

US EPA ARCHIVE DOCUMENT

BAS 670H/123009

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Health Evaluation Division

Date 8/30/05

Template version 11/01

TXR#: 0052097

DATA EVALUATION RECORD

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

PC CODE: 123009

DP BARCODE: D292904

TEST MATERIAL (PURITY): BAS 670H (95.8% a.i.)

SYNONYMS: [3-(4-5-Dihydro-isoxazol-3-yl)-4-methanesulfonyl-2-methyl-phenyl]-(5-hydroxy-1-methyl-1H-pyrazol-4-yl)-methanone ✓

CITATION: Kaufmann W., S. Schneider, and B. Ravenzwaay, (2003) BAS 670H: Developmental neurotoxicity study in Wistar rats: Administration in the diet. Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany. Laboratory Project ID: 67R0124/98140, March 11, 2003. MRID 45902304. Unpublished.

SPONSOR: BASF Corporation, Agricultural Products, P.O. Box 13528, Research Triangle Park, NC

EXECUTIVE SUMMARY - In a developmental neurotoxicity study (MRID 45902304), BAS 670H (95.8% a.i.; Batch/Lot #: N26) was administered in the diet to pregnant Wistar rats (38-39/dose) from gestation day (GD) 6 to postnatal day (PND) 21 at nominal doses of 0, 8, 80, or 800 mg/kg/day (actual doses were 0/0, 8.2/6.7, 83.7/69.6, and 848.6/739.1 mg/kg/day [gestation/lactation]). Dams were allowed to deliver naturally and were killed on lactation day (LD) 21. On PND 4, at least twenty-two litters of appropriate size (≥ 8 pups/litter) were available. These litters were standardized to 8 pups/litter; the remaining offspring and dams were sacrificed and discarded without further examinations. Subsequently, 10 pups/sex/group were allocated to Subsets 1-6 for neurobehavioral testing and neuropathological examination.

No treatment-related effects were observed in the dams on survival. There were transient decreases in body weight, body weight gain and food consumption at the mid (80 mg/kg/day) and high dose (800 mg/kg/day) dams during gestation and/or lactation. Corneal opacities in females were considered a treatment-related effect at all doses. The incidences were: 4/34, 22/35 and 12/32 at the low, mid and high dose groups, respectively compared to 0/35 in the controls.

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The maternal LOAEL is 8 mg/kg/day based on corneal opacities. A maternal NOAEL was not established.

Treatment-related effects seen at the mid and high dose groups include decreases in body weight and bodyweight gain in both sexes, and delayed preputial separation in males. Treatment had no adverse effects on offspring survival, clinical signs, FOB, motor activity, or learning and memory. Treatment-related effects were seen in the auditory startle response in both sexes on PND 24 at all dose levels. For males, maximum auditory startle response amplitude was decreased 30%, 27%, and 38% on PND 24 at 8, 80, and 800 mg/kg/day, respectively. For females, maximum auditory startle response amplitude was decreased 22%, 34%, and 54% on PND 24 at 8, 80, or 800 mg/kg/day, respectively. No significant differences from control were noted in startle response maximum amplitude at any dose in either sex on PND 60. Treatment-related decreases in absolute brain weights were seen in males on PND 62 and in females on PND 22 at all doses. Changes in the various regions of the brain were observed in pups of both sexes at all dose levels at PND 22 and PND 62.

The offspring LOAEL is 8 mg/kg/day, based on decreased maximum auditory startle reflex response, decreased brain weights and changes in the brain morphology. The offspring NOAEL was not established.

This study is classified **Acceptable** 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) at this time pending a comprehensive review of all available positive control data.

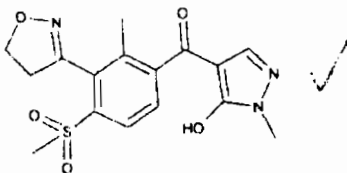
COMPLIANCE - Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

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I. MATERIALS AND METHODS

A. MATERIALS

- 1. Test Material:** BAS 670H
Description: Beige crystalline solid
Batch/Lot #: N26
Purity: 95.8% a.i.
Compound Stability: The test material was shown to be stable in the diet for up to 47 days at room temperature.
CAS # of TGA1: 210631-68-8
Structure:



2. Vehicle - Diet

3. Test animals (P)

- Species:** Rat
Strain: Wistar (CrI:GLX/Brl/Han:WI (formerly CRL: WI (GLX/BRL/HAN) IGS BR))
Age at study initiation: Approximately 11-13 weeks
Weight on arrival: 141.9-184.2 g (females)
Source: Charles River Laboratories, Germany
Housing: Individually in type DK III stainless steel wire mesh cages, except from GD 18 to LD 21 where the animals were housed individually in Makrolon type M III cages with nesting material.
Diet: Kliba maintenance diet rat/mouse/hamster (Provimi Kliba SA, Kaiseraugst, Switzerland), *ad libitum*, except during behavioral testing.
Water: Tap water, *ad libitum*, except during behavioral testing
Environmental conditions: **Temperature:** 20-24 °C
Humidity: 30-70%
Air changes: Not reported
Photoperiod: 12 hrs light/12 hrs dark
Acclimation period: 6 days

B. PROCEDURES AND STUDY DESIGN

1. In life dates - Start: 2/11/01 End: 5/09/01

2. Study schedule - The maternal animals were mated and assigned to study. The P females were administered the test substance continuously in the diet from gestation day (GD) 6 until postnatal day (PND) 21. After parturition, only the litters containing ≥ 8 pups and whose littering date was over a period of 4 consecutive days (February 27 through March 2, 2001) were kept for further examinations. All other litters and all P females without a litter were sacrificed, and were discarded without further examinations. On PND 4, the litters were standardized to 8 pups/litter to reduce the variability. Subsequently, one male or one female pup from each litter (10 pups/sex/group) were allocated to the subsets (1-6). Litters not selected were kept as reserve animals until PND 21, and were then sacrificed along with all remaining dams. F₁ pups remained on study for up to PND 60 \pm 2 (study termination).

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3. Mating procedure - The animals were mated by the breeder, and successful mating was verified by the presence of a copulatory plug or sperm in a vaginal smear. The animals were supplied on the same day that successful breeding was determined (GD 0).

4. Animal assignment - Mated females were randomly assigned (stratified by body weight) to test groups as shown in Table 1. Offspring were assigned (one male or one female pup from each litter) to testing subgroups at the time of litter standardization on PND 4.

Table 1. Study design. ^a

Experimental Parameter	Dose (mg/kg/day)				Subsets No.
	0	8	80	800	
Dams					
No. of maternal animals assigned	38	39	39	39	NA
FOB (GDs 7, 14 & LDs 7, 14)	10	10	10	10	NA
Offspring					
Perfusion fixation, preservation of the brain (PND 11)	10/sex	10/sex	10/sex	10/sex	1
Perfusion fixation, brain weight, and neuropathology (PND 22) (PND 60±2)	10/sex	10/sex	10/sex	10/sex	2
	10/sex	10/sex	10/sex	10/sex	4
FOB (PND 4, 11, 21, 35, 45, 60)	10/sex	10/sex	10/sex	10/sex	3
Motor activity (PND 13, 17, 21, 60±2)	10/sex	10/sex	10/sex	10/sex	3
Auditory startle test (PND 24, 60)	10/sex	10/sex	10/sex	10/sex	4
Watermaze (PND 23, 30) (PND 60, 67)	10/sex	10/sex	10/sex	10/sex	5
	10/sex	10/sex	10/sex	10/sex	6

^a Data were obtained from pages 28-30, 40, 43, & 49 of the study report.
 NA Not applicable

5. Dose selection rationale - No dose selection rationale was provided.

6. Dosage preparation, administration, and analysis - The report stated that during the first week of gestation period, the concentrations of BAS 670H in the diet were calculated on the basis of historical body weight (approx. 195 g) and food consumption data of day 6 p.c. (approx. 18 g) and day 3-6 p.c. (approx. 36 g), respectively. Test diets were prepared by mixing the appropriate amount of the test material with a small amount of diet to form a premix. The premix was further diluted with diet to achieve the appropriate doses. It was stated that the test diets were prepared at intervals considering the proven stability (no further information was provided). The dams were supplied dietary admixtures beginning on GD 6 and continuing through PND 21. During the lactation period, the concentrations of test material in the diet were

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adjusted to 50% of the concentrations used during the gestation period because of the increased food consumption during this period. F₁ animals were not directly supplied with the test diets. The stability of the test material in the diet was verified prior to initiation of the study (Bayer analytical report#: 08B0124/986045) for 47 days at room temperature. Homogeneity was determined from 3 samples of each concentration at the beginning of the study and from each subsequent dietary formulation. Concentration was determined for each dose formulation using the samples collected for homogeneity determinations.

Results - Stability: Up to 47 days at room temperature

Homogeneity and Concentration (range as % of nominal):

Dose (ppm*)	% of Nominal
GD 6 to PND 0	
87	89.3-93.8
867	86.0-97.0
8667	101.4-101.7
PND 1 to PND 21	
43	97.2-100.0
433	100.9-102.0
4333	100.3-101.1

* The reported unit was mg/kg (pages 705-706). However, this reviewer believes that the unit for nominal concentration should be "ppm" instead.

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

C. OBSERVATIONS

1. In-life observations

a. Maternal animals - The dams were checked for mortality twice daily (once daily on weekends and holidays), and once daily for clinical signs of toxicity. Additionally, nesting, littering, and lactation behavior of the dams were checked in the mornings and an additional check for littering behavior was performed in the afternoon. Body weights were measured on GDs 0, 6, 13, and 20, and females with a litter were weighed on PNDs 1, 7, 14, and 21. Food consumption was recorded on GDs 0, 6, 13, and 20, and on PNDs 1, 7, and 14. Test substance intake (mg/kg/day) was calculated for GDs 6-20 and LDs 1-14 from the individual body weight and food consumption data.

Ten dams/dose were subjected to a modified functional observation battery (FOB) outside of the home cage on GDs 7 and 14, and on PNDs 7 and 14. It was not reported if the technicians were blind as to the dose group. The following functional observations were recorded.

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FUNCTIONAL OBSERVATIONS	
X	Signs of autonomic function, including: 1) Lacrimation and salivation 2) Nasal discharge 3) Urination and defecation 4) Respiration 5) Palpebral closure 6) Pupil size
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, activity/arousal levels, altered fur or skin appearance.

b. Offspring

1) **Litter observations** - On the day of birth, the status (sex, liveborn or stillborn) and number of all delivered pups were determined as soon as possible, and all pups were examined macroscopically for any changes. Pups were evaluated for mortality and morbidity twice daily (once daily on weekends and holidays). Clinical observations were recorded daily throughout the study. Body weights were recorded on PNDs 1, 4 (pre-cull and post-cull), 11, 17, and 21, and then weekly thereafter until sacrifice. Post-weaning food consumption was not reported. The following additional litter observations (X) were made (Table 2):

Table 2. Litter observations. ^a

Observation	Post-natal Day						
	0	1	4 ^c	4 ^d	11	17	21
Number of live pups ^b	X	X	X	X	X	X	X
Pup weight		X	X	X	X	X	X
Number of dead pups ^b	X	X	X		X	X	X
Sex of each pup	X						X

- a Data were obtained from pages 46-47 of the study report.
- b Observed daily
- c Preculling
- d Post-culling

On PND 4, the litters were standardized by randomly selecting 8 pups/litter; excess pups were sacrificed and discarded. Of the remaining pups, one male or one female pup from each litter (10 pups/sex/group) was allocated to 1 of 6 subsets for further evaluation.

2) **Developmental landmarks** - Beginning on PND 40, male offspring (except for Subset 5) were examined daily for preputial separation. Beginning on PND 27, female offspring (except for Subset 5) were examined daily for vaginal patency. The exact days of preputial separation or vaginal patency were recorded, and the body weight of the respective animals on these days was recorded.

