DATA EVALUATION RECORD

BAS 083W (MEPIQUAT CHLORIDE)

Study Type: OPPTS 870.6300 [§83-6], Developmental Neurotoxicity Study in Rats

Work Assignment No. 4-1-131 A (MRIDs 46953501, 46953502, and 46953503)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2777 South Crystal Drive
Arlington, VA 22202

Prepared by

Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
1910 Sedwick Road, Bldg 100, Ste B.
Durham, NC 27713

Primary Reviewer
David A. McEwen, B.S.

Signature: David A. McEwen
Date: 2/2/07

Secondary Reviewer
Michael E. Viana, Ph.D., D.A.B.T.

Signature: Michael E Viana
Date: 2/2/07

Program Manager:
Michael E. Viana, Ph.D., D.A.B.T.

Signature: Michael E Viana
Date: 2/2/07

Quality Assurance:
Steven Brecher, Ph.D., D.A.B.T.

Signature: Steven Brecher
Date: 2/8/07

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EPA Reviewer: Jessica P. Ryman, Ph.D. **Signature:** _____
Registration Action Branch 2, Health Effects Division (7509P) **Date:** _____
EPA Work Assignment Manager: Myron Ottley, Ph. D. **Signature:** _____
Registration Action Branch 3, Health Effects Division (7509P) **Date:** _____

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DATA EVALUATION RECORD

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

PC CODE: 109105 **DP BARCODE:** D333787
TXR#: 0054475

TEST MATERIAL (PURITY): BAS 083W (56.7% a.i.)

SYNONYMS: Mepiquat chloride; 1,1-dimethylpiperidinium chloride

CITATION: Schneider, S., W. Kauffman, E. Fabian, *et. al.* (2006) BAS 083W (Mepiquat chloride): developmental neurotoxicity study in Wistar rats; Oral administration to the dams and pups (gavage). Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen, Germany. Laboratory Report No.: 66R0189/97018, September 20, 2006. MRID 46953501. Unpublished.

Schneider, S., B. van Ravenzwaay (2006) BAS 083W (Mepiquat chloride): range finding developmental neurotoxicity study in Wistar rats; Oral administration to the dams and pups (gavage). Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen, Germany. Laboratory Report No.: 29R0189/97025, June 2, 2006. MRID 46953502. Unpublished.

Schneider, S., B. van Ravenzwaay (2006) BAS 083W (Mepiquat chloride): range finding developmental neurotoxicity study in Wistar rats; Oral administration to the dams and pups (gavage). Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen, Germany. Laboratory Report No.: 29R0189/97038, July 13, 2006. MRID 46953503. Unpublished.

Schneider, S., B. van Ravenzwaay (2006) BAS 083W (Mepiquat chloride): study on acute effects in pre-weaning Wistar rats; oral administration (gavage). Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen, Germany. Laboratory Report No.: 6R0189/97074, September 12, 2006. MRID 46953504. Unpublished.

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EXECUTIVE SUMMARY – In a developmental neurotoxicity study (MRID 46953501),

aqueous BAS 083W (Mepiquat chloride; 56.7% a.i., Batch # CP028814) was administered daily to mated female Wistar rats (Crl:WI(Han)), 40 per dose via oral gavage (10 mL/kg) at doses of 0 (doubly distilled water vehicle), 15, 30, or 60 mg (a.i.) /kg bw/day from gestation day (GD) 6 through lactation day (LD) 10. Dams were allowed to deliver naturally and were killed on LD 21, following weaning of their respective litters. Subsequently, the pups were directly dosed via gavage at the same doses as their dams from post-natal day (PND) 11 through 21. These doses were chosen based on two DNT range finding studies (MRIDs 46953502 and 46953503, described in Appendix I and II) and another preliminary study (BASF Project #06R0189/97026), which together showed that doses above 100 mg/kg bw/day produced unacceptable pup mortality, while a dose at 75 mg/kg bw/day produced no or low mortality and clinical signs (tremor and lateral positioning), and doses at or below 50 mg/kg bw/day produced no adverse effects in the offspring.

There were no unscheduled deaths in dams. No biologically meaningful, treatment-related differences in body weight, body weight gain, or food consumption were observed. There were no treatment-related clinical signs or treatment-related differences observed in a modified functional observational battery, which measured autonomic function, movement, posture and gait, and behavior and appearance. Dams showed no effects of treatment on reproductive performance, which measured fertility index, live birth index, gestation index, and gestation length.

The maternal LOAEL was not determined. The maternal NOAEL is 60 mg (a.i.)/kg bw/day.

Pups from at least twenty litters per dose group were standardized to 8 pups/litter on PND 4. Neurobehavioral testing, neuropathological examination, and a nicotine probe study (to measure the effects of the test substance on brain nicotinic receptors) were performed on 10 pups per treatment group.

There were no compound-related effects on the number of litters, litter size, total number of pups, number of pups born dead, sex ratio, viability index, or lactation index. There were no dose-related effects on body weight or sexual maturation. There was a significant increase ($p \leq 0.01$) in mortality in the 60 mg/kg bw/day dose group (9.8%) compared to controls (0.5%) from PNDs 5-21. The deaths in the 60 mg/kg bw/day dose group occurred during PNDs 11-21, when the animals were dosed with the test material. It was stated that this was mortality was probably due to toxicity resulting from bolus dosing over this time period, and not from exposure during development.

There were no treatment related effects on motor activity (both horizontal distance traveled and rearing) or auditory startle response (both maximum amplitude and latency).
The learning and memory studies contained a deficiency that limited the interpretation of the data. This deficiency was in the second phase of the learning studies on PNDs 29 and 67 when only 3-6 male and female controls reached criterion. This indicated that the animals could not learn the altered maze pattern. Therefore, this data was not usable. Data from the first phase of the learning studies and from the memory studies were used. Water maze performance time was

increased for males on PND 60 at doses of 30 and 60 mg/kg bw/day during the first learning trial. However, this increase was not dose-dependent and the data were highly variable, therefore it was not considered biologically relevant. The nicotine probe study showed no effects of treatment with the test compound on habituation or sensitivity to nicotine, as measured by motor activity (horizontal distance traveled and number of rears) before and after challenge with nicotine or a saline vehicle.

There were no differences in brain weights for male or female pups. There were no differences in brain morphometric parameters for male pups. Female pups showed significant ($p \leq 0.05$ compared to controls) decreases in the size of the corpus callosum (↓14%), the left hippocampus (↓6%), and the cerebellum (↓7%) at 60 mg/kg bw/day, but these values were within range of historical controls and are considered incidental.

An acute study (MRID 46953504) was performed in pre-weaning Wistar rats (Crl:WI(Han), (6 to 41/sex) from dams untreated with the test material that were dosed orally by gavage from PND 11-21 with 0, 30, 60, 120, or 200 mg/kg bw/day. A dose-dependent increase in mortality was observed within 2-4 hours after dosing, with 100%, 55%, and 4% of pups dying at doses of 200, 120, or 60 mg/kg bw/day.

Together, both the present study and MRID 46953504 indicate that neurotoxicity in the offspring is a result of bolus dosing with the test compound and not developmental neurotoxicity, and that *in utero* exposure to the test compound does not increase sensitivity to the neurotoxic effects of the test compound.

