70)	3 (30)	5 (50)
	Trial 6	7 (70)	6 (60)	2 (20)	4 (40)
Females					
Learning 1	Trial 2	4 (40)	5 (50)	5 (50)	4 (40)
	Trial 3	7 (70)	7 (70)	7 (70)	7 (70)
	Trial 4	5 (50)	8 (80)	7 (70)	7 (70)
	Trial 5	9 (90)	9 (90)	8 (80)	7 (70)
	Trial 6	9 (90)	8 (80)	10 (100)	9 (90)
Memory		7 (70)	8 (80)	8 (80)	8 (80)
Learning 2	Trial 2	0 (0.0)	1 (10)	1 (10)	2 (20)
	Trial 3	2 (20)	1 (10)	3 (30)	6 (60)
	Trial 4	2 (20)	5 (50)	2 (20)	6 (60)
	Trial 5	4 (40)	8 (80)	3 (30)	8 (80)
	Trial 6	4 (40)	7 (70)	6 (60)	8 (80)

^a Data obtained from pages 164-165, MRID 46740201.

N = 10

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TABLE 11b. Water Maze Performance in PND 23 Offspring - time to criterion (sec \pm SD) ^a					
Session/Parameter		Dose (mg/kg/day)			
		0	5	10	15
Males					
Learning 1	Trial 2	21 \pm 10.8	33 \pm 25.1	28 \pm 20.6	22 \pm 15.5
	Trial 3	11 \pm 6.1	17 \pm 10.7	15 \pm 7.4	19 \pm 17.5
	Trial 4	11 \pm 9.3	18 \pm 16.4	14 \pm 13.8	17 \pm 15.2
	Trial 5	10 \pm 7.4	14 \pm 14.1	9 \pm 4.4	11 \pm 15.2
	Trial 6	7 \pm 5.2	11 \pm 8.9	15* \pm 11.4	6 \pm 2.8
Memory		7 \pm 5.1	10 \pm 5.3	9 \pm 6.5	6 \pm 4.1
Learning 2	Trial 2	18 \pm 10.6	15 \pm 7.8	21 \pm 11.0	21 \pm 12.1
	Trial 3	10 \pm 7.6	10 \pm 6.7	16 \pm 9.4	13 \pm 6.8
	Trial 4	9 \pm 7.3	8 \pm 4.6	13 \pm 9.3	12 \pm 8.6
	Trial 5	8 \pm 6.1	8 \pm 5.5	10 \pm 4.6	8 \pm 3.7
	Trial 6	7 \pm 4.6	9 \pm 7.5	12 \pm 6.1	9 \pm 7.2
Females					
Learning 1	Trial 2	21 \pm 10.9	18 \pm 11.8	30 \pm 23.1	28 \pm 19.1
	Trial 3	18 \pm 16.6	13 \pm 7.9	17 \pm 9.9	15 \pm 11.0
	Trial 4	16 \pm 17.1	11 \pm 5.6	13 \pm 10.3	12 \pm 7.8
	Trial 5	12 \pm 10.4	11 \pm 7.9	12 \pm 9.3	15 \pm 12.6
	Trial 6	12 \pm 11.5	12 \pm 7.3	9 \pm 8.5	13 \pm 9.5
Memory		9 \pm 3.5	9 \pm 8.2	11 \pm 7.1	8 \pm 6.0
Learning 2	Trial 2	17 \pm 5.6	9 \pm 4.3	21 \pm 9.2	19 \pm 11.4
	Trial 3	17 \pm 9.5	14 \pm 6.7	16 \pm 6.4	10 \pm 6.9
	Trial 4	11 \pm 3.9	9 \pm 4.3	14 \pm 6.6	7* \pm 4.6
	Trial 5	12 \pm 8.7	7 \pm 4.7	14 \pm 10.6	5* \pm 3.1
	Trial 6	9 \pm 4.9	7 \pm 4.1	10 \pm 8.2	5 \pm 3.0

^a Data obtained from pages 166-167, MRID 46740201.