3) **Postweaning observations** - After weaning on PND 21, offspring were examined for mortality and morbidity twice daily (once daily on weekends and holidays). Clinical observations and body weights were recorded weekly until sacrifice. Additionally, body weights were determined on the day of preputial separation or vaginal patency.

4) **Neurobehavioral evaluations**

i) **Functional observational battery (FOB)** - The evaluation criteria for the modified FOB were presented in Supplement III on pages 708-712 of the study report. On PNDs 4, 11, 21, 35, 45, and 60, the Subset 3 animals (10 pups/sex/dose) were subjected to a modified FOB in the open-field, as appropriate for the developmental stage being observed. The same parameters assessed in the maternal FOB were examined in the offspring. It was not reported if the technicians were blind as to the dose group.

ii) **Motor activity testing** - Motor activity measurements were performed on animals in Subset 3 on PNDs 13, 17, 21, and 60 using the Tru Scan Photobeam Linc (Coulbourn Instruments, L.L.C., Allentown, PA) in a darkened room. It was not stated if the technicians were blind as to the dose group. Data were collected in five-minute intervals over the course of 60 minutes. Total movement distance (cm) and number of rears were evaluated.

iii) **Auditory startle reflex habituation** - Auditory startle response and habituation of responses with repeated presentation of stimuli were evaluated for animals in Subset 4 (10 pups/sex/dose) on PNDs 24 and 60. The rats were tested using the SR-LAB; Startle Response System (San Diego Instruments, San Diego, CA). The rats were initially given an acclimation period of five minutes within the chamber with 70 dBA background noise. The rats were then presented with 50 msec, 120 dBA bursts of noise at 5-second intervals for 50 trials. It was not reported if any "blank" (baseline) trials were performed. The peak amplitude and latency to the peak of the response were analyzed in 5 blocks of 10 trials each.

iv) **Learning and memory testing** - Learning and memory testing was performed on animals in Subsets 5 and 6 (10 pups/sex/dose each). Watermaze testing was performed beginning on PNDs 23 (Subset 5) and 60 (Subset 6) and again seven days later for each group.

The watermaze test consisted of 3 parts (learning ability in the first week, and memory and relearning ability seven days later). The learning ability phase consisted of 6 trials at 1 hour intervals for each rat. On each test trial, the rat was placed into the starting position (base of a M-maze stem farthest from the two arms) and required to find the escape ladder in the right arm of the M-maze. If the animal found the correct path right away it was scored as a positive. If the animal went the wrong way (whole body in wrong alley), it was scored as a negative; however it was allowed to remain in the water until it found the correct route or it reached the maximum swimming duration (6 minutes per trial). After 1 week, the memory phase was performed (one trial for each animal) using the same animals and the same (right side) escape route. The relearning phase was performed within 1 hour following the memory phase. The same procedure as was used in the learning phase was followed; however, the escape route was then placed on the left arm of the M-maze. It was stated that the initial trials of the learning and relearning phases were acclimation trials and were not evaluated.

2. Postmortem observations

a. Maternal animals - Dams that did not deliver a litter were sacrificed, and their uteri were stained for 5 minutes with a 10% ammonium sulfide solution according the methods of Salewski (1964). The uteri were rinsed, and the number of implantation sites were recorded for calculation of post-implantation loss. All other dams were sacrificed on PND 21 (after weaning) and discarded without further examination.

b. Offspring - All pups culled on PND 4, sacrificed on PND 21, and those from Subsets 3, 5, and 6 (after conclusion of their investigations) were killed by cervical dislocation and discarded without further examination.

On PND 11, the pups in Subset 1 (10 pups/sex/dose) were sacrificed under Narcoren® anesthesia via perfusion fixation with Soerensen phosphate buffer followed by 4% neutral buffered formaldehyde. The entire skull (containing the brain) was stored in 4% neutral buffered formaldehyde.

The offspring (10 pups/sex/dose in each subset) selected for brain weight and neuropathological evaluation were sacrificed on PNDs 22 (Subset 2) or 60±2 (Subset 4) under Narcoren® anesthesia via perfusion fixation with Soerensen phosphate buffer followed by 4% neutral buffered formaldehyde. These animals were subjected to gross necropsy with regard to neuropathology. The cranial vault and spinal cord were opened and the skin from both hindlimbs was removed. These carcasses were stored in 4% neutral buffered formaldehyde for at least 48 hours, and then were subjected to postmortem examinations as described below.

The brains (with olfactory bulbs) were removed, weighed, and measured. Sections from all major brain regions were prepared following the methods of Sherwood and Timiras (1970). Tissues from the control and 800 mg/kg groups were examined microscopically. The thickness of the following brain sections was measured: (i) neocortex [frontal and parietal cortices], (ii) caudate nucleus/putamen, (iii) hippocampus, (iv) corpus callosum, and (v) cerebellum. Measurements were carried out on both the right and left sides of the brain, with the exception of the corpus callosum and the cerebellum.

The following CHECKED (X) central (Subsets 2 and 4) and peripheral (Subset 4) nervous system tissues were collected:

CENTRAL NERVOUS SYSTEM		PERIPHERAL NERVOUS SYSTEM	
	BRAIN		SCIATIC NERVE
X	Olfactory bulbs	X	Sciatic Nerve (proximal)
X	Frontal lobe		
X	Parietal lobe with diencephalon		OTHER
X	Midbrain with occipital and temporal lobe		Sural Nerve
X	Pons	X	Tibial Nerve (proximal and distal)
X	Medulla oblongata		Peroneal Nerve
	SPINAL CORD	X	Lumbar dorsal root ganglion
		X	Lumbar dorsal root fibers

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X	Cervical swelling I (C1-C3)	X	Lumbar ventral root fibers
X	Cervical swelling II (C3-C5)	X	Cervical dorsal root ganglion
X	Thoracic cord (T5-T8)	X	Cervical dorsal root fibers
X	Lumbar swelling (L1-L4)	X	Cervical ventral root fibers
	OTHER	X	All gross lesions
X	Gasserian ganglia with nerve		
X	Olfactory epithelium (nasal cavity, level III)		
X	Pituitary gland		
X	Eyes (with retina and optic nerve)		
X	Skeletal muscle (gastrocnemius)		

^a Data were obtained from page 55 of report MRID 45902304

All tissues collected from the control and 800 mg/kg groups, as well as the frontal lobe, parietal lobe, cerebellum, eyes, and gross lesions from all dose groups were routinely processed for microscopic evaluation.

D. DATA ANALYSIS

1. **Statistical analyses** - The data were analyzed using the following statistical methods, and the level of significance was set at $p \leq 0.05$ for all tests:

Parameter	Statistical Methods
Food consumption (maternal), body weight and body weight gain (maternal and pups, for pups the litter means were used), duration of gestation, # of pups delivered per litter	Dose groups were compared to controls using Dunnett's test for the hypothesis of equal means.
Fertility index, gestation index, # of females with liveborn pups, # of females with stillborn pups, # of females with all stillborn pups, live birth index, # of stillborn pups, # of dead pups, # of pups cannibalized, # of pups sacrificed moribund, viability index, lactation index, water maze evaluation	Each dose group was compared pairwise to the control using Fisher's Exact test for the hypothesis of equal proportions.
Water maze evaluation	Each dose group was compared pairwise to the control using Wilcoxon test for the hypothesis of equal medians.
Motor activity, startle response	A non-parametric Kruskal-Wallis test was performed followed by a Mann-Whitney U-test, as necessary.
Brain weights	A non-parametric Kruskal-Wallis test was performed followed by a Wilcoxon test, as necessary.
Morphometric parameters	Each dose group was compared pairwise to the control using Wilcoxon test for the hypothesis of equal medians. (Brain width and length; with Bonferroni-Holm-adjustment)

2. **Indices** - The following indices were calculated by the Sponsor:

Fertility index (%) = $\frac{\text{\# of females pregnant}}{\text{\# of females}} \times 100$

of females mated

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

$$\text{Live birth index (\%)} = \frac{\text{\# of live born pups at birth}}{\text{Total \# of pups born}} \times 100$$

It was stated that the following indices were calculated; however, the data were not provided. Therefore, the reviewers calculated these indices using the formulas provided and included the data in the summary tables.

$$\text{Viability index (\%)} = \frac{\text{\# live pups on PND 4 (pre cull)}}{\text{\# live born pups on PND 0}} \times 100$$

$$\text{Lactation index (\%)} = \frac{\text{\# live pups on PND 21 (weaning)}}{\text{\# live pups on PND 4 (post cull)}} \times 100$$

3. Positive control data - Positive control data were provided with the concurrently submitted acute and subchronic neurotoxicity studies (MRIDs 45902303 and 45902201, respectively). Summaries of seven studies (MRIDs 45540501 through 45540507) performed to generate positive control data and validate the procedures and observers of the performing lab to conduct the FOB and to assess motor activity, neurotoxicity and behavioral effects were provided. Exposure to **3,3-Iminodipropionitrile** (2000 mg/kg, single i.p. dose) induced the following in both sexes: (i) decreased body weight; (ii) FOB effects (eg. ataxia, females only); (iii) decreased fore- and hindlimb grip strength; (iv) corneal opacities; (v) blood lacunae in the iris; (vi) anisocoria; and (vii) hematobulbus. Additionally, the following histopathological effects were noted: (i) axonal atrophy in the distal segments of the tibial, sural, and sciatic nerves; (ii) intraocular hemorrhage; (iii) retinal degeneration with atrophy; and (iv) degeneration and atrophy of the optic nerve. **Acrylamide** (40 mg/kg, 11 daily gavage doses in 2 weeks) induced the following in both sexes: (i) abnormal gait (ataxia, splay of toes of the hindlimbs and/or splay of the hind limbs); (ii) decreased fore- and hindlimb grip strength; and (iii) increased hindlimb foot splay. Additionally in the males, body weight and body weight gains were decreased, and decreased activity, reduced tail pinch response, and increased reaction time to hot-plate test were observed. In addition to decreased brain weight in both sexes, the following histopathological effects were noted: (i) selective Purkinje cell necrosis and vacuolation of the molecular layer of the cerebellar cortex; (ii) cytoplasmic remodeling in the lumbar spinal ganglia cells which resembles chromatolysis; (iii) Wallerian-like axonal degeneration of the sciatic, sural, tibial, and plantar nerves; (iv) neurofilament accumulation, decrease in or loss of synaptic vesicles, and swelling of synaptic terminals in the gastrocnemius muscle; and (v) neuronal necrosis in the mesencephalic trigeminal nucleus region of the midbrain in one male. In addition to the effects given above, acrylamide (30 mg/kg, daily gavage doses up to 4 weeks) induced mortality in both sexes. **Trimethyltin chloride** (6, 9, or 12 mg/kg, single i.p. dose) induced ataxia, tremors, convulsions, decreased grip strength, increased foot splay, and increased motor activity. Additionally, the following neuropathological effects were noted: (i) neuronal necrosis of the olfactory bulbs and midbrain; (ii) axonal degeneration of the cervical ganglia and peripheral

nerves; (iii) hydrocephalus internus of the frontal and parietal lobes; (iv) Purkinje cell necrosis in the pons with cerebellar cortex, mid-cerebellum, and medulla oblongata; (v) chromatolysis of alpha motor neurons in the cervical and lumbar spinal cord; and (vi) vacuolar degeneration of the lumbar ganglia. Inter-observer reliability was demonstrated using **carbaryl** (10 or 30 mg/kg, single i.p. dose), **nomifensin** (10 mg/kg, gavage on 2 days), and **diazepam** (3 mg/kg, i.p. on 2 days). All observers detected the FOB effects from carbaryl (abnormal body posture, tremors, repetitive chewing, impaired gait, and reduced rearing), the increased motor activity from nomifensin, and the decreased motor activity from diazepam.