The offspring LOAEL is 60 mg (a.i.)/kg bw/day, based on mortality in males and females. The offspring NOAEL is 30 mg (a.i.)/kg bw/day.

This study is classified **Acceptable/Non-guideline** and may be used for regulatory purposes, however it does not satisfy the guideline requirement for a developmental neurotoxicity study in rats ((OPPTS 870.6300, § 83-6); OECD 426 (draft)) pending the evaluation of the submitted positive control data.

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

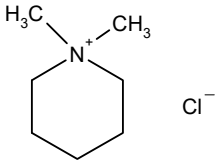
I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: BAS 083W (Mepiquat chloride)

Description: Clear liquid
Batch #: CP028814
Purity: 56.7% a.i. (56.7 g BAS 083W per 100 g of aqueous solution)

Stability: It was stated that the test material was stable during storage at ambient temperature for the duration of the exposure period. The test material was shown to be stable in the vehicle for up to 7 days at room temperature.
CAS # of TGAI: 24307-26-4
Structure:



2. Vehicle – Doubly distilled water

3. Test animals (P)

Species:	Rat	
Strain:	Wistar (Crl:WI(HAN))	
Age at study initiation:	Approximately 10-12 weeks	
Body weights on GD 0:	146.2-186.4 g females only	
Source:	Charles River Laboratories, Inc. (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 mouse/rat "GLP" (Provimi Kliba SA, Kaiseraugst, Switzerland), *ad libitum*, except during behavioral testing.	
Water:	Tap water, *ad libitum*, except during neurobehavioral 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 - Dams received the test material starting on 2/27/05 and ending on approximately 3/27/05.

2. Study schedule - The maternal animals were time-mated at the breeder and assigned to the study. The test substance was administered to the dams from gestation day (GD) 6 through lactation day (LD) 10. Subsequently, the pups were directly dosed via gavage at the same doses as their dams from post-natal day (PND) 11 through 21. After parturition, only the litters containing ≥8 pups and whose littering date was over a period of 4 consecutive days

(March 14-17, 2005) 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 (4 pups/sex where possible) to reduce the variability. Subsequently, one male or one female pup from each litter (10 pups/sex/group) were allocated to Subsets 1-7. Litters not selected were kept as reserve animals until PND 21, and were then sacrificed along with all remaining dams.

3. **Mating procedure** - The animals were paired by the breeder ('time mated'). 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** - Time-mated females were randomly assigned to test groups as shown in Table 1. Offspring were assigned to testing subgroups at the time of litter standardization on PND 4. Dams were assigned to functional observation testing as shown.

TABLE 1. Study design [a]

Experimental Parameter	Subset	Dose (mg/kg bw/day)			
		0	15	30	60
Maternal Animals					
No. of dams assigned	NA	40	40	40	40
FOB (GD 7 & 14, LD 7 & 14)	NA	10	10	10	10
Offspring (F_1)					
Motor activity					
(PND 13, 17, 22, 60)	3	10/sex	10/sex	10/sex	10/sex
(PND 68-70)	6	10/sex	10/sex	10/sex	10/sex
(PND 72-74)	7	10/sex	10/sex	10/sex	10/sex
FOB					
(PND 4, 11, 22, 35, 45, & 60)	3	10/sex	10/sex	10/sex	10/sex
Auditory startle habituation					
(PND 24 and 60)	2	10/sex	10/sex	10/sex	10/sex
Water maze					
(PND 22 and 29)	4	10/sex	10/sex	10/sex	10/sex
(PND 60±2 and 7 days later)	5	10/sex	10/sex	10/sex	10/sex
Perfusion, brain weights, neuropathology, and morphometric analysis					
(PND 22)	1	10/sex	10/sex	10/sex	10/sex
(PND 62)	2	10/sex	10/sex	10/sex	10/sex
Nicotine Probe Study					
(Saline challenge, PND 71±4)	6	10/sex	10/sex	10/sex	10/sex
Nicotine Probe Study					
(Nicotine challenge, PND 71±4)	7	10/sex	10/sex	10/sex	10/sex

a Data obtained from pages 32-35 of the study report.
NA Not applicable

5. **Dose selection rationale** - Dose levels were chosen based on the results of two developmental neurotoxicity range-finding studies (MRIDs 46953502 and 46953503, summarized in Appendices I and II) and another preliminary study (BASF Project

#06R0189/97026). In MRID 36953502 doses of 0, 50, 200, and 300 mg/kg bw/day on GD 6-LD10 in the dams and PND 11-21 in the pups resulted in death of the offspring at 200 and 300 mg/kg/day with no adverse effects in offspring at 50 mg/kg bw/day. In BASF Project #06R0189/97026, pups (approximately 9/dose) were directly dosed with the test material at 75, 100, 125, 150, or 200 mg/kg bw/day beginning on PND 11 without previous dosing to the dams. Mortality was observed at 100 mg/kg bw/day and above. In MRID 4693503 doses of 0, 75 and 90 mg/kg bw/day on GD 6-LD10 in the dams and PND 11-21 in the pups resulted in some pup mortality (2.7%) and pup clinical signs (tremors and lateral position) at 75 mg/kg bw/day, with greater pup mortality (29%) at 90 mg/kg bw/day. There were no adverse effects in the dams at either dose of the test material. Based on the results of these three studies, doses of 15, 30, and 60 mg/kg bw/day were chosen for the current study.

6. **Dosage preparation and analysis -** Formulations were prepared weekly by mixing appropriate amounts of test substance with doubly distilled water. Prior to initiation of the study, stability for up to 7 days at room temperature was determined. Actual concentration at each dose was tested at the beginning and end of the dosing period. It was stated that as the dose preparations were true solutions, no homogeneity analysis was performed.

Results

Stability analysis (range as % of Day 0)
At room temperature for up to 7 days: 98.1-101.9%

Concentration analysis:

Target dose (mg/10 ml) as active ingredient (a.i.)[a]	(ml of 56.7% stock/100 ml)	Nominal concentration (mg/100 ml)[a]	% of nominal
15	0.26	147	91.5-96.2
30	0.53	301	99.1-99.8
60	1.06	601	94.3-102.1

[a]Calculated by the reviewers.

The analytical data indicated that the variation between nominal and actual dosage to the 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 overt clinical signs of toxicity. Additionally, nesting, littering, and lactation behavior of the dams were checked in the mornings during clinical inspection and an additional check for littering behavior was performed in the afternoon. Body weights were measured on GD 0 and 6-20, and females with a litter were weighed on LD 0-10, 14, and 21. Food consumption was recorded on GD 0, 6, 13, and 20,

and on LD 1, 7, 14, and 21.

Ten dams/dose were subjected to a modified functional observation battery (FOB) outside of the home cage on GD 7 and 14, and on LD 7 and 14. It was not reported if the technicians were blind as to the dose group. Details of the scoring for the modified FOB were presented on pages 1182-1186 of the study report. The following functional observations were recorded.

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). During direct dosing (PND 11-21), the pups were checked for mortality and moribundity daily every 2 hours for 6 hours post-dosing. Clinical observations were recorded daily from PND 1-10 and every 2 hours for 6 hours post-dosing on PND 11-21. Body weights were recorded on PNDs 1, 4 (precull and post-culling), and 11-21, and then weekly thereafter until sacrifice. 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 44-45 of the study report.
b Observed daily
c Pre-culling
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 7 subsets for further evaluation.