N = 10

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TABLE 11c. Water Maze Performance in PND 60 Offspring – Number (Percent) of Animals Reaching Criteria ^a					
Session/Parameter		Dose (mg/kg/day)			
		0	5	10	15
Males					
Learning 1	Trial 2	5 (50)	2 (20)	6 (60)	5 (50)
	Trial 3	6 (60)	6 (60)	7 (70)	7 (70)
	Trial 4	9 (90)	8 (80)	8 (80)	8 (80)
	Trial 5	9 (90)	8 (80)	9 (90)	7 (70)
	Trial 6	9 (90)	10 (100)	9 (90)	10 (100)
Memory		8 (80)	7 (70)	8 (80)	9 (90)
Learning 2	Trial 2	2 (20)	2 (20)	3 (30)	4 (40)
	Trial 3	3 (30)	6 (60)	5 (50)	4 (40)
	Trial 4	4 (40)	6 (60)	5 (50)	5 (50)
	Trial 5	7 (70)	8 (80)	5 (50)	5 (50)
	Trial 6	6 (60)	7 (70)	7 (70)	4 (40)
Females					
Learning 1	Trial 2	4 (40)	3 (30)	3 (30)	5 (50)
	Trial 3	3 (30)	5 (50)	4 (40)	9 (90)
	Trial 4	7 (70)	6 (60)	7 (70)	5 (50)
	Trial 5	5 (50)	5 (50)	4 (40)	6 (60)
	Trial 6	7 (70)	6 (60)	8 (80)	8 (80)
Memory		5 (50)	4 (40)	7 (70)	8 (80)
Learning 2	Trial 2	1 (10)	2 (20)	3 (30)	1 (10)
	Trial 3	3 (30)	6 (60)	4 (40)	3 (30)
	Trial 4	3 (30)	4 (40)	6 (60)	4 (40)
	Trial 5	6 (60)	4 (40)	6 (60)	6 (60)
	Trial 6	5 (50)	4 (40)	6 (60)	7 (70)

^a Data obtained from pages 168-169, MRID 46740201 in the study report.
N = 10

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TABLE 11d. Water Maze Performance in PND 60 Offspring – time to criterion (sec ± SD) ^a					
Session/Parameter		Dose (mg/kg/day)			
		0	5	10	15
Males					
Learning 1	Trial 2	17 ± 8.6	22 ± 8.1	17 ± 14.0	27 ± 42.2
	Trial 3	12 ± 6.2	13 ± 5.5	11 ± 5.8	12 ± 9.2
	Trial 4	8 ± 2.0	9 ± 3.0	10 ± 6.6	24 ± 31.7
	Trial 5	11 ± 7.5	11 ± 9.0	9 ± 5.2	18 ± 21.2
	Trial 6	7 ± 2.4	7 ± 2.7	8 ± 4.5	7 ± 3.8
Memory		13 ± 8.2	15 ± 4.2	12 ± 9.8	10 ± 7.6
Learning 2	Trial 2	22 ± 10.7	23 ± 15.3	17 ± 9.3	18 ± 12.4
	Trial 3	22 ± 19.2	17 ± 21.9	16 ± 10.7	17 ± 17.9
	Trial 4	12 ± 7.8	9 ± 5.0	11 ± 6.1	17 ± 21.9
	Trial 5	7 ± 3.3	7 ± 4.4	10 ± 7.3	13 ± 13.2
	Trial 6	8 ± 6.0	7 ± 5.0	18 ± 34.5	18 ± 21.1
Females					
Learning 1	Trial 2	28 ± 27.7	17 ± 5.7	17 ± 9.8	15 ± 6.9
	Trial 3	18 ± 13.8	16 ± 7.6	13 ± 8.1	8* ± 2.9
	Trial 4	16 ± 4.2	10 ± 4.7	11 ± 8.3	12 ± 6.8
	Trial 5	25 ± 25.5	17 ± 15.2	13 ± 7.6	10 ± 4.8
	Trial 6	18 ± 15.7	16 ± 13.2	8 ± 4.2	9 ± 7.5
Memory		12 ± 7.0	14 ± 5.8	9 ± 4.1	9 ± 5.0
Learning 2	Trial 2	29 ± 23.6	19 ± 8.6	16 ± 9.5	23 ± 15.3
	Trial 3	13 ± 6.6	11 ± 9.7	14 ± 11.0	16 ± 14.8
	Trial 4	17 ± 13.9	17 ± 17.5	9 ± 6.8	11 ± 6.1
	Trial 5	9 ± 5.1	16 ± 22.7	8 ± 5.9	8 ± 3.9
	Trial 6	11 ± 7.5	15 ± 21.5	7 ± 4.4	6 ± 2.5

^a Data obtained from pages 170-171, MRID 46740201.