II. RESULTS

A. PARENTAL ANIMALS

1. **Mortality, clinical signs, and functional observations** - No unscheduled deaths occurred during the study. No treatment-related clinical signs were noted at any dose during gestation. During lactation, corneal opacity was observed in the dams at all doses (Table 3). Other than the corneal opacity noted during clinical examinations, no treatment-related findings were observed during the open-field observations.

Table 3. Incidence (# affected) of corneal opacity in P females during lactation (PND 0-21).^a

Dose (mg/kg/day)			
0 (n=35)	8 (n=34)	80 (n=35)	800 (n=32)
0	4 ^b (12%)	22 ^c (63%)	12 ^c (38%)

a Data were obtained from page 107 of the study report.

b Observed on PNDs 13-21

c Observed on PNDs 7-21

2. **Body weight and food consumption** - Body weights and body weight gains for the P females are presented in Tables 4a and 4b, respectively. At 800 mg/kg/day, body weights were decreased ($p \leq 0.05$) on GD 13 (13%) and LD 14 (14%). Body weight gains were decreased ($p \leq 0.05$) in the ≥ 80 mg/kg/day dams during GDs 6-13 (10-15%). No significant decreases in body weight gain were noted at any dose during the lactation period; however, it should be noted that all groups (including controls) lost weight between LDs 14-21 (12.5-7.6 g). These decreases corresponded to the reductions ($p \leq 0.05$) noted in absolute (15-12%) food consumption during the gestation and lactation periods (Table 5).

Table 4a. Selected mean (\pm SD) body weights (g) for P females administered BAS 670H from GD 6 to LD 21. ^a

Interval (Days)	Dose (mg/kg/day)			
	0	8	80	800
Gestation (n=32-36)				
0	156.0 \pm 7.19	155.8 \pm 7.03	154.8 \pm 7.29	155.8 \pm 8.24
6	187.6 \pm 9.96	187.3 \pm 9.78	185.4 \pm 8.39	185.5 \pm 8.57
13	223.4 \pm 13.47	219.6 \pm 12.26	217.6 \pm 11.70	215.9 \pm 10.67* (13)
20	280.2 \pm 19.39	273.6 \pm 20.31	274.0 \pm 19.28	272.1 \pm 15.51
Lactation (n=22-33)				
1	218.5 \pm 16.69	219.9 \pm 12.90	217.2 \pm 14.30	212.1 \pm 10.38
7	243.6 \pm 17.94	240.3 \pm 12.84	235.2 \pm 14.26	235.3 \pm 10.91
14	258.9 \pm 17.70	255.7 \pm 14.98	254.3 \pm 14.73	247.7 \pm 13.42* (14)
21	252.7 \pm 15.57	248.7 \pm 13.57	246.7 \pm 16.09	245.2 \pm 11.49

a Data were obtained from pages 111 and 113 of the study report. Percent difference from control (calculated by reviewers) is presented parenthetically.

* Significantly different from controls at $p \leq 0.05$

Table 4b. Selected mean (\pm SD) body weight gains (g) for P females administered BAS 670H from GD 6 to LD 21. ^a

Interval (Days)	Dose (mg/kg/day)			
	0	8	80	800
Gestation (n=32-36)				
0-6	31.6 \pm 4.31	31.5 \pm 5.70	30.6 \pm 5.46	29.7 \pm 4.83
6-13	35.8 \pm 6.27	32.3 \pm 5.90	32.2 \pm 5.15* (110)	30.4 \pm 6.63** (115)
13-20	56.8 \pm 9.95	54.0 \pm 13.65	56.4 \pm 11.73	56.2 \pm 9.55
Overall (0-20)	124.2 \pm 14.33	117.9 \pm 19.22	119.2 \pm 16.31	116.3 \pm 15.72
Lactation (n=22-30)				
1-7	22.7 \pm 5.98	21.3 \pm 7.45	19.7 \pm 7.20	24.0 \pm 9.33
7-14	15.3 \pm 8.76	15.4 \pm 9.89	19.0 \pm 6.36	12.4 \pm 6.58
14-21	-6.2 \pm 10.68	-7.0 \pm 6.74	-7.6 \pm 9.65	-2.5 \pm 7.95
Overall (1-21)	31.8 \pm 10.61	29.8 \pm 8.76	31.2 \pm 10.20	33.9 \pm 10.88

a Data were obtained from pages 112 and 114 of the study report. Percent difference from control (calculated by reviewers) is presented parenthetically.

* Significantly different from controls at $p \leq 0.05$

** Significantly different from controls at $p \leq 0.01$

Food consumption (g/animal/day) was reduced ($p \leq 0.05$) in the >80 mg/kg/day dams during GDs 6-13 (15% each), and LDs 1-7 (16% each) and 7-14 (18-12%, Table 5). Additionally, overall (LDs 1-14) food consumption during lactation was decreased (not statistically significant) by 8-10% in the >80 mg/kg/day dams compared to controls.

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Table 5. Selected mean (\pm SD) absolute (g/animal/day) food consumption for P females administered BAS 670H from GD 6 to LD 21. ^a

Interval (Days)	Dose (mg/kg/day)			
	0	8	80	800
Gestation (n=32-36)				
0-6	17.4 \pm 1.44	17.5 \pm 1.34	17.1 \pm 1.38	17.1 \pm 1.22
6-13	21.3 \pm 1.56	20.9 \pm 1.63	20.3 \pm 1.52* (15)	20.3 \pm 1.63* (15)
13-20	23.2 \pm 1.81	23.1 \pm 1.97	22.7 \pm 1.94	23.1 \pm 1.70
Overall (0-20) ^b	20.6 \pm 2.94	20.5 \pm 2.84	20.0 \pm 2.82	20.2 \pm 3.04
Lactation (n=22-30)				
1-7	35.9 \pm 2.81	35.8 \pm 1.97	33.7 \pm 2.92** (16)	33.8 \pm 2.52* (16)
7-14	52.0 \pm 3.60	50.2 \pm 2.93	47.7 \pm 3.14** (18)	45.9 \pm 3.58** (112)
Overall (1-14) ^b	44.0 \pm 11.41	43.0 \pm 10.22	40.7 \pm 9.89 (18)	39.9 \pm 8.59 (110)

a Data were extracted from pages 109-110 of the study report. Percent difference from control (calculated by reviewers) is presented parenthetically.

b Values reported as mean of means; n=2-3.

* Significantly different from controls at $p \leq 0.05$

** Significantly different from controls at $p \leq 0.01$

3. **Test substance intake** - Mean compound intake (mg/kg bw/day) during the gestation and lactation periods was determined based on maternal food consumption and body weight (Table 6).

Table 6. Mean (\pm SD) test substance intake (mg/kg/day) for P females administered BAS 670H from GD 6 to LD 21. ^a

Interval	Nominal Dose (mg/kg/day)	Actual Dose (mg/kg/day)
GD 6-20	0	0.0
	8	8.2
	80	83.7
	800	848.6
LD 1-14	0	0.0
	8	6.7
	80	69.6
	800	739.1

a Data were obtained from pages 115-116 of the study report.

4. **Reproductive performance** - The fertility index was slightly decreased at 800 mg/kg/day (82%) compared to controls (92%). Additionally, the incidence (# treated vs 0 controls) of females with stillborn pups was increased ($p \leq 0.05$) at all doses (3-6). All other indices (gestation length, gestation index, mean # of pups/litter, live birth index, and sex ratio) were comparable between treated and control animals (Table 7). **Note:** In a rat multigeneration reproduction study with BAS 670H (MRID 45902214), there was an increase in the number of pups born dead at 4 ppm (13) (lowest dose tested) in the F2 litter resulting in a lower live birth index compared to controls (2).

Table 7. Delivery observations in P females administered BAS 670H from GD 6 to LD 21. ^a

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Observation	Dose (mg/kg/day)			
	0	8	80	800
# of females mated	38	39	39	39
# of females pregnant	35	35	36	32
Fertility index (%)	(92)	(90)	(92)	(82)
Mean (\pm SD) gestation length (days)	21.7 \pm 0.5	21.9 \pm 0.3*	21.9 \pm 0.3*	21.9 \pm 0.3*
# of females with liveborn	35	34	35	32
Gestation index (%)	(100)	(97)	(97)	(100)
# of females with stillborn pups (%)	0	6 (18)*	6 (17)*	3 (9)*
# of females with all stillborn pups	0	0	0	0
Total # of pups delivered	314	279	325	279
Mean (\pm SD) # of pups/litter	9.0 \pm 2.18	8.2 \pm 1.92	9.3 \pm 1.69	8.7 \pm 2.07
Total # of liveborn pups	314	273* (113%)	319*(12%)	275* (112%)
Live birth index (%)	(100)	(98)	(98)	(99)
Total # of stillborn pups (%)	0 (0.0)	6 (2.2)*	6 (1.8)*	4 (1.4)*
Sex ratio (% males) on Day 0	45.9	49.5	48.3	48.7

a Data were obtained from pages 117 and 120 of the study report.

* Significantly different from controls at $p \leq 0.05$

5. Maternal postmortem results

a. **Macroscopic examination** - Other than staining the uteri and counting the number of implantation sites in the dams that did not deliver a litter, no macroscopic evaluations of the dams were performed.

b. **Microscopic examination** - No microscopic examinations were conducted on the dams.

B. OFFSPRING

1. **Viability and clinical signs** - No significant treatment-related differences in live litter size, post-natal survival, or sex ratios were observed in any treated group through PND 21 (Table 8). Clinical signs were limited to corneal opacity in both sexes at 80 mg/kg (1/sex) and 800 mg/kg (3/sex).

Table 8. F₁ live litter size and viability. ^a

Observation	Dose (mg/kg/day)			
	0	8	80	800
Number of litters	35	34	35	32
Total # of pups delivered	314	279	325	279
# of liveborn	314	273*	319*	275*
# of stillborn	0	6*	6*	4*
Live birth index (%)	100	98	98	99
Mean live pups/litter (total pups)				
PND 0	9.0 \pm 2.18 (314)	8.0 \pm 1.98 (273)	9.1 \pm 1.71 (319)	8.6 \pm 2.03 (275)
PND 4 ^b	7.5 \pm 4.02 (264)	5.8 \pm 4.43 (198)	8.3 \pm 3.20 (289)	6.5 \pm 4.30 (209)

PND 4 ^c	6.2±3.41 (216)	5.2±3.88 (176)	6.9±2.84 (240)	5.8±3.65 (184)
PND 11	6.2±3.41 (216)	5.2±3.88 (176)	6.9±2.84 (240)	5.7±3.62 (182)
PND 17	5.6±3.12 (196)	4.6±3.45 (156)	6.3±2.64 (220)	5.0±3.22 (161)
PND 21	5.6±3.12 (196)	4.6±3.45 (156)	6.3±2.64 (220)	5.0±3.22 (161)
Sex ratio (% male)				
PND 0	45.9	49.5	48.3	48.7
PND 21	43.9	48.7	48.2	48.4
# of deaths (PNDs 1-4)	3	1	7	8
(PNDs 5-7)	0	0	0	0
(PNDs 8-14)	0	0	0	2
(PNDs 15-21)	0	0	0	0
Viability index (%) ^d	84.0	72.5	90.6	76.0
Lactation index (%) ^e	90.7	88.6	91.7	87.5

a Data were obtained from pages 118-120 of the study report.

b Before culling

c After culling

d Calculated by reviewers using the formula: Viability index (%) = $\frac{\# \text{ live pups on PND 4 (pre cull)}}{\# \text{ live born pups on PND 0}} \times 100$

e Calculated by reviewers using the formula: Lactation index (%) = $\frac{\# \text{ live pups on PND 21 (weaning)}}{\# \text{ live pups on PND 4 (post cull)}} \times 100$

2. Body weight and food consumption - Throughout pre-weaning (Days 4-21), body weights were decreased in both sexes at ≥ 80 mg/kg (18-15%, Table 9a). Likewise, overall (Days 4-21) pre-weaning body weight gain was decreased in both sexes at ≥ 80 mg/kg (115-17%). The post-weaning body weight data were presented by subset. To better present the data, the reviewers calculated the means of the means for the body weights and body weight gains. Throughout post-weaning, body weights were decreased in the ≥ 80 mg/kg males (17-19%) and females (16-20%, Table 9b); however, the differences became less over time. Body weight gains were decreased in the ≥ 80 mg/kg males during Weeks 0-2 (112-15) and Weeks 3-4 (19-12), and in the ≥ 80 mg/kg females during Weeks 0-1 (110-13%). Overall (Weeks 0-5) body weight gains were slightly decreased in the ≥ 80 mg/kg males (19% each); however, overall gains were similar between treated females and controls. Food consumption was not reported for the F₁ animals.