2. **Developmental landmarks -** Beginning on PND 40, male offspring were examined daily for preputial separation. Beginning on PND 27, female offspring 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. **Post-weaning 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** - Observations and the schedule for those observations are summarized as follows from the report.

i. **Functional observational battery (FOB)** - On PNDs 4, 11, 22, 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 PND 13, 17, 22, and 60 and Subsets 6 and 7 on PND 68-70 and 72-74 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 habituation** - Auditory startle response and habituation of responses with repeated presentation of stimuli were evaluated for animals in Subset 2 (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 5-10 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 4 and 5 (10 pups/sex/dose each). Water maze testing was performed beginning on PNDs 22 (Subset 4) and 60 (Subset 5) and again seven days later for each group.

The water maze 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 first trial

in both the learning and relearning phases were acclimation trials and were not evaluated.

5. **Cholinesterase determination** – Cholinesterase activity was not determined.

6. **Nicotine probe study** – A pharmacological challenge study using a specifically designed motor activity measurement was performed to detect a potential effect of the test material on the nicotinic receptor. Details of the methodology were reported on pages 51-54 of the study report. The animals (10/sex) in Subset 7 received a single i.p. dose of 0.4 mg/kg nicotine base and the animals in Subset 6 were similarly treated with saline. The results of this study as well as a range finding study are summarized in Appendix III of this DER.

7. **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, 4, 5, 6, and 7 (after conclusion of their investigations) were killed by cervical dislocation and discarded without further examination.

The offspring (10 pups/sex/dose in each subset) selected for brain weight and neuropathological evaluation were sacrificed on PND 22 (Subset 1) or 62 (Subset 2) under Isofluran® 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. The length and width of the cerebrum and cerebellum were measured. Sections from all major brain regions were prepared following the methods of Sherwood and Timiras (1970). Tissues from the control and 60 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 and peripheral nervous system tissues were collected (Subsets 1 and 2):

	CENTRAL NERVOUS SYSTEM		PERIPHERAL NERVOUS SYSTEM
	BRAIN		**SCIATIC NERVE**
X	Olfactory bulb	X	Proximal
X	Prosencephalon with frontal lobe		Distal
X	Diencephalon with parietal lobe		
X	Mesencephalon with occipital lobe and temporal lobe		**OTHER**
X	Pons		Sural nerve
X	Cerebellum	X	Tibial nerve (proximal and distal)
X	Medulla oblongata		Peroneal nerve
		X	Cervical dorsal root ganglion
	SPINAL CORD	X	Cervical dorsal root fibers
X	Cervical swelling	X	Cervical ventral root fibers
X	Thoracic swelling		Thoracic dorsal root ganglion
X	Lumbar swelling		Thoracic dorsal root fibers
	OTHER		Thoracic ventral root fibers
X	Gasserian ganglion	X	Lumbar dorsal root ganglion
X	Pituitary gland	X	Lumbar dorsal root fibers
X	Eyes (with optic nerve)	X	Lumbar ventral root fibers
X	Skeletal muscle (gastrocnemius)	X	All gross lesions
X	Olfactory epithelium (nasal cavity, level III)		

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, time to sexual maturity	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, sexual maturity data	Each dose group was compared pairwise to the control using Fisher's Exact test for the hypothesis of equal proportions.
Water maze evaluation, motor activity, startle response	Each dose group was compared pairwise to the control using Wilcoxon test for the hypothesis of equal medians.
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)
Nicotine probe study (motor activity data)	A non-parametric Kruskal-Wallis test was performed followed by a Wilcoxon test, as necessary.

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

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

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

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

The reviewers calculated the following indices using the formulas below and included the data in the summary tables.

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

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

3. **Positive and historical control data –** Positive control data were not provided with the current study. However, 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 submitted. The available positive control studies are currently under review. 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) intraoccular 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 and clinical and functional observations -** No treatment-related mortalities were observed during the study, all dams survived to scheduled sacrifice. No treatment-related clinical signs were observed during gestation or lactation. No adverse effects were observed in any FOB parameter at any time point.

2. **Body weight and food consumption -** Selected group mean body weights and body weight gains for pregnant and nursing dams are summarized in Table 3.

   No treatment-related effects on body weight, body weight gain, or food consumption were observed during gestation or lactation. The statistically significant increases noted in body weight gain (↑4-6%, $p \leq 0.05$) in the 15 mg/kg dams were not dose-dependent and the decreased food consumption (↓5%, $p \leq 0.05$) noted in the 60 mg/kg dams during LD 7-14 was minor, transient, and did not result in a corresponding decrease in body weight.

TABLE 3. Selected mean (±SD) body weight, body weight gain, and food consumption in dams orally dosed with BAS 083W from GD 6 through LD 10. [a]

Observations	Dose (mg/kg bw/day)			
	0	15	30	60
Gestation (n=23-30)				
Body weight (g)				
GD 0	164.0±9.71	168.7±9.68	164.6±9.18	164.1±10.22
GD 20	286.9±16.06	292.5±20.34	285.6±16.64	280.4±18.97
Body weight gain (g)				
GD 0-20	122.9±11.34	123.8±17.50	120.9±10.39	116.2±10.76
Food consumption (g)				
GD 0-20	20.0±1.77	20.6±1.94	20.0±1.88	19.4±2.01
Lactation (n=22-30)				
Body weight (g)				
LD 0	224.3±14.66	230.5±16.27	224.5±14.10	224.5±16.38
LD 21	249.6±14.04	260.2±10.76* (↑4)	254.3±15.12	245.8±14.29
Body weight gain (g)				
LD 0-21	29.6±11.52	28.4±12.34	32.5±8.52	28.5±8.38
Food consumption (g)				
LD 0-21	46.0±10.91	47.4±11.06	45.8±10.96	44.1±10.93

a Data were extracted from pages 121-130 of the study report. Numbers presented parenthetically are percent difference from controls (calculated by reviewers).
* Statistically significantly different from controls at p≤0.05.

3. **Reproductive performance** – Reproductive parameters were similar to controls in all dose groups (Table 4).

TABLE 4. Reproductive performance [a]

Observation	Dose (mg/kg bw/day)			
	0	15	30	60
Number mated	40	40	40	40
Fertility index (%)	80	88	93	95
Gestation index (%)	100	97	100	100
Live birth index (%)	99	99	99	100
Gestation length (mean # of days ± SD)	21.4 ± 0.50	21.6 ± 0.50	21.5 ± 0.56	21.6 ± 0.55

a Data were extracted from page 131 of the study report.

B. OFFSPRING

1. **Viability and clinical signs** - Litter size and viability results from pups during lactation are summarized in Table 5. No compound related effects on any litter parameter were noted at any dose. Viability and lactation indices were similar to controls at all doses. It was stated that the relatively high incidence of mortality at 60 mg/kg bw/day was due to the direct dosing of the pups on PND 11 and was considered to be related to direct dosing with the test material.