N = 10

* Significantly different from controls at p#0.05

5. Postmortem results:

- a. **Brain weight:** Mean brain weight data are presented Table 12. No treatment-related effects were noted at PND 22, 62 or 111.

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TABLE 12. Mean (\pm SD) brain weight data ^a				
Parameter	Dose (mg/kg/day)			
	0	5	10	15
Males				
Day 22				
Terminal body weight (g)	49.70 \pm 2.88	48.20 \pm 2.73	48.13 \pm 3.28	47.87 \pm 4.12
Brain weight (g)	1.62 \pm 0.05	1.60 \pm 0.06	1.61 \pm 0.06	1.60 \pm 0.06
Brain-to-body weight ratio	3.27 \pm 0.15	3.33 \pm 0.20	3.36 \pm 0.13	3.40 \pm 0.22
Day 62				
Terminal body weight (g)	294.1 \pm 15.89	285.66 \pm 24.86	280.0 \pm 26.0	284.92 \pm 16.71
Brain weight (g)	1.96 \pm 0.08	1.98 \pm 0.10	2.01 \pm 0.07	2.0 \pm 0.06
Brain-to-body weight ratio	0.67 \pm 0.04	0.70 \pm 0.05	0.72 \pm 0.06	0.70 \pm 0.04
Day 111				
Terminal body weight (g)	386.65 \pm 26.48	379.45 \pm 34.39	389.19 \pm 33.33	389.44 \pm 19.60
Brain weight (g)	2.13 \pm 0.06	2.08 \pm 0.06	2.05 \pm 0.09	2.10 \pm 0.07
Brain-to-body weight ratio	0.55 \pm 0.04	0.55 \pm 0.04	0.53 \pm 0.04	0.54 \pm 0.03
Females				
Day 22				
Terminal body weight (g)	46.49 \pm 4.55	49.17 \pm 3.73	45.15 \pm 5.0	46.29 \pm 4.94
Brain weight (g)	1.56 \pm 0.07	1.58 \pm 0.06	1.54 \pm 0.07	1.55 \pm 0.05
Brain-to-body weight ratio	3.38 \pm 0.28	3.23 \pm 0.27	3.45 \pm 0.32	3.38 \pm 0.41
Day 62				
Terminal body weight (g)	180.95 \pm 15.01	173.84 \pm 12.54	182.74 \pm 17.97	187.39 \pm 10.19
Brain weight (g)	1.86 \pm 0.10	1.82 \pm 0.04	1.86 \pm 0.07	1.83 \pm 0.06
Brain-to-body weight ratio	1.03 \pm 0.06	1.05 \pm 0.08	1.03 \pm 0.09	0.98 \pm 0.04
Day 111				
Terminal body weight (g)	227.78 \pm 14.72	228.05 \pm 20.54	224.26 \pm 16.50	233.95 \pm 13.23
Brain weight (g)	1.96 \pm 0.08	1.90 \pm 0.08	1.91 \pm 0.06	1.92 \pm 0.11
Brain-to-body weight ratio	0.87 \pm 0.05	0.84 \pm 0.07	0.85 \pm 0.04	0.82 \pm 0.07

^a Data obtained from pages 302-313, MRID 46740201.

N = 10

b) Neuropathology:

1. **Macroscopic examination:** No treatment-related lesions were observed.
2. **Microscopic examination:** At the PND 22 necropsy, minimal to moderate vacuolation of the white matter was observed in several areas of the brain, including the frontal lobe, parietal lobe, midbrain, pons, cerebellum and medulla oblongata, in up to 4/10 males and females in the high dose group compared to none in the control group. The low- and mid-dose groups were examined and no lesions were observed. No treatment-related findings were observed at the PND 62 necropsy. The histopathological findings are presented in Table 13.

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TABLE 13. Histopathology findings -- number affected (severity) ^a				
Parameter	Dose (mg/kg/day)			
	0	5	10	15
Males				
Day 22				
Number examined	10	10	10	10
Frontal lobe, vacuolation, white matter	0	0	0	4 (1.25)
Parietal lobe, vacuolation, white matter	0	0	0	2 (1.50)
Pons, vacuolation, white matter	0	0	0	1 (1.00)
Cerebellum, vacuolation, white	0	0	0	1 (1.00)
Females				
Day 22				
Number examined	10	10	10	10
Frontal lobe, vacuolation, white matter	0	0	0	4 (1.75)
Parietal lobe, vacuolation, white matter	0	0	0	4 (1.50)
Midbrain, vacuolation, white matter	0	0	0	1 (1.00)
Pons, vacuolation, white matter	0	0	0	2 (1.50)
Cerebellum, vacuolation, white matter	0	0	0	3 (1.33)
Medulla oblongata, vacuolation, white matter	0	0	0	1 (1.00)

^a Data obtained from pages 320-321 and 874, MRID 64740201.