Table 9a. Selected mean (\pm SD) F₁ pup pre-weaning body weights and body weight gains (g).^a

Post-natal Day	Dose (mg/kg/day)			
	0	8	80	800
Males				
1	6.9±0.71	7.0±0.68	6.5±0.68	6.6±0.71
4 ^b	10.3±1.32	10.4±0.86	9.3±1.17** (110)	9.4±0.93* (19)
4 ^c	10.3±1.34	10.4±0.86	9.3±1.19** (110)	9.5±0.93* (18)
11	23.8±2.47	22.9±1.78	20.9±2.59** (112)	20.7±1.71** (113)
21 ^d	48.7±4.35	47.3±2.95	41.8±4.81** (114)	41.4±2.73** (115)
Overall (Days 4-21) Gain	38.4±3.37	37.0±2.63	32.5±4.02** (115)	32.0±2.73** (117)

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Females				
1	6.5±0.56	6.5±0.59	6.2±0.67	6.3±0.70
4 ^b	9.9±1.17	9.8±0.67	8.9±1.15** (110)	9.1±0.96* (18)
4 ^c	9.9±1.16	9.8±0.76	9.0±1.14** (19)	9.1±0.93* (18)
11	23.4±2.29	22.0±1.58	20.1±2.38** (114)	20.1±1.52** (114)
21 ^d	47.4±3.69	45.4±2.85	40.2±4.38** (115)	40.1±2.31** (115)
Overall (Days 4-21) Gain	37.5±2.76	35.6±2.66	31.2±3.57** (117)	31.0±2.26** (117)

a Data were obtained from pages 121-124 of the study report. Percent difference from controls (calculated by reviewers) is presented parenthetically. During pre-weaning, n=22-33 litters (pre-culling) or n=22-30 litters (post-culling).

b Pre-culling

c Post-culling

d Excludes values for rats from Subset 1, these animals were sacrificed on PND 11.

* Significantly different from controls at p≤0.05

** Significantly different from controls at p≤0.01

Table 9b. Selected mean F₁ pup post-weaning body weights and body weight gains (g).^a

Weeks	Dose (mg/kg/day)				Included Subsets
	0	8	80	800	
Males					
0	54.2	51.4	44.9 (117)	43.7 (119)	3, 4, 5, 6
1	96.2	89.0	80.7 (116)	79.2 (118)	3, 4, 5, 6
2	150.0	138.4	127.2 (115)	126.6 (116)	3, 4, 6
3	197.6	186.4	172.9 (113)	173.4 (112)	3, 4, 6
4	243.0	228.5	214.3 (112)	213.4 (112)	3, 4, 6
5	286.0	271.2	256.2 (110)	255.8 (111)	3, 4, 6
6	309.2	299.3	281.0 (19)	287.1 (17)	6
BW gain (Weeks 0-1)	42.0	37.7	35.9 (115)	35.5 (115)	3, 4, 5, 6
BW gain (Weeks 1-2)	53.1	48.1	46.7 (112)	46.4 (113)	3, 4, 6
BW gain (Weeks 3-4)	45.4	42.1	41.3 (19)	40.0 (112)	3, 4, 6
Overall (Weeks 0-5) gain	231.5	219.6	211.5 (19)	211.6 (19)	3, 4, 6
Females					
0	52.6	49.1	42.1 (120)	42.9 (118)	3, 4, 5, 6
1	89.0	84.6	73.9 (117)	75.5 (115)	3, 4, 5, 6
2	125.7	122.0	110.7 (112)	109.8 (113)	3, 4, 6
3	149.3	150.7	137.8 (18)	135.7 (19)	3, 4, 6
4	169.0	169.0	156.7 (17)	153.9 (19)	3, 4, 6
5	186.3	188.6	176.0 (16)	172.1 (18)	3, 4, 6
6	198.6	206.2	187.6 (16)	182.5 (18)	6
BW gain (Weeks 0-1)	36.4	35.5	31.8 (113)	32.6 (110)	3, 4, 5, 6
BW gain (Weeks 1-2)	36.1	37.5	35.9	34.8	3, 4, 6
Overall (Weeks 0-5) gain	133.7	139.4	133.4	129.8	3, 4, 6

a The values in this table (mean of means) were calculated by the reviewers from the data obtained from pages 135-150 of the study report. Percent difference from control (calculated by reviewers) is presented parenthetically.: n = 10/subset.

3. Developmental landmarks

a. **Sexual maturation** - A slight delay ($p \leq 0.01$) in time to preputial separation was noted at 80 (45.6 days) and 800 mg/kg (46.3 days) compared to controls (43.6 days, Table 10). No treatment-related effect on time to vaginal patency was observed.

Table 10. Sexual maturation (mean days \pm SD) in F₁ generation rats.^a

Parameter	Dose (mg/kg/day)			
	0	8	80	800
N (M/F)	30/30	30/30	30/30	30/30
Preputial separation (Males)	43.6 \pm 2.08	44.3 \pm 1.42	45.6 \pm 1.89**	46.3 \pm 2.06**
Vaginal patency (Females)	31.0 \pm 1.75	31.8 \pm 2.25	31.9 \pm 1.66	32.0 \pm 1.30

a Data were obtained from pages 125-126 of the study report.

** Significantly different from controls at $p \leq 0.01$

4. Behavioral assessments

a. **Functional observational battery** - No treatment-related behavioral effects were observed. Incidence (#affected/10 treated vs 0/10 controls) of corneal opacity was observed in one 800 mg/kg male on Day 60, one 80 mg/kg female on Day 21, and one 800 mg/kg female on Days 45 and 60.

b. **Motor activity** - No significant differences from controls were noted in overall session cumulative distance or number of rears in either sex at any dose (Tables 11a and 11b). Several isolated significant findings were noted at various intervals throughout motor activity testing in distance (Tables 12a and 12b) and number of rears (Tables 12c and 12d). Habituation was unaffected by treatment.

Table 11a. Mean (\pm SD) motor activity data (cumulative distance [cm]) in F₁ pups in Subset 3.^a

Post-natal Day	Dose (mg/kg/day)			
	0	8	80	800
Males				
13	2272.3 \pm 826.0	1920.0 \pm 953.7	3016.5 \pm 912.6	2696.7 \pm 824.7
17	3690.5 \pm 2221.5	3894.1 \pm 2321.6	2917.8 \pm 858.8	5062.2 \pm 2747.5
21	3057.9 \pm 920.4	2738.3 \pm 1245.8	3610.6 \pm 2965.7	4584.2 \pm 3252.0
60	9470.4 \pm 1590.7	10856.0 \pm 1267.3	10198.0 \pm 913.7	10990.0 \pm 1832.3
Females				
13	2572.5 \pm 943.0	2663.3 \pm 1126.9	2160.0 \pm 730.8	1693.1 \pm 859.3
17	3901.8 \pm 2154.4	3734.2 \pm 1663.8	4362.1 \pm 4042.5	4181.6 \pm 4501.5
21	3333.0 \pm 1207.9	2274.1 \pm 475.7	3443.6 \pm 1644.7	2747.7 \pm 1821.5
60	12006.0 \pm 3253.3	12128.0 \pm 2572.8	13621.0 \pm 2427.9	13000.0 \pm 1440.9

a Data were obtained from pages 169-184 of the study report; n=6-10.

Table 11b. Mean (\pm SD) motor activity data (# of rears) in F₁ pups in Subset 3. ^a

Post-natal Day	Dose (mg/kg/day)			
	0	8	80	800
Males				
13	13.7 \pm 11.1	9.4 \pm 12.5	5.0 \pm 3.9	14.3 \pm 11.1
17	130.1 \pm 105.1	155.7 \pm 155.8	59.5 \pm 25.7	137.1 \pm 125.9
21	55.9 \pm 33.0	35.0 \pm 19.6	49.5 \pm 47.9	62.5 \pm 64.2
60	307.8 \pm 90.0	358.5 \pm 101.1	304.8 \pm 105.6	334.3 \pm 58.7
Females				
13	22.2 \pm 14.6	14.9 \pm 13.4	10.4 \pm 8.9	7.8 \pm 13.9
17	166.2 \pm 116.7	131.0 \pm 87.6	115.3 \pm 101.4	103.8 \pm 120.5
21	57.1 \pm 41.4	33.4 \pm 12.0	53.2 \pm 44.4	34.7 \pm 26.8
60	308.6 \pm 96.3	336.0 \pm 68.8	394.1 \pm 59.0	374.3 \pm 55.5

a Data were obtained from pages 185-200 of the study report; n=6-10.

Table 12a. Mean (\pm SD) sub-session motor activity (distance) in F₁ male pups in Subset 3. ^a

Sub-session		Dose (mg/kg/day)			
		0	8	80	800
PND 13	1	413.6 \pm 185.9	353.2 \pm 107.9	426.2 \pm 191.0	362.7 \pm 150.9
	2	167.0 \pm 218.2	187.1 \pm 121.8	257.5 \pm 176.8	177.6 \pm 108.7
	3	296.6 \pm 330.9	121.5 \pm 116.0	163.8 \pm 162.2	179.9 \pm 175.6
	4	254.6 \pm 212.0	192.3 \pm 202.2	266.7 \pm 243.4	159.2 \pm 138.1
	5	411.1 \pm 319.4	226.7 \pm 221.5	270.2 \pm 271.1	251.4 \pm 186.4
	6	257.3 \pm 275.4	85.9 \pm 137.3	284.0 \pm 247.2	246.1 \pm 289.1
	7	111.3 \pm 118.0	138.1 \pm 158.5	460.5 \pm 433.3	136.8 \pm 141.1
	8	120.2 \pm 108.9	70.2 \pm 111.7	256.4 \pm 272.6	225.6 \pm 213.1
	9	61.5 \pm 80.7	116.1 \pm 204.5	182.0 \pm 141.6*(1196)	258.1 \pm 231.0*(1320)
	10	70.6 \pm 80.7	126.8 \pm 239.7	191.4 \pm 197.7	235.3 \pm 248.3
	11	48.6 \pm 23.2	143.2 \pm 219.9	185.2 \pm 299.1	247.0 \pm 264.9
	12	59.8 \pm 38.7	158.9 \pm 394.6	72.5 \pm 94.9	217.2 \pm 137.0
PND 17	1	1086.3 \pm 235.1	817.2 \pm 187.8	930.9 \pm 306.3	823.7 \pm 265.9
	2	607.5 \pm 278.9	573.0 \pm 267.3	517.2 \pm 302.4	582.7 \pm 322.6
	3	347.5 \pm 368.0	358.2 \pm 360.4	166.8 \pm 230.3	397.9 \pm 305.4
	4	297.3 \pm 446.2	251.0 \pm 420.0	166.0 \pm 255.4	372.6 \pm 343.6
	5	298.3 \pm 450.6	179.1 \pm 276.4	249.2 \pm 377.8	414.2 \pm 404.7
	6	234.8 \pm 315.1	127.6 \pm 154.0	210.1 \pm 234.0	344.5 \pm 323.1
	7	179.1 \pm 274.9	101.0 \pm 164.5	64.3 \pm 35.7	320.9 \pm 296.4
	8	150.9 \pm 218.0	229.9 \pm 318.0	113.6 \pm 168.0	522.6 \pm 480.4
	9	93.1 \pm 166.3	329.1 \pm 382.2	94.0 \pm 137.8	372.2 \pm 514.4
	10	74.6 \pm 86.2	386.1 \pm 482.7	198.3 \pm 371.0	250.6 \pm 409.1
	11	178.9 \pm 327.3	269.6 \pm 330.2	146.8 \pm 257.5	350.9 \pm 456.3
	12	142.2 \pm 154.6	272.5 \pm 443.9	60.7 \pm 76.1	309.6 \pm 369.5
PND 21	1	1462.9 \pm 276.0	1033.1 \pm 242.0**(129)	1082.0 \pm 273.3**(126)	1387.1 \pm 590.1