TABLE 5. Litter size and viability [a]

Observation	Dose (mg/kg bw/day)			
	0	15	30	60
No. of litters	32	34	37	38
Total number of pups born	302	298	344	331
Number born dead	3	2	2	1
Sex Ratio Day 0 (% live males)	52.8	48.6	49.4	49.7
Mean (±SD) litter size:				
PND 0 (Total # of pups) (#litters)	9.3±1.84 299 (32)	8.7±2.05 296 (34)	9.2±1.80 342 (37)	8.7±2.12 330 (38)
PND 4 [b] (Total # of pups) (# litters)	7.3±4.73 233 (32)	6.3±4.83 215 (32)	8.0±4.04 295 (32)	7.1±4.40 269 (32)
PND 4 [c,d] (Total # of pups) (#litters)	8 184 (23)	8 176 (22)	8 240 (30)	8 224 (28)
PND 21[d] (Total # of pups)/ #litters	7.95 183 (23)	7.63 168 (22)	7.83 235 (30)	7.21 202 (28)
# Deaths Days 1-4[b]	0	1	0	0
# Deaths Days 11-21 (dosing)[c]	0	2	2	22
#Deaths Days 5-21[c]	1	2	2	22**
Viability index (%) [d]	77.9	72.6	86.3	81.5
Lactation index (%) [d]	99.5	95.5	97.9	90.2

a Data were extracted from pages 132-134 of the study report.
b Pre-culling
c Post-culling
d Calculated by reviewers from data within this table. Standard deviations were not available.
** Statistically different from controls at p≤0.01. Mortality was 9.8% (22/224 pups post-cull) compared to 0.5% (1/184 pups post-cull) in controls.

2. **Body weight** – No treatment-related effects on offspring pre-weaning body weights were observed (Table 6a). The slightly increased body weights (↑6-8%, p≤0.05) noted in the 15 mg/kg bw/day pups during pre-weaning were not dose-related or adverse. Body weight gains (Table 6b) were generally slightly increased compared to controls throughout most pre-weaning intervals in the treated pups. The statistically significant differences (p≤0.05) noted at various intervals were not dose-related and/or were not considered to be adverse.

TABLE 6a. Mean (±SD) pre-weaning F_1 pup body weights (g) [a]

Postnatal Day	Dose (mg/kg bw/day)			
	0	15	30	60
Males				
1	6.4±0.45	6.9±0.63*(↑8)	6.8±0.59	6.7±0.71
4[b]	10.0±0.82	10.8±1.08*(↑8)	10.6±1.15	10.3±1.11
4[c]	10.0±0.82	10.8±1.05*(↑8)	10.6±1.16	10.3±1.13
11	24.3±2.01	25.9±2.13*(↑7)	25.2±2.42	24.2±2.06
21	47.8±3.93	51.4±4.36*(↑7)	49.3±4.36	49.2±3.75
Females				
1	6.1±0.37	6.5±0.74	6.4±0.59	6.4±0.63
4[b]	9.7±0.69	10.4±1.20*(↑7)	10.2±1.08	9.9±1.01
4[c]	9.7±0.69	10.4±1.16*(↑7)	10.2±1.08	10.0±1.05
11	23.7±1.81	25.1±2.18	24.6±2.17	23.7±2.06
21	46.6±3.01	49.4±3.91*(↑6)	48.1±3.59	47.8±3.62

a Data were extracted from on pages 135-139 of the study report; n=22-30 litters. Numbers presented parenthetically are percent difference from controls (calculated by reviewers).
b Pre-culling
c Post-culling
* Statistically significantly different from controls at p≤0.05

TABLE 6b. Selected mean (±SD) pre-weaning F_1 pup body weight gains (g) [a]

Interval (PND)	Dose (mg/kg bw/day)			
	0	15	30	60
Males				
1-4	3.6±0.46	3.9±0.51	3.8±0.67	3.6±0.47
4-11	14.3±1.43	15.1±1.54	14.5±1.48	14.0±1.26
19-20	2.9±0.62	3.5±0.79*(↑21)	3.2±0.70	3.5±0.73*(↑21)
4-21	37.8±3.30	40.6±3.83*(↑7)	38.6±3.51	38.9±3.05
Females				
1-4	3.6±0.43	3.9±0.50	3.8±0.57	3.6±0.43
4-11	14.0±1.34	14.7±1.43	14.3±1.37	13.8±1.31
19-20	2.9±0.63	3.3±0.79	3.2±0.61	3.3±0.64
4-21	36.9±2.47	39.0±3.16	37.9±2.80	37.8±2.92

a Data were extracted from pages 140-144 of the study report; n=22-30 litters. Numbers presented parenthetically are percent difference from controls (calculated by reviewers).
* Statistically significantly different from controls at p≤0.05

During post-weaning, body weights and body weight gains remained slightly increased compared to controls at various intervals throughout the study in both sexes with statistical significance occurring at several intervals in the ≥30 mg/kg bw/day groups (Table 7). As no adverse effects were noted in post-weaning body weight and weight gain, and as the data were presented in the study report broken down by subset, Table 7 only contains data from Subset 2 as a representative example of the increases noted.

TABLE 7. Selected mean (±SD) post-weaning F_1 pup body weight and body weight gains (g) [a]

Post-weaning Week	Dose (mg/kg bw/day)			
	0	15	30	60
Males				
0	50.9±5.91	53.3±7.40	53.5±4.21	50.3±6.04
5	251.1±16.94	262.9±23.13	274.6±13.69	265.3±28.84
Overall (0-5) gain	200.1±13.15	209.7±18.48	221.1±13.71*(↑10)	214.9±23.30
Females				
0	47.9±5.28	51.5±6.91	52.8±6.13	49.3±6.31
5	164.4±9.46	170.4±13.29	173.3±15.32	166.0±12.26
Overall (0-5) gain	116.6±7.32	118.9±8.94	120.5±13.12	116.6±8.64

a Data were presented in pages 162-185 of the study report; n=10/subset. Data presented in this table are for Subset 2 only. Numbers presented parenthetically are percent difference from controls (calculated by reviewers).
* Statistically significantly different from controls at p≤0.05

3. Developmental landmarks

a. Sexual maturation – The time to reach preputial separation was slightly reduced (p≤0.05) in the 15 and 30 mg/kg bw/day males (42.3 days each treated vs. 43.3 controls, Table 8). The time to reach vaginal patency was also slightly reduced (p≤0.01) in the 15 mg/kg bw/day females (31.4 days treated vs. 32.7 controls). Body weight at criterion was similar to controls in both the males and females. As these findings were within or slightly below the range of historical controls and were likely due to the increased body weights noted in these groups, they were not considered to be adverse.

TABLE 8. Sexual maturation in F_1 pups [a]

Parameter	Dose (mg/kg bw/day)			
	0	15	30	60
Preputial separation (mean ±SD day of onset)	43.3±1.56	42.3±1.42*	42.3±1.39*	43.0±1.83
Body weight at criterion (g) (mean ±SD)	177.5±10.49	182.2±9.85	185.1±10.21	184.4±12.74
Vaginal patency (mean ±SD day of onset)	32.7±2.47	31.4±1.30**	32.0±1.72	32.0±1.28
Body weight at criterion (g) (mean ±SD)	97.5±7.04	96.4±6.78	101.2±9.91	99.0±7.08

a Data were extracted from page 145-147 of the study report; n=49-50.
* Statistically significantly different from controls at p≤0.05
** Statistically significantly different from controls at p≤0.01

b. Physical landmarks – Evaluation of physical landmarks (eye opening, pinna unfolding, incisor erupting) was not performed.