N = 10

No treatment-related changes were found in the length or width of the cerebrum and cerebellum on PNDs 22, 62 and 111. The decrease in the length of the cerebellum in low-dose females on PND 22 is considered incidental. Data are presented in Table 14.

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TABLE 14. Brain measurements (cm \pm SD) in pups ^a				
Organ/Measurement	Dose (mg/kg/day)			
	0	5	10	15
Males				
Day 22				
Cerebrum				
Length	1.36 \pm 0.02	1.38 \pm 0.03	1.38 \pm 0.05	1.37 \pm 0.04
Width	1.47 \pm 0.02	1.45 \pm 0.04	1.46 \pm 0.04	1.44 \pm 0.03
Cerebellum				
Length	0.61 \pm 0.06	0.59 \pm 0.04	0.60 \pm 0.04	0.58 \pm 0.02
Width	1.10 \pm 0.03	1.10 \pm 0.05	1.12 \pm 0.04	1.11 \pm 0.02
Day 62				
Cerebrum				
Length	1.47 \pm 0.03	1.46 \pm 0.05	1.50 \pm 0.02	1.49 \pm 0.03
Width	1.53 \pm 0.03	1.54 \pm 0.03	1.55 \pm 0.03	1.54 \pm 0.04
Cerebellum				
Length	0.78 \pm 0.33	0.69 \pm 0.02	0.69 \pm 0.04	0.69 \pm 0.02
Width	1.18 \pm 0.03	1.17 \pm 0.03	1.19 \pm 0.02	1.19 \pm 0.03
Day 111				
Cerebrum				
Length	1.52 \pm 0.03	1.51 \pm 0.05	1.51 \pm 0.03	1.53 \pm 0.02
Width	1.56 \pm 0.03	1.56 \pm 0.03	1.56 \pm 0.05	1.55 \pm 0.02
Cerebellum				
Length	0.73 \pm 0.04	0.71 \pm 0.04	0.72 \pm 0.03	0.71 \pm 0.03
Width	1.21 \pm 0.03	1.23 \pm 0.02	1.23 \pm 0.03	1.22 \pm 0.04
Females				
Day 22				
Cerebrum				
Length	1.34 \pm 0.02	1.35 \pm 0.03	1.33 \pm 0.03	1.36 \pm 0.03
Width	1.44 \pm 0.03	1.44 \pm 0.03	1.44 \pm 0.03	1.44 \pm 0.03
Cerebellum				
Length	0.60 \pm 0.03	0.55* \pm 0.06	0.60 \pm 0.04	0.58 \pm 0.02
Width	1.11 \pm 0.04	1.10 \pm 0.04	1.00 \pm 0.32	1.11 \pm 0.03
Day 62				
Cerebrum				
Length	1.44 \pm 0.03	1.44 \pm 0.03	1.45 \pm 0.03	1.46 \pm 0.03
Width	1.50 \pm 0.03	1.49 \pm 0.03	1.50 \pm 0.03	1.49 \pm 0.03
Cerebellum				
Length	0.67 \pm 0.02	0.67 \pm 0.02	0.68 \pm 0.04	0.67 \pm 0.04
Width	1.16 \pm 0.04	1.16 \pm 0.03	1.17 \pm 0.03	1.15 \pm 0.02
Day 111				
Cerebrum				
Length	1.50 \pm 0.02	1.47 \pm 0.03	1.48 \pm 0.03	1.49 \pm 0.04
Width	1.52 \pm 0.02	1.51 \pm 0.03	1.52 \pm 0.02	1.52 \pm 0.03
Cerebellum				
Length	0.69 \pm 0.04	0.70 \pm 0.04	0.70 \pm 0.03	0.71 \pm 0.03
Width	1.20 \pm 0.04	1.21 \pm 0.03	1.19 \pm 0.03	1.20 \pm 0.03

^a Data obtained from pages 325-330, MRID 46740201.