(table continues next page)

Sub-session		Dose (mg/kg/day)			
		0	8	80	800
	2	756.2±377.4	663.7±255.6	578.7±316.5	558.0±392.3
	3	383.6±345.6	258.7±212.4	419.1±304.7	426.2±286.5
	4	293.8±278.5	107.8±125.2	272.8±302.7	225.0±250.0
	5	30.5±42.0	62.9±104.9	222.1±246.7	299.7±424.3
	6	14.2±12.0	91.4±151.5	223.7±405.1	318.4±331.3
	7	31.1±24.0	88.7±169.2	160.1±288.7	197.6±295.8
	8	9.5±10.5	66.1±87.0*(1596)	204.3±368.6**(12051)	176.6±218.1**(11759)
	9	15.0±15.3	147.9±272.9	152.4±325.1	215.5±352.2
	10	28.0±21.2	69.1±149.6	68.8±143.2	261.9±380.6
	11	24.1±15.3	64.0±73.5	95.4±203.8	302.5±361.9
	12	9.0±12.0	85.0±210.0	131.2±318.1*(11358)	215.7±328.1**(12297)

(table continues next page)

Sub-session		Dose (mg/kg/day)			
		0	8	80	800
PND 60	1	1586.2±279.3	1536.5±177.7	1461.8±186.7	1580.2±273.3
	2	1318.4±233.7	1409.0±195.0	1395.3±171.9	1318.9±233.8
	3	1116.3±286.4	1147.3±369.9	1190.4±217.3	1224.9±126.3
	4	894.9±242.4	1034.0±231.4	984.4±200.4	1093.9±187.4
	5	816.4±301.3	1041.7±203.5	957.6±124.1	1056.7±229.8
	6	794.0±264.2	864.1±236.8	862.3±276.8	932.2±208.4
	7	718.2±205.4	853.5±258.2	708.0±168.2	830.2±144.9
	8	724.4±196.6	863.6±295.4	752.5±221.3	782.9±316.0
	9	646.3±330.4	575.1±230.0	720.3±338.6	679.9±293.3
	10	385.9±290.5	602.6±207.9	462.4±307.3	699.1±313.0
	11	285.4±324.2	523.8±368.2	356.4±230.3	466.7±312.9
	12	184.1±244.5	404.7±467.1	346.1±335.3	324.7±241.4

a Data were obtained from pages 169-176 of the study report; n=6-10. Percent difference from control (calculated by reviewers) is presented parenthetically.

* Significantly different from controls at $p \leq 0.05$

** Significantly different from controls at $p < 0.01$

Table 12b. Mean (\pm SD) sub-session motor activity (distance) in F₁ female pups in Subset 3. ^a

Sub-session		Dose (mg/kg/day)			
		0	8	80	800
PND 13	1	540.3±243.3	353.3±182.1	302.9±98.9	325.7±160.5
	2	382.0±367.8	244.7±147.9	262.8±97.5	141.5±118.0
	3	315.5±309.6	178.6±208.1	146.7±107.4	22.9±24.0**(193)
	4	218.2±204.1	187.2±140.3	165.7±188.6	153.0±170.8
	5	290.6±264.5	216.4±207.2	263.3±161.0	234.9±165.0
	6	208.7±233.8	223.6±206.0	241.0±205.9	286.7±232.2
	7	109.1±172.8	124.7±199.3	196.1±214.5	151.6±128.0
	8	80.4±133.3	301.9±275.4	117.2±134.6	138.8±184.8
	9	103.8±203.4	255.6±264.7	74.0±85.1	61.1±24.5
	10	108.6±164.2	145.3±147.2	220.6±232.8	49.0±43.6
	11	145.0±274.1	233.3±266.6	105.5±109.0	89.5±147.7
	12	70.3±71.9	198.7±340.2	64.2±43.3	38.3±47.5

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Sub-session		Dose (mg/kg/day)			
		0	8	80	800
PND 17	1	917.8±264.9	962.3±289.9	818.9±197.3	700.0±296.1
	2	649.1±307.2	771.2±214.3	678.8±195.9	551.0±353.7
	3	326.5±183.4	362.6±244.1	321.9±238.2	324.2±331.3
	4	308.8±388.7	201.1±207.6	271.8±475.2	335.0±343.8
	5	250.5±472.2	121.0±229.0	121.8±216.5	279.4±481.0
	6	344.9±382.9	289.4±336.5	285.0±367.9	233.5±495.5
	7	211.4±271.0	352.1±525.4	232.3±317.0	295.1±549.1
	8	83.4±113.6	109.2±130.8	210.1±434.7	243.3±369.0
	9	216.8±330.5	123.7±142.1	93.1±137.1	243.1±327.7
	10	253.1±414.1	128.4±170.3	305.7±727.7	441.2±599.9
	11	232.5±340.6	139.4±193.9	466.6±702.3	301.3±550.9
	12	107.1±215.2	173.8±257.1	556.4±939.3	234.6±421.6
PND 21	1	1319.4±255.8	1287.1±194.8	1227.0±215.7	1207.9±350.6
	2	679.9±229.2	521.3±184.3	551.7±218.6	512.0±275.4
	3	487.1±245.7	181.7±187.7	425.3±291.2	287.5±292.6
	4	331.0±269.1	56.3±109.1**(183)	284.4±265.7	185.5±313.2
	5	198.1±215.1	36.3±70.7*(182)	242.8±200.9	143.3±310.5
	6	102.4±128.5	47.0±98.0	291.5±334.3	107.1±231.8
	7	31.2±30.2	46.5±79.2	81.2±99.8	150.5±267.8
	8	65.7±114.2	26.7±30.3	54.5±101.7	25.7±37.2
	9	46.0±55.4	13.0±12.3	96.6±136.9	20.9±17.1
	10	16.1±15.0	22.8±14.2	136.3±206.9	31.7±41.6
	11	22.8±17.7	17.1±11.6	35.7±44.0	38.5±56.7
	12	33.3±22.2	18.2±12.0	16.4±13.2	37.3±38.0
PND 60	1	1843.4±337.6	1741.6±180.7	1646.3±135.2	1772.1±123.6
	2	1497.7±224.9	1357.2±215.0	1558.8±186.5	1453.0±265.4
	3	1305.8±348.4	1338.4±427.4	1332.6±277.5	1337.9±199.6
	4	1234.9±183.7	1166.9±208.9	1299.8±348.2	1262.3±245.0
	5	1093.4±457.6	1113.5±363.3	1181.4±328.9	1056.7±245.4
	6	922.7±142.7	1134.9±338.3	1066.8±468.5	1076.3±258.7
	7	874.5±436.0	806.7±302.8	1095.7±214.2	1031.5±290.5
	8	934.3±499.6	956.8±480.6	1055.0±419.2	927.4±135.1
	9	727.2±405.4	916.7±454.7	854.4±206.6	796.6±374.3
	10	802.7±421.8	663.8±397.3	985.1±364.2	865.1±188.5
	11	422.8±352.2	483.6±388.1	822.3±362.8	801.5±55.3
	12	346.5±508.1	448.3±349.7	723.0±238.0	619.9±171.7

a Data were obtained from pages 177-184 of the study report; n=6-10. Percent difference from control (calculated by reviewers) is presented parenthetically.

* Significantly different from controls at p≤0.05

** Significantly different from controls at p≤0.01

Table 12c. Mean (\pm SD) sub-session motor activity (# of rears) in F₁ male pups in Subset 3. ^a

Sub-session		Dose (mg/kg/day)			
		0	8	80	800
PND 13	1	3.1 \pm 4.3	1.4 \pm 1.8	0.6 \pm 0.8	0.2 \pm 0.4
	2	0.9 \pm 1.2	0.3 \pm 0.5	0.6 \pm 1.0	1.3 \pm 1.5
	3	2.8 \pm 3.9	0.3 \pm 1.0	0.3 \pm 0.5	1.3 \pm 3.3
	4	1.1 \pm 1.3	0.6 \pm 0.9	0.0 \pm 0.0	0.7 \pm 1.2
	5	1.8 \pm 2.6	1.1 \pm 1.5	0.7 \pm 1.5	0.8 \pm 1.2
	6	3.0 \pm 5.2	0.0 \pm 0.0	0.3 \pm 0.5	2.3 \pm 4.8
	7	0.1 \pm 0.3	0.9 \pm 1.7	0.6 \pm 0.8	0.2 \pm 0.4
	8	0.2 \pm 0.7	0.2 \pm 0.4	0.3 \pm 0.5	2.0 \pm 3.2
	9	0.1 \pm 0.3	1.7 \pm 4.6	0.3 \pm 0.8	1.8 \pm 3.0
	10	0.6 \pm 1.7	0.6 \pm 1.7	0.0 \pm 0.0	1.7 \pm 3.6
	11	0.0 \pm 0.0	0.9 \pm 1.8	0.7 \pm 1.9	0.8 \pm 1.3
	12	0.0 \pm 0.0	1.4 \pm 4.3	0.7 \pm 1.9	1.2 \pm 1.3
PND 17	1	37.1 \pm 17.1	33.2 \pm 6.5	21.7 \pm 6.5** (142)	17.0 \pm 10.4** (154)
	2	29.5 \pm 17.1	26.4 \pm 14.6	14.4 \pm 8.0* (151)	13.9 \pm 9.9* (153)
	3	14.2 \pm 15.7	15.2 \pm 18.6	3.0 \pm 4.9	9.7 \pm 9.7
	4	8.9 \pm 12.2	9.6 \pm 18.0	0.9 \pm 1.6	12.8 \pm 13.2
	5	9.4 \pm 14.1	6.8 \pm 12.8	6.3 \pm 12.6	12.3 \pm 16.6
	6	10.8 \pm 18.1	7.0 \pm 12.6	3.2 \pm 5.7	9.7 \pm 11.7
	7	5.8 \pm 10.8	4.7 \pm 8.5	0.1 \pm 0.3	7.9 \pm 12.1
	8	3.4 \pm 7.8	7.6 \pm 14.0	0.9 \pm 2.8	13.7 \pm 17.4
	9	2.2 \pm 6.6	9.3 \pm 15.9	1.7 \pm 3.8	10.3 \pm 16.6
	10	1.8 \pm 3.4	13.9 \pm 23.7	2.8 \pm 6.9	8.2 \pm 15.9
	11	5.0 \pm 13.8	13.3 \pm 18.0	3.4 \pm 8.6	11.9 \pm 17.9
	12	2.0 \pm 4.7	8.7 \pm 16.2	1.1 \pm 3.5	9.7 \pm 17.9
PND 21	1	24.4 \pm 11.2	16.5 \pm 6.6	12.6 \pm 5.1	17.4 \pm 9.7
	2	18.2 \pm 15.8	9.5 \pm 5.8	9.4 \pm 7.3	8.9 \pm 7.2
	3	9.3 \pm 11.0	3.5 \pm 5.5	7.0 \pm 11.0	7.4 \pm 7.2
	4	3.9 \pm 4.3	0.7 \pm 1.6	3.6 \pm 5.3	1.7 \pm 4.7
	5	0.0 \pm 0.0	0.6 \pm 1.9	4.3 \pm 6.7*	3.8 \pm 6.4
	6	0.0 \pm 0.0	0.8 \pm 2.2	3.6 \pm 6.9	3.3 \pm 6.8
	7	0.0 \pm 0.0	0.4 \pm 1.0	3.0 \pm 8.8	2.8 \pm 7.8
	8	0.0 \pm 0.0	0.1 \pm 0.3	2.8 \pm 6.2	1.8 \pm 5.0
	9	0.0 \pm 0.0	1.0 \pm 2.1	1.7 \pm 3.7	2.4 \pm 4.7
	10	0.0 \pm 0.0	0.4 \pm 1.3	0.0 \pm 0.0	4.9 \pm 8.7
	11	0.0 \pm 0.0	0.2 \pm 0.4	0.3 \pm 0.7	4.4 \pm 7.0*
	12	0.0 \pm 0.0	1.3 \pm 4.1	1.2 \pm 3.8	3.7 \pm 6.8