4. Behavioral assessments

a. **Functional observational battery** – No treatment-related FOB effects were observed at any dose in any group.

b. **Motor activity** – No treatment-related differences in total session motor activity, reported as distance traveled or number of rears, were observed at any dose in either sex (Tables 9a and 9b). Several statistically significant differences ($p \leq 0.05$) in activity (distance and rears) were noted at various intervals. However, these findings were not considered to be related to treatment as they were transient, not dose-dependent, and did not result in significant differences in total session activity. The interval data were reported on pages 260-291 and are included as Appendix IV in this DER. Levels of activity progressively increased with age compared to the levels on PND 13. Habituation was evident in both sexes at all ages, with the expected decrease in activity at day 22.

TABLE 9a. Mean (±SD) total session motor activity (cumulative distance, cm) in F_1 pups [a]

Interval (PND)	Dose (mg/kg bw/day)			
	0	15	30	60
Males				
13	4648.1±3674.4	3473.3±2002.7	4867.4±3526.3	3342.6±1771.8
17	5109.3±3655.2	4808.5±3629.7	6830.5±2599.6	7275.1±3456.0
22	2096.2±1141.3	2181.3±1110.7	2148.4±1129.7	2664.0±635.9
60	6811.1±1154.8	7208.3±1440.9	7470.2±1395.3	6662.9±1514.9
Females				
13	3565.8±1524.5	3941.0±2244.7	4335.7±4011.9	2720.1±1711.1
17	5448.3±3089.0	5946.6±4212.7	5709.0±3608.1	6514.1±2664.2
22	2328.6±1183.8	2739.4±695.2	2337.5±805.7	2531.9±864.2
60	9054.2±1853.9	9512.7±1646.2	8691.2±1404.0	9842.3±1793.7

a Data were extracted from pages 260-275 of the study report; n=10 pups.

TABLE 9b. Mean (±SD) total session motor activity (# of rears) in F_1 pups [a]

Interval (PND)	Dose (mg/kg bw/day)			
	0	15	30	60
Males				
13	113.8±66.1	125.6±73.7	158.1±126.7	83.4±49.9
17	194.2±131.3	170.9±90.5	230.5±82.9	239.1±95.6
22	73.7±43.8	73.7±42.7	74.0±43.0	102.4±42.1
60	170.9±46.9	192.1±48.5	204.2±55.0	172.7±48.8
Females				
13	126.3±53.4	143.6±105.9	143.0±127.5	73.4±77.3
17	200.6±123.0	209.0±114.3	174.5±69.0	223.5±79.7
22	84.6±52.3	91.2±27.3	81.6±31.0	74.6±28.2
60	227.5±39.2	254.6±51.6	242.2±58.0	243.5±56.9

a Data were extracted from pages 276-291 of the study report; n=10 pups.

c. **Auditory startle reflex habituation** – No treatment-related effect on total session peak amplitude, latency, or habituation were observed in either sex at PND 24 or 60 (Table 10). The amplitude of the startle response increased with age in both sexes. At both ages,

habituation was apparent in the control animals as a decrease in amplitude during the course of the test session.

TABLE 10. Mean (±SD) overall (Blocks 1-5) acoustic startle max. amplitude (g) and latency to peak (msec) in F_1 rats [a]

Dose (mg/kg bw/day)	Parameter	Males		Females	
		PND 24	PND 60	PND 24	PND 60
0	Max. Amp.	549.0±336.2	1668.7±1034.9	411.3±219.0	918.7±477.1
	Latency	34.9±10.8	42.6±12.6	32.5±6.7	31.9±6.1
15	Max. Amp.	355.7±123.7	1619.6±652.4	453.5±263.7	1061.8±265.7
	Latency	28.9±6.2	36.6±6.7	30.3±7.9	30.4±4.1
30	Max. Amp.	390.5±128.2	2104.3±1514.3	383.5±146.6	1166.5±401.6
	Latency	30.8±8.0	37.7±10.1	29.8±9.3	34.4±6.7
60	Max. Amp.	353.6±72.4	1548.9±860.0	425.3±384.3	955.1±491.8
	Latency	28.1±5.6	36.3±8.3	26.9±9.3	29.8±3.6

a Data were extracted from pages 292-299 of the study report; n=10.

d. <u>Learning and memory testing</u> – The learning and memory studies contained a deficiency that limited the interpretation of the data. This deficiency was in the second phase of the learning studies on PNDs 29 and 67 (e.g. Learning 2, Table 11a), when only 3-6 male and female controls reached criterion. This indicated that the animals could not learn the altered maze pattern. Therefore, this data was not usable. Most animals were able to reach criteria for the first phase of the learning studies (Learning 1) and for the memory studies, therefore these data were used. Water maze performance time was significantly ($p \leq 0.05$) increased for males on PND 60 at doses of 30 and 60 mg/kg bw/day during the first learning trial in Trials 4 and 5. (e.g. Learning 1, Table 11b). However, this increase was not dose-dependent and the data were highly variable, therefore it was not considered biologically relevant. No other treatment-related effects on learning and memory were observed in either sex at any time point.

TABLE 11a. Water maze performance (# of animals reaching criteria) in F_1 rats [a]

Session/Parameter		Dose (mg/kg bw/day)							
		0	15	30	60	0	15	30	60
		Males				Females			
Learning 1 (PND 22)	Trial 2	4	4	4	4	7	5	6	3
	Trial 3	5	6	3	3	5	6	9	7
	Trial 4	6	7	6	7	9	6	10	7
	Trial 5	8	8	9	10	10	8	8	6*
	Trial 6	9	9	10	9	9	9	9	8
Memory (PND 29)		8	8	9	6	8	8	6	9
Learning 2 (PND 29)	Trial 2	0	0	0	1	1	2	2	3
	Trial 3	0	1	1	1	2	3	2	5
	Trial 4	3	3	2	3	3	3	6	6
	Trial 5	5	3	4	6	4	3	3	7
	Trial 6	4	6	6	5	4	3	5	7
Learning 1 (PND 60)	Trial 2	3	6	4	8	6	3	7	6
	Trial 3	8	5	6	8	9	5	7	8
	Trial 4	9	7	6	6	7	7	7	7
	Trial 5	10	9	7	7	7	7	6	8
	Trial 6	9	10	6	7	6	9	6	7
Memory (PND 67)		9	10	7	8	9	9	8	7
Learning 2 (PND 67)	Trial 2	3	3	2	2	1	1	3	2
	Trial 3	2	6	5	5	2	2	6	4
	Trial 4	3	7	5	4	3	3	7	6
	Trial 5	6	7	5	6	3	3	6	5
	Trial 6	6	8	6	6	3	5	5	4

a Data were extracted from pages 186-187 and 190-191 of the study report; n=10.
* Statistically significantly different from controls at $p \leq 0.05$

TABLE 11b. Mean (±SD) water maze performance (Time [sec]) in F_1 rats that reached criteria [a]