N = 10

* Significantly different from controls at p#0.05

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Morphometric data are presented in Table 15. Dimensions of the left and right hippocampus in females at 15 mg/kg/day were significantly decreased on PND 62. These tissues in females at 5 and 10 mg/kg/day were comparable to those of the control group.

TABLE 15. Mean (\pm SD) morphometric data ^a				
Parameter	Dose (mg/kg/day)			
	0	5	10	15
Males				
Day 22				
Frontal cortex, left brain (μ m)	1865 \pm 100	-	-	1865 \pm 161
Frontal cortex, right brain (μ m)	1873 \pm 118	-	-	1871 \pm 119
Parietal cortex, left brain (μ m)	1954 \pm 143	-	-	1996 \pm 138
Parietal cortex, right brain (μ m)	1884 \pm 120	-	-	1885 \pm 143
Nucleus caudatus, left brain (μ m)	3413 \pm 107	-	-	3337 \pm 97
Nucleus caudatus, right brain (μ m)	3395 \pm 117	-	-	3479 \pm 127
Corpus callosum (μ m)	343 \pm 121	-	-	321 \pm 78
Hippocampus, left (μ m)	1741 \pm 83	-	-	1816 \pm 52
Hippocampus, right (μ m)	1767 \pm 91	-	-	1795 \pm 58
Folium pyramis of cerebellum half (μ m)	354 \pm 26	-	-	336 \pm 15
Day 62				
Frontal cortex, left brain (μ m)	1785 \pm 111	-	-	1611 \pm 541
Frontal cortex, right brain (μ m)	1797 \pm 121	-	-	1839 \pm 71
Parietal cortex, left brain (μ m)	2002 \pm 192	-	-	1893 \pm 83
Parietal cortex, right brain (μ m)	1847 \pm 127	-	-	1846 \pm 88
Nucleus caudatus, left brain (μ m)	3828 \pm 137	-	-	3758 \pm 151
Nucleus caudatus, right brain (μ m)	3629 \pm 97	-	-	3683 \pm 104
Corpus callosum (μ m)	332 \pm 55	-	-	307 \pm 35
Hippocampus, left (μ m)	1860 \pm 72	-	-	1794 \pm 91
Hippocampus, right (μ m)	1837 \pm 74	-	-	1789 \pm 88
Folium pyramis of cerebellum half (μ m)	372 \pm 35	-	-	338 \pm 115
Females				
Day 22				
Frontal cortex, left brain (μ m)	1781 \pm 104	-	-	1816 \pm 129
Frontal cortex, right brain (μ m)	1758 \pm 130	-	-	1784 \pm 164
Parietal cortex, left brain (μ m)	1786 \pm 122	-	-	1811 \pm 210
Parietal cortex, right brain (μ m)	1751 \pm 68	-	-	1789 \pm 183
Nucleus caudatus, left brain (μ m)	3272 \pm 130	-	-	3279 \pm 81
Nucleus caudatus, right brain (μ m)	3414 \pm 83	-	-	3316 \pm 125
Corpus callosum (μ m)	255 \pm 45	-	-	332 \pm 113
Hippocampus, left (μ m)	1777 \pm 89	-	-	1718 \pm 50
Hippocampus, right (μ m)	1783 \pm 86	-	-	1738 \pm 71
Folium pyramis of cerebellum half (μ m)	335 \pm 21	-	-	350 \pm 27
Day 62				
Frontal cortex, left brain (μ m)	1749 \pm 121	-	-	1727 \pm 82
Frontal cortex, right brain (μ m)	1756 \pm 106	-	-	1784 \pm 59
Parietal cortex, left brain (μ m)	1799 \pm 92	-	-	1842 \pm 144
Parietal cortex, right brain (μ m)	1777 \pm 170	-	-	1777 \pm 114
Nucleus caudatus, left brain (μ m)	3713 \pm 151	-	-	3697 \pm 131
Nucleus caudatus, right brain (μ m)	3593 \pm 143	-	-	3615 \pm 145
Corpus callosum (μ m)	322 \pm 50	-	-	327 \pm 56
Hippocampus, left (μ m)	1779 \pm 71	1739 \pm 78	1716 \pm 100	1697** \pm 94

TABLE 15. Mean (\pm SD) morphometric data ^a				
Parameter	Dose (mg/kg/day)			
	0	5	10	15
Hippocampus, right (μ m)	1769 \pm 67	1791 \pm 64	1759 \pm 40	1672** \pm 73
Folium pyramis of cerebellum half (μ m)	374 \pm 28	-	-	354 \pm 29

^a Data obtained from pages 331-335, MRID 46740201.