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Sub-session		Dose (mg/kg/day)			
		0	8	80	800
PND 60	1	54.1±14.5	51.6±12.7	47.1±13.6	53.5±10.3
	2	47.8±13.0	51.1±11.3	44.8±13.4	45.1±4.0
	3	36.2±13.7	41.1±8.4	37.3±13.0	39.4±8.4
	4	29.4±11.5	34.8±12.7	32.8±10.3	34.5±10.4
	5	26.1±12.5	34.6±12.4	28.8±6.8	32.8±7.1
	6	26.6±13.0	25.9±8.5	24.2±11.4	25.9±11.7
	7	24.2±10.3	27.4±15.1	20.6±10.9	21.5±8.4
	8	21.8±11.0	27.2±12.9	19.6±9.6	20.6±6.8
	9	18.0±12.6	20.7±11.8	15.8±10.8	20.4±11.0
	10	13.5±11.1	17.7±10.3	14.8±12.3	19.6±11.1
	11	6.2±6.1	16.3±13.5	9.9±9.5	13.2±9.7
	12	3.9±6.7	10.1±11.3	9.2±9.1	7.8±6.9

a Data were obtained from pages 185-192 of the study report; n=6-10. Percent difference from control (calculated by reviewers) is presented parenthetically.

* Significantly different from controls at $p \leq 0.05$

** Significantly different from controls at $p \leq 0.01$

Table 12d. Mean (\pm SD) sub-session motor activity (# of rears) in F₁ female pups in Subset 3. ^a

Sub-session		Dose (mg/kg/day)			
		0	8	80	800
PND 13	1	6.1±6.3	1.8±2.2	0.5±0.8**(192)	0.6±1.3*(190)
	2	3.9±3.3	0.8±1.2*(179)	1.1±1.0	0.0±0.0*(1100)
	3	2.9±5.4	1.5±3.2	0.4±0.5	0.0±0.0
	4	1.6±1.8	0.1±0.4	1.0±2.4	1.2±2.7
	5	1.4±2.0	0.6±1.4	1.5±2.5	0.4±0.9
	6	1.8±3.7	1.3±2.4	0.9±0.8	2.2±3.2
	7	1.3±4.1	0.4±1.1	0.9±1.1	0.0±0.0
	8	0.1±0.3	2.0±3.5	1.0±2.8	1.2±2.7
	9	0.2±0.6	2.0±3.9	0.3±0.5	0.0±0.0
	10	0.4±1.3	0.5±1.1	1.1±2.2	0.0±0.0
	11	2.0±6.3	2.0±3.7	1.4±2.6	2.2±4.9
	12	0.5±1.3	2.0±4.9	0.4±1.1	0.0±0.0

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Sub-session		Dose (mg/kg/day)			
		0	8	80	800
PND 17	1	37.7±15.4	33.7±12.3	20.5±9.6*(146)	21.3±9.1*(144)
	2	34.9±17.0	32.8±15.5	21.0±16.5	16.2±9.4*(154)
	3	12.4±12.5	14.0±15.1	11.9±15.0	7.9±9.5
	4	13.2±16.3	7.0±8.9	7.5±17.0	4.8±6.7
	5	10.2±18.2	3.9±10.6	4.9±11.6	5.8±11.8
	6	13.6±15.7	10.0±12.6	8.5±10.6	4.2±9.6
	7	11.7±18.6	10.8±18.2	6.4±11.5	8.1±15.9
	8	2.1±6.6	4.1±9.0	3.3±8.8	6.1±10.7
	9	5.8±12.4	3.2±6.5	2.0±3.2	5.5±9.3
	10	11.2±20.3	3.4±7.4	4.2±11.2	10.2±17.8
	11	9.3±18.5	3.1±6.9	14.2±20.5	7.1±17.2
	12	4.1±10.7	5.0±10.9	10.9±17.8	6.6±13.3
PND 21	1	21.1±9.6	20.1±8.9	20.5±14.5	15.7±9.7
	2	17.8±18.5	9.1±8.1	10.5±9.2	7.8±6.8
	3	9.7±7.5	2.4±4.5	6.2±5.7	4.6±7.2
	4	5.5±8.0	0.1±0.3	4.1±4.9	2.5±5.8
	5	1.7±2.5	0.7±2.2	3.2±3.6	1.4±4.1
	6	0.5±1.3	0.9±2.8	5.6±7.8	1.0±3.2
	7	0.0±0.0	0.1±0.3	0.7±1.5	1.7±3.8
	8	0.5±1.6	0.0±0.0	0.4±1.3	0.0±0.0
	9	0.3±0.7	0.0±0.0	0.8±1.5	0.0±0.0
	10	0.0±0.0	0.0±0.0	1.2±2.8	0.0±0.0
	11	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0
	12	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0
PND 60	1	55.4±16.2	58.8±8.8	60.0±10.2	55.0±10.3
	2	50.6±9.6	48.8±6.6	52.9±5.2	47.7±7.9
	3	33.5±10.3	40.0±7.5	40.6±8.6	42.8±9.8
	4	31.4±5.0	33.6±5.2	39.7±11.0	34.2±7.2
	5	27.1±12.2	27.0±8.0	34.6±11.2	30.8±12.6
	6	21.6±3.5	27.5±13.1	28.3±6.9	30.8±10.0
	7	18.6±11.9	19.6±7.0	27.7±7.4	27.7±10.4
	8	20.3±11.4	21.8±12.4	26.4±11.3	29.7±9.1
	9	16.8±9.9	22.6±11.6	21.0±6.1	18.5±6.4
	10	16.3±11.3	15.8±11.4	26.0±10.5	19.2±6.2
	11	8.8±10.3	10.4±9.8	19.9±9.0	20.0±5.3
	12	8.4±11.7	10.3±9.0	17.1±7.4	18.0±4.7

a Data were obtained from pages 193-200 of the study report; n=6-10. Percent difference from control (calculated by reviewers) is presented parenthetically.

* Significantly different from controls at p≤0.05

** Significantly different from controls at p≤0.01

c. **Auditory startle reflex habituation** -The mean auditory startle response data are presented in Table 13a. For males, maximum auditory startle response amplitude was decreased 30%, 27%,

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and 38% on PND 24 at 8, 80, and 800 mg/kg/day, respectively. For females, maximum auditory startle response amplitude was decreased 22%, 34%, and 54% on PND 24 at 8, 80, and 800 mg/kg/day, respectively. No significant differences from control were noted in startle response maximum amplitude at any dose in either sex on PND 60. On PND 24, latency was increased ($p \leq 0.05$) in the 800 mg/kg females during Blocks 3 & 4 (131-34%, Table 13b); however, no significant increase was observed in the average latency (over all 5 blocks). Additionally, latency was increased by 26-27% in the 8 mg/kg females during blocks 3 and 4. No significant differences in latency (individual blocks or overall) were observed in the males on PNDs 24 or 60, or in the females on PND 60.

Table 13a. Mean (\pm SD) auditory startle reflex maximum amplitude (G) data from F₁ rats in Subset 3. ^a

Observation ^b		Dose (mg/kg)			
		0	8	80	800
Males					
PND 24	Block 1	464.4 \pm 206.4	383.2 \pm 106.4(117)	380.9 \pm 159.7(118)	283.4 \pm 91.3(139)
	Block 2	417.2 \pm 173.1	330.0 \pm 175.3(121)	321.9 \pm 209.1(123)	220.3 \pm 118.4(147)
	Block 3	437.5 \pm 149.3	260.2 \pm 113.8**(141)	274.7 \pm 138.7**(137)	227.7 \pm 88.1**(148)
	Block 4	463.6 \pm 180.4	247.9 \pm 92.7*(147)	287.1 \pm 102.0*(138)	313.3 \pm 145.8(132)
	Block 5	394.0 \pm 139.7	309.6 \pm 108.2(121)	318.6 \pm 133.1(119)	300.5 \pm 135.7(124)
	Average	435.3 \pm 117.0	306.2 \pm 95.8*(130)	316.6 \pm 127.6(127)	269.0 \pm 104.3**(138)
PND 60	Block 1	1414.2 \pm 1021.6	769.0 \pm 251.8(146)	982.7 \pm 437.4(131)	830.8 \pm 505.9(141)
	Block 2	1055.0 \pm 1038.4	453.5 \pm 168.8(157)	621.3 \pm 271.6(141)	461.2 \pm 277.0(156)
	Block 3	997.6 \pm 982.3	378.5 \pm 169.1(162)	537.2 \pm 203.9(146)	436.6 \pm 226.2(156)
	Block 4	856.7 \pm 694.4	376.4 \pm 214.3(144)	430.6 \pm 155.9(150)	387.1 \pm 233.6(155)
	Block 5	832.6 \pm 609.6	347.9 \pm 170.5(158)	450.0 \pm 166.9(146)	390.8 \pm 203.8(153)
	Average	1031.2 \pm 810.2	465.0 \pm 152.5(155)	604.4 \pm 190.6(141)	501.3 \pm 253.9(151)
Females					
PND 24	Block 1	374.6 \pm 116.5	416.9 \pm 109.4	328.5 \pm 89.9(112)	279.7 \pm 87.0(125)
	Block 2	434.3 \pm 166.7	267.1 \pm 92.8*(138)	226.0 \pm 89.7**(148)	164.3 \pm 78.7**(162)
	Block 3	416.4 \pm 184.4	321.0 \pm 155.7(123)	234.7 \pm 77.0**(144)	166.7 \pm 99.1**(160)
	Block 4	403.3 \pm 179.8	272.4 \pm 113.8*(132)	249.9 \pm 65.7*(138)	155.3 \pm 72.4**(161)
	Block 5	372.1 \pm 172.2	291.0 \pm 119.3(122)	271.6 \pm 85.6(127)	147.7 \pm 75.8**(160)
	Average	400.1 \pm 145.3	313.7 \pm 102.2(122)	262.1 \pm 55.9**(134)	182.7 \pm 66.7**(154)
PND 60	Block 1	738.2 \pm 424.7	761.7 \pm 532.4	637.6 \pm 232.0(114)	626.1 \pm 244.7(115)
	Block 2	601.1 \pm 398.3	612.2 \pm 259.1	558.0 \pm 184.4(117)	473.3 \pm 174.1(121)
	Block 3	565.9 \pm 433.1	598.0 \pm 469.6	416.6 \pm 147.1(126)	354.8 \pm 136.9(137)
	Block 4	524.7 \pm 343.0	456.3 \pm 269.6(113)	398.9 \pm 187.9(124)	414.8 \pm 155.2(121)
	Block 5	469.6 \pm 208.3	511.3 \pm 533.3	375.2 \pm 159.3(120)	419.7 \pm 185.8(111)
	Average	579.9 \pm 348.5	587.9 \pm 372.9	477.3 \pm 162.7(118)	457.7 \pm 138.3(121)

a Data were obtained from pages 201-204; n=10. Percent difference from control (calculated by reviewers) is presented parenthetically.