Session/Parameter		Dose (mg/kg bw/day)							
		0	15	30	60	0	15	30	60
		Males				Females			
PND 22 and 29									
Learning 1	Trial 2	23±17.9	22±10.0	26±16.4	27±16.6	27±21.2	27±12.1	27±16.4	39±29.7
	Trial 3	19±11.5	24±21.4	19±9.7	24±15.2	25±18.1	12±6.1	17±13.0	25±22.9
	Trial 4	16±9.8	13±9.6	18±14.8	11±3.6	12±5.3	11±5.9	9±5.3	14±9.6
	Trial 5	10±6.6	9±5.8	11±6.3	9±6.9	10±9.0	10±5.7	10±9.1	12±9.4
	Trial 6	7±5.1	8±4.1	10±7.2	7±5.3	8±6.9	9±5.3	6±3.8	13±18.8
Memory		8±4.3	9±7.2	9±2.2	13±8.8	9±7.6	9±3.4	12±9.7	8±5.5
Learning 2	Trial 2	23±17.0	26±12.5	26±11.8	21±6.4	19±12.4	15±5.7	21±17.0	13±6.3
	Trial 3	13±4.0	17±6.8	15±4.1	16±6.9	11±2.9	9±4.3	16±8.5	9±4.6
	Trial 4	10±3.3	12±6.2	15±7.0	12±6.1	12±5.5	11±7.9	10±8.1	8±4.9
	Trial 5	9±4.4	12±5.9	10±6.9	8±4.8	8±3.7	9±4.1	9±4.8	6±3.0
	Trial 6	9±7.2	8±4.5	8±5.5	7±4.2	7±3.5	9±4.0	8±4.4	6±3.6
PND 60 and 67									
Learning 1	Trial 2	25±18.0	14±5.8	22±14.5	16±10.1	16±8.8	21±13.4	16±9.1	18±19.7
	Trial 3	8±4.2	15±11.9	12±5.7	9±6.0	9±2.9	19±23.7	13±5.5	10±5.7
	Trial 4	6±3.2	8±6.1	12±5.9** (↑100)	9±4.2* (↑50)	13±10.5	9±4.9	16±16.3	8±6.5
	Trial 5	5±2.3	5±2.1	10±6.0** (↑100)	11±6.8* (↑120)	17±19.7	13±13.8	14±10.8	8±9.0
	Trial 6	6±4.5	4±2.0	13±10.4** (↑117)	13±13.6	19±18.4	11±11.4	13±8.2	10±11.0
Memory		7±3.4	5±3.7	11±5.8	9±9.7	8±4.0	7±2.9	12±8.8	7±4.9
Learning 2	Trial 2	15±6.8	16±8.5	27±24.9	21±20.6	17±16.1	17±8.3	21±15.3	13±8.9
	Trial 3	20±13.5	10±8.9	19±28.7	11±6.6	13±7.4	15±11.1	14±12.1	12±14.8
	Trial 4	21±14.4	5±2.5** (↓76)	16±26.7	10±7.2* (↓52)	17±15.9	15±10.5	11±11.4	13±17.4
	Trial 5	10±6.3	6±5.3	19±29.7	9±7.6	11±6.6	19±13.7	12±11.1	11±9.5
	Trial 6	11±10.1	7±8.5	13±14.4	11±10.2	15±15.9	11±7.5	12±6.4	14±12.6

a Data were extracted from pages 188-189 and 192-193 of the study report; n=10.
* Statistically significantly different from controls at $p \leq 0.05$.

5. Nicotine probe study – See Appendix III of this DER for summarized results.

6. Postmortem results

a. Brain weights – No treatment-related effects were noted in terminal body weights or absolute and relative (to body) brain weights on PND 22 or 62 in either sex (Table 12).

TABLE 12. Mean (±SD) brain weights in F_1 rats [a]

Parameter	Dose (mg/kg bw/day)			
	0	15	30	60
Males				
PND 22				
Terminal body weight (g)	49.9±4.9	55.3±6.1	53.0±4.2	50.2±3.6
Brain weight (g)	1.68±0.05	1.63±0.04	1.65±0.06	1.63±0.06
PND 62				
Terminal body weight (g)	264.1±14.1	278.4±22.5	288.5±15.0**(↑9)	281.3±27.8
Brain weight (g)	2.01±0.08	2.07±0.09	2.07±0.07	2.06±0.07
Females				
PND 22				
Terminal body weight (g)	47.1±3.9	49.5±4.6	49.8±5.8	50.0±5.3
Brain weight (g)	1.59±0.04	1.62±0.07	1.61±0.11	1.54±0.06
PND 62				
Terminal body weight (g)	167.7±7.7	177.8±11.0	179.0±13.3	171.3±9.5
Brain weight (g)	1.86±0.09	1.89±0.08	1.91±0.08	1.86±0.05

a Data were extracted from pages 396-403 of the study report; n=10.
** Statistically significantly different from controls at $p \leq 0.01$.

b) Neuropathology

1. **Macroscopic examination** – No gross lesions or significant differences in cerebellum and cerebrum lengths or widths were observed on PND 22 or at termination in either sex.

2. **Microscopic examination** – No treatment-related microscopic lesions were noted at any dose in either sex on PND 22 or at termination.

   No treatment-related differences in morphometric brain measurements were noted in the 60 mg/kg bw/day animals compared to controls on PND 22 (Tables 13a and 13b). On PND 62, the following decreases ($p \leq 0.05$) in thickness were noted in the 60 mg/kg bw/day females: (i) corpus callosum (↓14%); (ii) left hippocampus (↓6%); and (iii) cerebellum (↓7%). These findings were all within the historical control ranges provided and were not significant when the results from all treated groups were compared to controls using the Wilcoxon test with the Bonferoni-Holm adjustment. Therefore, these findings were considered incidental.

TABLE 13a. Mean (±SD) morphometric brain measurements in male F_1 rats [a]

Parameter	Dose (mg/kg bw/day)			
	0	15	30	60
PND 22				
Cerebrum Length (cm)	1.38±0.04	1.38±0.02	1.37±0.02	1.37±0.03
Cerebrum Width (cm)	1.48±0.02	1.46±0.04	1.48±0.03	1.47±0.03
Cerebellum Length (cm)	0.64±0.02	0.64±0.05	0.63±0.04	0.62±0.02
Cerebellum Width (cm)	1.15±0.03	0.94±0.44	1.14±0.03	1.15±0.03
Frontal Cortex, left (µm)	1697±136	NM	NM	1674±119
Frontal Cortex, right (µm)	1707±117	NM	NM	1680±137
Parietal Cortex, left (µm)	1774±136	NM	NM	1683±149
Parietal Cortex, right (µm)	1762±138	NM	NM	1679±118
Caudate putamen, left (µm)	3263±170	NM	NM	3323±123
Caudate putamen, right (µm)	3295±140	NM	NM	3405±124
Corpus callosum (µm)	366±83	NM	NM	315±76
Hippocampus, left (µm)	1674±114	NM	NM	1692±51
Hippocampus, right (µm)	1659±75	NM	NM	1667±79
Cerebellum (folia pyrimidus, µm)	330±26	NM	NM	333±15
PND 62 (Termination)				
Cerebrum Length (cm)	1.48±0.02	1.49±0.02	1.50±0.03	1.49±0.04
Cerebrum Width (cm)	1.53±0.04	1.56±0.01	1.55±0.03	1.56±0.03
Cerebellum Length (cm)	0.73±0.04	0.72±0.03	0.72±0.03	0.73±0.03
Cerebellum Width (cm)	1.20±0.03	1.24±0.03	1.23±0.02	1.23±0.04
Frontal Cortex, left (µm)	1581±58	NM	NM	1653±69
Frontal Cortex, right (µm)	1631±46	NM	NM	1692±81
Parietal Cortex, left (µm)	1670±109	NM	NM	1778±135
Parietal Cortex, right (µm)	1645±83	NM	NM	1721±108
Caudate putamen, left (µm)	3725±173	NM	NM	3736±122
Caudate putamen, right (µm)	3611±239	NM	NM	3646±212
Corpus callosum (µm)	366±55	NM	NM	346±60
Hippocampus, left (µm)	1832±75	NM	NM	1781±58
Hippocampus, right (µm)	1819±100	NM	NM	1787±78
Cerebellum (folia pyrimidus, µm)	351±34	NM	NM	350±28