- = Not examined

N = 10

* Statistically different from control, $p < 0.05$

** Statistically different from control, $p < 0.01$

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS: The study author concluded that the test material produced the following effects at 15 mg/kg/day: slight increases in the mean latency to the peak effect of the auditory startle response in male offspring on PND 24; intramyelinic edema of the brain at various locations in PND 22 offspring of both sexes; and decrease in the size of the hippocampus in female offspring on PND 62. The NOAEL was 10 mg/kg/day for developmental toxicity and 15 mg/kg/day for systemic toxicity.

B. REVIEWER COMMENTS: Administration of technical grade BAS 306 I (chlorfenapyr) by gavage at dose levels up to 15 mg/kg/day produced no systemic or neurotoxicity in dams. Reproductive performance was unaffected by treatment. Mean numbers of pups per dam and percentage of liveborn and stillborn pups were not affected by treatment. There was no effect on sex ratio on the day of birth or on PND 21. The number of cannibalized pups was significantly increased at 10 and 15 mg/kg/day. A higher number of pups at 10 and 15 mg/kg/day died during PNDs 1-4 but the increase was not statistically significant. The higher mortality at 15 mg/kg/day was caused predominately by the cannibalism 1-2 days after birth in two litters. The offspring cannibalized in the 10 mg/kg/day group were individuals from different litters. The increased cannibalism may have been due to excretion of test substance in the urine and milk. Although cannibalization of this magnitude is rare in the rat, it is not considered toxicologically significant in the maternal animals given the fact that the subjects do not show any signs of toxicity.

Among surviving offspring, no treatment-related effects were reported on clinical signs, pre- and post-weaning body weight and FOB results. The mean day of achieving sexual maturation was comparable in all groups. A dose-related decrease in total movement on PND 13 was observed in treated males and females; the decrease was significant at 15 mg/kg/day. The total movement distance for females at 15 mg/kg/day (2272.5 cm) was within the range of the historical control data (1838.8-2898.5 cm), whereas the control value (4321.3 cm) was above the historical control value. During the PND 13 sub-session, the distance moved was generally lower in males and females at 15 mg/kg/day but the change was significant for only one sub-session in each sex. No treatment-related effects were found on total distance moved on PNDs 17, 21 or 60 or on the total number of rearings at any of the testing periods. The decrease in motor activity is considered treatment-related in males and females at 10 mg/kg/day since it was dose-related.

In acoustic startle testing, no treatment-related effects were observed on overall peak amplitude on PNDs 24 or 60. On PND 24, a significant increase in latency to peak amplitude was observed in males at 15 mg/kg/day, but there was no dose response. The only

significant change in latency interval was an increase in block 2 for high dose males on PND 24; however, the values at all intervals were higher than control values. No treatment-related changes were observed in the interval data on PND 60. Historical control data were included for maximum amplitude startle response but not for latency. Although latency was increased at this dose, there was no dose-response effect at any of the time periods. The increase in latency in males at 15 mg/kg/day is not considered treatment-related.

No treatment-related changes were observed in overall learning, memory, relearning or time to success in the water maze testing.

At necropsy, brain weight and measurement of the cerebrum and cerebellum were comparable between treated and control groups. On microscopic examination on PND 22, treatment-related minimal to moderate vacuolation of the white matter was observed in several areas of the brain, including the frontal lobe, parietal lobe, midbrain, pons, cerebellum and medulla oblongata, in up to 4/10 males and females in the high dose group compared to none in the control group. The low- and mid-dose groups were examined and no lesions were observed. No treatment-related microscopic findings were observed at PND 62. On morphometric examination, size of the left and right hippocampus in females at 15 mg/kg/day was significantly decreased on PND 62. Dimensions of these tissues in females at 5 and 10 mg/kg/day were comparable to those of the control group. The decreases in hippocampal size are considered treatment-related since they occurred bilaterally.

The maternal LOAEL for BAS 306 I in rats was not established and the maternal NOAEL is 15 mg/kg/day.

The offspring LOAEL for BAS 306 I in rats is 10 mg/kg/day, based on pup deaths on PND 1-4 and cannibalization and decreased motor activity in males and females on PND 13. The offspring NOAEL is 5 mg/kg/day.

C. STUDY DEFICIENCIES: None observed.