b Block=10 consecutive trials

* Statistically different from controls at $p \leq 0.05$

** Statistically different from controls at $p \leq 0.01$

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Table 13b. Mean (\pm SD) auditory startle reflex latency (msec) data from F₁ rats in Subset 3. ^a

Observation ^b		Dose (mg/kg)			
		0	8	80	800
Males					
PND 24	Block 1	32.6 \pm 7.1	40.3 \pm 12.1	34.5 \pm 6.8	37.9 \pm 6.5
	Block 2	33.2 \pm 4.9	36.9 \pm 8.6	34.8 \pm 6.7	34.5 \pm 8.4
	Block 3	34.4 \pm 6.9	35.1 \pm 9.3	32.6 \pm 8.0	31.4 \pm 4.7
	Block 4	33.2 \pm 6.7	31.1 \pm 4.5	32.2 \pm 5.9	34.8 \pm 8.9
	Block 5	30.1 \pm 6.5	32.4 \pm 3.7	31.0 \pm 6.1	33.3 \pm 7.0
	Average	32.7 \pm 3.8	35.2 \pm 6.1	33.0 \pm 5.5	34.4 \pm 4.7
PND 60	Block 1	50.9 \pm 18.5	39.4 \pm 9.6	42.3 \pm 13.2	38.0 \pm 16.8
	Block 2	42.5 \pm 20.9	36.0 \pm 8.9	34.2 \pm 10.1	31.5 \pm 9.0
	Block 3	41.3 \pm 21.5	29.6 \pm 5.0	31.5 \pm 7.3	29.0 \pm 7.1
	Block 4	37.4 \pm 16.2	28.1 \pm 3.7	31.3 \pm 7.7	29.0 \pm 8.8
	Block 5	31.8 \pm 9.1	25.6 \pm 4.2	28.8 \pm 5.6	26.2 \pm 4.7
	Average	40.7 \pm 16.0	31.7 \pm 3.9	33.6 \pm 6.6	30.8 \pm 6.4
Females					
PND 24	Block 1	33.4 \pm 7.9	37.1 \pm 12.1	34.1 \pm 10.4	39.5 \pm 10.0
	Block 2	28.5 \pm 6.3	35.1 \pm 11.7	38.0 \pm 13.4	42.2 \pm 14.1
	Block 3	27.8 \pm 4.9	35.2 \pm 7.5*(127)	30.1 \pm 6.4	37.3 \pm 8.9*(134)
	Block 4	27.6 \pm 5.9	34.9 \pm 8.0*(126)	26.7 \pm 2.5	36.1 \pm 8.7*(131)
	Block 5	31.0 \pm 8.5	32.1 \pm 7.1	27.8 \pm 3.3	32.1 \pm 4.5
	Average	29.7 \pm 4.9	34.9 \pm 7.4	31.3 \pm 5.9	37.4 \pm 7.6
PND 60	Block 1	33.9 \pm 8.1	37.1 \pm 13.5	33.3 \pm 9.2	36.6 \pm 12.7
	Block 2	33.5 \pm 10.7	31.7 \pm 8.3	28.1 \pm 5.4	29.8 \pm 8.9
	Block 3	32.8 \pm 8.6	31.7 \pm 13.2	27.1 \pm 6.3	26.4 \pm 6.7
	Block 4	29.9 \pm 6.5	28.4 \pm 8.4	25.3 \pm 5.1	26.2 \pm 6.6
	Block 5	28.2 \pm 7.6	26.7 \pm 9.7	25.2 \pm 4.4	23.4 \pm 3.3
	Average	31.7 \pm 7.4	31.1 \pm 8.5	27.8 \pm 5.2	28.5 \pm 6.5

a Data were obtained from pages 205-208; n=10. Percent difference from control (calculated by reviewers) is presented parenthetically.

b Block=10 consecutive trials

* Statistically different from controls at $p \leq 0.05$

d. Learning and memory testing - No treatment-related differences in learning or memory were noted in any treated group relative to concurrent controls in the water maze test (Table 14). The decrease ($p \leq 0.01$) in relearning noted in the 80 mg/kg females of Subset 6 was considered unrelated to treatment because it was not dose-dependent.

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Table 14. Mean (\pm SD) water maze performance data in F₁ rats from Subset 5.^a

Parameter	Dose (mg/kg)			
	0	8	80	800
Subset 5				
Males				
Learning 1 (PND 23) ^b	4.1 \pm 0.99	4.1 \pm 1.20	3.3 \pm 1.06	2.9 \pm 1.66
Memory (PND 30) ^c	10	9	7	7
Learning 2 (PND 30) ^b	2.1 \pm 1.45	1.4 \pm 1.78	2.5 \pm 1.51	3.4 \pm 1.65
Females				
Learning 1 (PND 23) ^b	3.5 \pm 1.58	2.8 \pm 1.93	3.1 \pm 1.73	3.5 \pm 0.97
Memory (PND 30) ^c	7	6	9	7
Learning 2 (PND 30) ^b	2.0 \pm 1.94	3.3 \pm 1.42	2.3 \pm 1.57	1.9 \pm 2.02
Subset 6				
Males				
Learning 1 (PND 60) ^b	3.4 \pm 1.43	4.0 \pm 0.94	3.7 \pm 1.16	3.5 \pm 1.84
Memory (PND 67) ^c	8	9	9	8
Learning 2 (PND 67) ^b	2.7 \pm 1.89	2.2 \pm 1.69	3.0 \pm 1.89	1.9 \pm 1.52
Females				
Learning 1 (PND 60) ^b	3.7 \pm 1.42	3.5 \pm 1.51	4.0 \pm 1.25	4.0 \pm 0.94
Memory (PND 67) ^c	9	9	9	9
Learning 2 (PND 67) ^b	2.0 \pm 1.83	2.1 \pm 2.28	0.3 \pm 0.67**	1.3 \pm 1.42

a Data were obtained from pages 151 and 152 of the study report; n=10.

b Average of successful attempts.

c Number of animals that scored positive on the single trial.

** Statistically different from controls at $p \leq 0.01$

5. Postmortem results

a. **Brain weights** - Treatment-related decreases in absolute brain weights were seen in PND 62 males and PND 22 females at all dose levels.

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Table 15. Mean (\pm SD) absolute (g) and relative (to body, %) brain weights in F₁ rats.^a

Parameter	Dose (mg/kg)			
	0	8	80	800
- Males				
PND 22 (Subset 2)				
Terminal Body Weight (g)	49.22 \pm 5.25	46.62 \pm 3.83	41.94 \pm 3.63** (115)	42.25 \pm 2.87** (114)
Absolute Brain Weight (g)	1.688 \pm 0.085	1.662 \pm 0.074	1.568 \pm 0.054** (17)	1.567 \pm 0.061** (17)
Relative (to body) Weight (%)	3.451 \pm 0.240	3.582 \pm 0.267	3.761 \pm 0.317** (19)	3.723 \pm 0.266** (18)
PND 62 (Subset 4)				
Terminal Body Weight (g)	305.43 \pm 31.28	280.44 \pm 13.44	275.54 \pm 12.88	276.88 \pm 19.98
Absolute Brain Weight (g)	2.084 \pm 0.069	2.008 \pm 0.062* (14)	1.966 \pm 0.077** (16)	1.982 \pm 0.093* (15)
Relative (to body) Weight (%)	0.688 \pm 0.059	0.717 \pm 0.038	0.714 \pm 0.022	0.719 \pm 0.054
Females				
PND 22 (Subset 2)				
Terminal Body Weight (g)	48.69 \pm 2.88	45.49 \pm 3.84* (17)	38.52 \pm 7.18** (121)	39.56 \pm 2.31** (119)
Absolute Brain Weight (g)	1.67 \pm 0.054	1.602 \pm 0.053** (14)	1.450 \pm 0.070** (113)	1.473 \pm 0.026** (112)
Relative (to body) Weight (%)	3.438 \pm 0.171	3.538 \pm 0.239	3.916 \pm 0.914** (114)	3.734 \pm 0.208** (19)
PND 62 (Subset 4)				
Terminal Body Weight (g)	191.83 \pm 11.17	193.25 \pm 17.18	185.59 \pm 15.02	180.49 \pm 5.14** (16)
Absolute Brain Weight (g)	1.915 \pm 0.065	1.911 \pm 0.098	1.808 \pm 0.068** (16)	1.804 \pm 0.087** (16)
Relative (to body) Weight (%)	1.000 \pm 0.050	0.993 \pm 0.070	0.979 \pm 0.076	1.000 \pm 0.041

^a Data were obtained from pages 233-240 of the study report; n=10.

* Statistically different from controls at p \leq 0.05

** Statistically different from controls at p \leq 0.01

b) Neuropathology

1) Macroscopic examination - No treatment-related gross pathological findings were noted in any treated group at either PND 22 or 62. The cloudiness of the cornea noted in the 800 mg/kg males and females (1/10 each) on PND 62 had no corroborative histopathological finding.

2) Microscopic examination - Increased incidence (# affect/10 vs 0/10 controls) of minimal to moderate, bi- or unilateral keratitis of the cornea in both sexes was noted on PND 22 at 8 (1 male), 80 (3/sex) and 800 mg/kg (10/sex, Table 16). No adverse histopathological findings in tissues other than the brain were noted in any group at PND 62. Morphometric decreases were also observed in various brain regions at all dose levels in both sexes at PND 22 and PND 62. Collectively, these observations suggest that there was no NOAEL for brain effects.

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Table 16. Incidence (# affected/10) of keratitis of the cornea in F₁ rats on PND 22.^a

Severity	Dose (mg/kg)							
	0	8	80	800	0	8	80	800
	Males				Females			
Minimal	0	1	2	0	0	0	2	3
Slight	0	0	1	7	0	0	1	5
Moderate	0	0	0	3	0	0	0	2
Total	0	1	3	10	0	0	3	10

a Data were obtained from pages 630-655 of the study report.