a Data were extracted from pages 409, 411, 413, and 415; n=10.
NM Not measured

TABLE 13b. Mean (±SD) morphometric brain measurements in female F_1 rats [a]

Parameter	Dose (mg/kg bw/day)			
	0	15	30	60
PND 22				
Cerebrum Length (cm)	1.35±0.02	1.36±0.02	1.35±0.03	1.35±0.03
Cerebrum Width (cm)	1.46±0.03	1.45±0.04	1.46±0.03	1.47±0.03
Cerebellum Length (cm)	0.61±0.02	0.62±0.02	0.62±0.02	0.62±0.01
Cerebellum Width (cm)	1.13±0.03	1.15±0.03	1.15±0.04	1.12±0.02
Frontal Cortex, left (µm)	1709±60	NM	NM	1686±109
Frontal Cortex, right (µm)	1721±104	NM	NM	1681±82
Parietal Cortex, left (µm)	1675±79	NM	NM	1680±131
Parietal Cortex, right (µm)	1684±71	NM	NM	1673±64
Caudate putamen, left (µm)	3260±120	NM	NM	3339±69
Caudate putamen, right (µm)	3307±136	NM	NM	3297±101
Corpus callosum (µm)	333±78	NM	NM	315±61
Hippocampus, left (µm)	1647±59	NM	NM	1653±68
Hippocampus, right (µm)	1625±88	NM	NM	1639±52
Cerebellum (folia pyrimidus, µm)	334±26	NM	NM	331±20
PND 62 (Termination)				
Cerebrum Length (cm)	1.44±0.04	1.45±0.05	1.45±0.03	1.44±0.03
Cerebrum Width (cm)	1.50±0.03	1.50±0.03	1.52±0.03	1.50±0.04
Cerebellum Length (cm)	0.70±0.04	0.74±0.03	0.71±0.02	0.68±0.03
Cerebellum Width (cm)	1.20±0.04	1.20±0.05	1.20±0.03	1.19±0.06
Frontal Cortex, left (µm)	1601±111	NM	NM	1571±57
Frontal Cortex, right (µm)	1647±68	NM	NM	1619±63
Parietal Cortex, left (µm)	1629±53	NM	NM	1607±100
Parietal Cortex, right (µm)	1594±68	NM	NM	1623±104
Caudate putamen, left (µm)	3641±126	NM	NM	3578±98
Caudate putamen, right (µm)	3543±136	NM	NM	3536±181
Corpus callosum (µm)	338±43	316±64	356±80	292±44*(↓14)
Hippocampus, left (µm)	1808±118	1793±85	1767±60	1702±96*(↓6)
Hippocampus, right (µm)	1761±115	NM	NM	1708±133
Cerebellum (folia pyrimidus, µm)	365±26	348±42	350±38	339±37*(↓7)

a Data were extracted from pages 410, 412, 414, 416, and 417; n=10.
NM Not measured
* Statistically significantly different from controls at $p \leq 0.05$.

III. DISCUSSION and CONCLUSIONS

A. <u>INVESTIGATORS CONCLUSIONS</u> – The investigators concluded that the offspring mortality at 60 mg/kg bw/day was a result of acute toxicity of a high bolus dose of the test material. No evidence of developmental neurotoxicity was observed at any dose in either sex. The offspring NOAEL is 30 mg/kg bw/day.

B. <u>EPA REVIEWER COMMENTS</u>

The doses chosen were both justified and adequate. Justification of the doses used in the present DNT study was provided by two DNT range finding studies (MRIDs 46953502 and 46953503, described in Appendix I and II) and another preliminary study (BASF Project

#06R0189/97026), which, in combination, showed that doses above 100 mg/kg bw/day produced unacceptable pup mortality, while a dose at 75 mg/kg bw/day produced no or low mortality and clinical signs (tremor and lateral positioning), and doses on or below 50 mg/kg bw/day produced no adverse effects in the offspring. The doses of 0, 15, 30, or 60 mg/kg bw/day used in the main DNT study (MRID 4693501) did not cause maternal toxicity and caused mortality in the pups at the highest dose (60 mg/kg bw/day) only after PND 11, when pups were dosed directly, with no adverse effects at doses of 30 and 15 mg/kg bw/day. The lack of systemic signs of toxicity and the observation of neurological effects preceding death in these high-dose pups indicates that the highest dose was adequate to provide observation of neurotoxicity, and that the neurotoxic signs were still observable even with mortality (9.8%).

The observation of mortality at 60 mg/kg bw/day in the main DNT study (MRID 4693501) was consistent with previous studies showing no mortality (BASF Project #06R0189/97026) or low mortality (2.7%) and clinical signs at 75 mg/kg bw/day (MRID 46953503) and 4% mortality at 60 mg/kg bw/day (MRID 46953504).

Learning and memory studies showed that only 3-6 males and females from the control groups reached criterion during the second phase of the learning studies on PNDs 21 and 67. Water maze performance time was increased for males on PND 60 at doses of 30 and 60 mg/kg bw/day during the first learning trial and during the memory phase, but this was not dose-dependent and did not persist at PND 67.

Several factors indicated that pup neurotoxicity and mortality were the result of an acute bolus dose of the test compound and not a result of developmental neurotoxicity. First, clinical signs (lateral position, tremor) preceded death in both the dams and the pups in some cases and occurred within hours of dosing. Second, death occurred within hours of dosing for both dams and pups. Third, mortality in pups occurred only after PND 11, when the pups were dosed directly. There were no effects of the test compound on litter size or pup viability pre-culling. Finally, an acute study performed in pre-weaning rats from dams untreated with the test material (MRID 46953504) showed similar results, with clinical signs and mortality also observed at 60 mg/kg bw/day. Thus, it appears unlikely that *in utero* exposure to the test material caused adverse effects or increased sensitivity.