Table 17a. Mean (\pm SD) morphometric measurements in F₁ rats from Subset 2 on PND 22.^a

Parameter	Dose (mg/kg)			
	0	8	80	800
Males				
Brain Length (cm)	1.860 \pm 0.03	1.847 \pm 0.03	1.814 \pm 0.03** (12)	1.806 \pm 0.02** (13)
Brain Width (cm)	1.497 \pm 0.02	1.499 \pm 0.03	1.468 \pm 0.01** (12)	1.471 \pm 0.02* (12)
Frontal Cortex, left (μ m)	1647 \pm 156	1800 \pm 107	1649 \pm 110	1595 \pm 110
Frontal Cortex, right (μ m)	1621 \pm 133	1781 \pm 104	1673 \pm 92	1625 \pm 115
Parietal Cortex, left (μ m)	1605 \pm 100	1725 \pm 84	1656 \pm 92	1574 \pm 122
Parietal Cortex, right (μ m)	1633 \pm 131	1711 \pm 93	1663 \pm 133	1635 \pm 99
Nucleus Caudatus, left (μ m)	3246 \pm 233	3411 \pm 171	3462 \pm 109	3297 \pm 197
Nucleus Caudatus, right (μ m)	3152 \pm 205	3485 \pm 172	3418 \pm 145	3112 \pm 138
Corpus Callosum (μ m)	236 \pm 41	241 \pm 45	232 \pm 30	244 \pm 38
Hippocampus, left (μ m)	1607 \pm 119	1511 \pm 92* (16)	1473 \pm 102** (18)	1504 \pm 101** (16)
Hippocampus, right (μ m)	1638 \pm 112	1477 \pm 97** (110)	1453 \pm 89** (11)	1521 \pm 100* (17)
Folium Pyramis (μ m)	348 \pm 30	328 \pm 38	320 \pm 25* (18)	301 \pm 17** (114)
Females				
Brain Length (cm)	1.851 \pm 0.03	1.831 \pm 0.02	1.783 \pm 0.04** (14)	1.780 \pm 0.02** (14)
Brain Width (cm)	1.494 \pm 0.03	1.469 \pm 0.02* (12)	1.432 \pm 0.04** (14)	1.446 \pm 0.02** (13)
Frontal Cortex, left (μ m)	1695 \pm 138	1751 \pm 87	1610 \pm 82	1521 \pm 80** (110)
Frontal Cortex, right (μ m)	1659 \pm 146	1709 \pm 104	1538 \pm 94* (17)	1512 \pm 69** (19)
Parietal Cortex, left (μ m)	1595 \pm 119	1682 \pm 78	1612 \pm 73	1512 \pm 99
Parietal Cortex, right (μ m)	1634 \pm 89	1658 \pm 113	1545 \pm 121* (15)	1523 \pm 85** (17)
Nucleus Caudatus, left (μ m)	3289 \pm 188	3449 \pm 219	3357 \pm 154	3285 \pm 162
Nucleus Caudatus, right (μ m)	3181 \pm 229	3345 \pm 195	3280 \pm 254	3201 \pm 181
Corpus Callosum (μ m)	212 \pm 42	227 \pm 24	214 \pm 29	216 \pm 37
Hippocampus, left (μ m)	1568 \pm 111	1464 \pm 133	1465 \pm 162	1466 \pm 69* (17)
Hippocampus, right (μ m)	1582 \pm 91	1472 \pm 138	1470 \pm 175* (17)	1499 \pm 53* (15)
Folium Pyramis (μ m)	322 \pm 44	323 \pm 35	312 \pm 22	311 \pm 26

a Data were obtained from pages 245-256 of the study report; n=10. Numbers presented parenthetically represent percent difference from control (calculated by reviewers).

* Statistically different from controls at $p \leq 0.05$

** Statistically different from controls at $p \leq 0.01$

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Table 17b. Mean (\pm SD) morphometric measurements in F₁ rats from Subset 4 on PND 62.^a

Parameter	Dose (mg/kg)			
	0	8	80	800
- Males				
Brain Length (cm)	2.095 \pm 0.04	2.042 \pm 0.04** (13)	2.027 \pm 0.03** (13)	2.024 \pm 0.05** (13)
Brain Width (cm)	1.538 \pm 0.03	1.543 \pm 0.03	1.541 \pm 0.03	1.542 \pm 0.03
Frontal Cortex, left (μ m)	1733 \pm 101	1715 \pm 52	1786 \pm 78	1643 \pm 97* (15)
Frontal Cortex, right (μ m)	1825 \pm 120	1740 \pm 94	1810 \pm 103	1631 \pm 131** (111)
Parietal Cortex, left (μ m)	1836 \pm 124	1710 \pm 81** (17)	1796 \pm 119	1660 \pm 208* (110)
Parietal Cortex, right (μ m)	1846 \pm 118	1576 \pm 93** (115)	1704 \pm 99* (18)	1693 \pm 160* (18)
Nucleus Caudatus, left (μ m)	3866 \pm 272	3882 \pm 196	3908 \pm 114	3728 \pm 363
Nucleus Caudatus, right (μ m)	3774 \pm 311	3782 \pm 119	3866 \pm 124	3647 \pm 296
Corpus Callosum (μ m)	264 \pm 41	261 \pm 34	273 \pm 35	266 \pm 64
Hippocampus, left (μ m)	1946 \pm 106	1750 \pm 139** (110)	1739 \pm 130** (111)	1827 \pm 162* (16)
Hippocampus, right (μ m)	1957 \pm 121	1742 \pm 111** (111)	1736 \pm 72** (111)	1822 \pm 142* (17)
Folium Pyramis (μ m)	344 \pm 25	343 \pm 23	350 \pm 27	361 \pm 42
- Females				
Brain Length (cm)	2.041 \pm 0.03	2.010 \pm 0.03* (12)	1.978 \pm 0.03** (13)	1.985 \pm 0.04** (13)
Brain Width (cm)	1.499 \pm 0.03	1.510 \pm 0.03	1.495 \pm 0.02	1.480 \pm 0.03
Frontal Cortex, left (μ m)	1713 \pm 71	1725 \pm 103	1575 \pm 82** (18)	1630 \pm 188
Frontal Cortex, right (μ m)	1770 \pm 56	1786 \pm 89	1616 \pm 84** (19)	1649 \pm 180
Parietal Cortex, left (μ m)	1821 \pm 115	1680 \pm 92** (18)	1669 \pm 80** (18)	1740 \pm 174
Parietal Cortex, right (μ m)	1808 \pm 94	1598 \pm 134** (112)	1590 \pm 125** (112)	1687 \pm 126* (17)
Nucleus Caudatus, left (μ m)	3862 \pm 153	3891 \pm 191	3815 \pm 176	3578 \pm 278** (17)
Nucleus Caudatus, right (μ m)	3709 \pm 147	3791 \pm 195	3626 \pm 238	3490 \pm 183** (16)
Corpus Callosum (μ m)	276 \pm 51	271 \pm 31	268 \pm 34	267 \pm 41
Hippocampus, left (μ m)	1852 \pm 146	1814 \pm 105	1691 \pm 119* (19)	1747 \pm 81* (16)
Hippocampus, right (μ m)	1861 \pm 121	1807 \pm 104	1663 \pm 77** (111)	1756 \pm 69** (16)
Folium Pyramis (μ m)	365 \pm 31	359 \pm 24	367 \pm 47	375 \pm 34

a Data were obtained from pages 245-256 of the study report; n=10. Numbers presented parenthetically represent percent difference from control (calculated by reviewers).

* Statistically different from controls at p \leq 0.05

** Statistically different from controls at p \leq 0.01

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS - The investigators concluded that signs of maternal toxicity were observed at all doses. Corneal opacities were noted at \geq 8 mg/kg, and decreased food consumption, body weight and body weight gains were observed at \geq 80 mg/kg. No adverse effects on reproductive performance were observed at any dose. In the offspring, general toxicity was characterized by retardation of general physical development (decreased body

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weight and body weight gains), which corresponded to a slight delay in a sexual maturation in the males. The decreased maximum amplitudes observed in the startle response test were also considered to be related to the decreased physical development, rather than signs of a disturbed motor/sensory function. No effects on motor activity or learning and memory were observed at any dose in either sex. No adverse neuropathological effects on various brain or peripheral nerve tissues were observed. Additionally, treatment-related minimal to moderate, bi- or unilateral keratitis of the cornea was noted in both sexes on PND 22 at ≥ 80 mg/kg. However, this finding was considered to be a result of high tyrosine levels in the blood commonly seen during treatment with this test material, rather than a direct effect of the test material. The maternal NOAEL was < 8 mg/kg/day (not established). The offspring NOAEL was 8 mg/kg/day.

B. REVIEWER'S COMMENTS -

In a developmental neurotoxicity study (MRID 45902304), BAS 670H was administered in the diet to pregnant Wistar rats (38-39/dose) from gestation day (GD) 6 to postnatal day (PND) 21 at nominal doses of 0, 8, 80, or 800 mg/kg/day (actual doses were 0/0, 8.2/6.7, 83.7/69.6, and 848.6/739.1 mg/kg/day [gestation/lactation]).

For maternal toxicity, clinical observations such as opacities of the cornea indicating general toxicity were noted in parental females of all dose groups. Food consumption and body weights/body weight gain were temporarily lowered in the mid (80 mg/kg body weight/day) and high dose (800 mg/kg body weight/day) dams during gestation and/or lactation. There are no indications from the clinical examinations that the administration of the test substance had adverse effects on reproductive performance of the parental females. Conception, gestation, parturition, lactation and weaning were comparable between the test substance- treated rats and the corresponding control.

For offspring, no significant treatment-related differences in live litter size, post-natal survival, or sex ratios were observed in any treated group through PND 21. Clinical signs were limited to corneal opacity in both sexes at 80 mg/kg (1/sex) and 800 mg/kg (3/sex). Throughout pre-weaning (Days 4-21), body weights were decreased in both sexes at ≥ 80 mg/kg (18-15%). Likewise, overall (Days 4-21) pre-weaning body weight gain was decreased in both sexes at ≥ 80 mg/kg (115-17%). Throughout post-weaning, body weights were decreased in the ≥ 80 mg/kg males (17-19%) and females (16-20%); however, the differences became less over time. Body weight gains were decreased in the ≥ 80 mg/kg males during Weeks 0-2 (112-15) and Weeks 3-4 (19-12), and in the ≥ 80 mg/kg females during Weeks 0-1 (110-13%). Overall (Weeks 0-5) body weight gains were slightly decreased in the ≥ 80 mg/kg males (19% each); however, overall gains were similar between treated females and controls. Food consumption was not reported for the F₁ animals.

A slight delay ($p \leq 0.01$) in time to preputial separation was noted at 80 (45.6 days) and 800 mg/kg (46.3 days) compared to controls (43.6 days). No treatment-related effect on time to vaginal patency was observed.

For behavioral assessments, no treatment-related effects were observed in FOB. Motor activity did not show significant differences from controls in overall session of cumulative distance or number of rears in either sex at any dose. Several isolated significant findings were noted at various intervals throughout motor activity testing in distance and number of rears. Habituation was unaffected by treatment.

Treatment-related effects were seen in the auditory startle response on PND 24 in both sexes at all dose levels. For auditory startle reflex response, the average maximum amplitude (over all 5 blocks) was decreased on PND 24 compared to controls in the 8 mg/kg/day (↓30% and ↓22%), 80 mg/kg (↓27% and ↓34%), and 800 mg/kg (↓38% and ↓54%) for males and females, respectively. No significant differences from control were noted in startle response maximum amplitude at any dose in either sex on PND 60. On PND 24, latency was increased ($p \leq 0.05$) in the 800 mg/kg females during Blocks 3 & 4 (↑31-34%); however, no significant increase was observed in the average latency (over all 5 blocks). Additionally, latency was increased by 26-27% in the 8 mg/kg females during blocks 3 and 4. No significant differences in latency (individual blocks or overall) were observed in the males on PNDs 24 or 60, or in the females on PND 60.

No treatment-related differences in learning or memory were noted in any treated group relative to concurrent controls in the water maze test. The decrease ($p \leq 0.01$) in relearning noted in the 80 mg/kg females of Subset 6 was considered unrelated to treatment because it was not dose-dependent.

Treatment-related decreases in absolute brain weights were seen in PND 62 males and PND 22 females at all doses.

Microscopic examination revealed increased incidences (# affect/10 vs 0/10 controls) of minimal to moderate, bi- or unilateral keratitis of the cornea in both sexes on PND 22 at 8 (1 male), 80 (3/sex) and 800 mg/kg (10/sex). No adverse histopathological findings in tissues other than the brain were noted in any group at PND 62. Numerous statistically significant ($p \leq 0.05$) decreases in thickness of the various brain tissues were noted in both sexes at all dose groups at PNDs 22 and 62.

The maternal LOAEL is 8 mg/kg/day based on corneal opacities. The maternal NOAEL was not established.

The offspring LOAEL is 8 mg/kg/day, based on decreased maximum auditory startle reflex response, decreased brain weights and changes in the brain morphology. The offspring NOAEL was not established.

This study is classified **Acceptable** 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) at this time pending a comprehensive review of all available positive control data.

C. STUDY DEFICIENCIES -

- Positive control data were not submitted with this study; however, summaries of positive control data previously submitted to the Agency were obtained and reviewed. The preliminary review indicate that the positive control data are marginal to inadequate

- A comprehensive analyses of the positive control data submitted for the testing laboratory.