C. <u>STUDY DEFICIENCIES</u> – The learning and memory studies contained a deficiency that limited the interpretation of the data. This deficiency was in the second phase of the learning studies on PNDs 29 and 67 (e.g. Learning 2, Table 11a), when only 3-6 male and female controls reached criterion. This indicated that the animals could not learn the altered maze pattern. Therefore, this data was not usable. Animals were able to reach criteria for the first phase of the learning studies (Learning 1) and from the memory studies, therefore these data were used.

APPENDIX I

Developmental Neurotoxicity Dose Range Finding Study in Rats

Since this is a range-finding study, only a summary is provided to confirm the adequacy of the dose selection rationale used in the definitive developmental neurotoxicity study in rats (MRID 46953501).

In a developmental neurotoxicity study (MRID 46953502), BAS 083W (Mepiquat chloride; 56.7% a.i., Batch # CP028814) was administered daily to 10 mated female Wistar rats per dose via stomach tube in a doubly distilled water vehicle (10 mL/kg) at nominal dose levels of 0 (vehicle), 50, 200, or 300 mg/kg bw/day from gestation day (GD) 6 through lactation day (LD) 10. Subsequently, the pups were to be dosed via oral gavage at the same dose as their dams from post-natal day (PND) 11 through 21. However, based on high pup mortality that precluded a meaningful evaluation of neurotoxicity at 200 and 300 mg/kg bw/day, these groups of pups were only dosed on PND 11 and were terminated for humane reasons. The control and 50 mg/kg bw/day pups were directly dosed from PND 11 through 21.

Dams were allowed to deliver naturally and were killed on LD 21, following weaning of their respective litters. On PND 4, litters were standardized to 8 pups/litter (4 pups/sex where possible); the remaining offspring were sacrificed and discarded without further examinations.

In the dams, no treatment-related effects were observed on food consumption, body weights, FOB, motor activity, reproductive parameters, or gross pathology.

Mortality in the dams was limited the 300 mg/kg bw/day group, with two animals found dead on GD 21 three to four hours after dosing. These same animals showed clinical signs of toxicity (abdominal position and tremors) within three hours after dosing. One animal was unable to deliver a litter (dystocia) and was sacrificed for humane reasons. The following treatment-related clinical signs of toxicity were noted at 200 mg/kg bw/day and above: salivation during gestation and lactation and tremors during lactation. Additional signs at 300 mg/kg bw/day included tremors during gestation and abdominal position. Body weight gains were decreased ($p \leq 0.05$) by 55% during GD 16-17 and by 21% on GD 6-20, but did not lead to significantly lower body weights during gestation.

The maternal LOAEL is 200 mg (a.i.) /kg bw/day, based on clinical signs (salivation and tremors. The maternal NOAEL is 50 mg (a.i.) /kg bw/day.

In the offspring, no treatment-related effects were observed on litter data, sex ratio, body weight, body weight gain, motor activity, or gross pathology.

One litter of 300 mg/kg bw/day pups and 7 litters of mg/kg bw/day pups were dosed on PND 12. 100% of the 300 mg/kg bw/day pups and 83% of the 200 mg/kg bw/day pups died within approximately 2-3 hours. The remaining litters for these dose groups were completely terminated for humane reasons. No treatment-related mortality was observed in the 50 mg/kg bw/day offspring.

No adverse clinical signs were observed in the offspring until dosing commenced. Lateral position was the only clinical sign of toxicity noted, and it was observed within 3-6 hours after dosing in the 200 mg/kg and above groups. Lateral position was observed in pups prior to death, as well as in surviving pups.

No treatment-related effects were noted in the 50 mg/kg bw/day offspring.

The offspring LOAEL is 200 mg (a.i.) kg bw/day, based on mortality. The offspring NOAEL is 50 mg (a.i.) /kg bw/day.

This study is classified as **acceptable/non-guideline.**

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

APPENDIX II

Developmental Neurotoxicity Dose Range Finding Study in Rats

Since this is a range-finding study, only a summary is provided to confirm the adequacy of the dose selection rationale used in the definitive developmental neurotoxicity study in rats (MRID 46953501).

In a range-finding developmental neurotoxicity study (MRID 46953503), BAS 083W (Mepiquat chloride; 56.7% a.i., Batch # CP028814) was administered daily to 10 mated female Wistar rats per dose via stomach tube in a doubly distilled water vehicle (10 mL/kg) at nominal dose levels of 0 (vehicle), 75, or 90 mg/kg bw/day from gestation day (GD) 6 through lactation day (LD) 10. Subsequently, the pups were directly dosed via oral gavage at the same dose as their dams from post-natal day (PND) 11 through 21.

Dams were allowed to deliver naturally and were killed on LD 21, following weaning of their respective litters. On PND 4, litters were standardized to 8 pups/litter (4 pups/sex where possible); the remaining offspring were sacrificed and discarded without further examinations.

In the dams, no treatment-related effects were observed on mortality, clinical signs of toxicity, food consumption, body weights, body weight gains, FOB, motor activity, reproductive parameters, or gross pathology.

The maternal LOAEL was not observed. The maternal NOAEL is 90 mg (a.i.)/kg bw/day.

In the offspring, no treatment-related effects were observed on litter data, sex ratio, body weight, body weight gain, motor activity, or gross pathology.

At 75 mg/kg bw/day, 2/73 pups (2.7%) died after dosing, with ½ pups showing tremors. At 90 mg/kg bw/day, 21/72 pups (29%) died after dosing with tremors and/or lateral position observed in some pups prior to death, although surviving pups also showed these clinical signs. It was stated that the timing of clinical signs and mortality were consistent with acute toxicity of a high, bolus dose of the test material.

The offspring LOAEL is 75 mg (a.i.) /kg bw/day, based on clinical signs (tremors, lateral position) and mortality. The offspring NOAEL was not established.

This study is classified as **acceptable/non-guideline.**

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

APPENDIX III

Nicotine Probe Study in Rats

A pharmacological challenge study using a specifically designed motor activity measurement was performed to detect a potential effect of the test material on nicotinic receptor responsivity. This challenge study, called the probe study, was performed on animals in Subsets 6 and 7 of the main DNT study (MRID 46953501).

In a range finding study to determine the dose of nicotine for use in the probe study (pp 100-101 and Volume III of the main DNT study (MRID 46953501)), Wistar rats 10/sex/dose at an age of 70 ± 40 post partum received a single intraperitoneal injection (5 mL/kg) of nicotine in physiological saline at doses of 0, 0.05, 0.10, 0.20, or 0.40 mg/kg. Motor activity assessments (distance traveled and number of rears) were performed for a duration of 1 h prior to dosing (e.g. during habituation) and at approximately 5 minutes post-dosing (e.g. after probing) for a duration of 1 h. Total distance traveled was dose-dependently increased ($p \leq 0.05$) at 0.20 and 0.40 mg/kg in both sexes (↑65-125%). Additionally, activity was increased in the females at 0.05 and 0.10 mg/kg. Based on these results, a dose of 0.4 mg/kg was chosen for the nicotine probe study.

In the probe study (pp 102-107 and Volume III of the main DNT study (MRID 46953501)), two groups of 10 pups/sex/dose of BAS 083W main study groups (dosed at 15, 30 or 60 mg (a.i.)/kg/day) were treated with either saline (Subset 6) or 0.4 mg/kg nicotine (Subset 7) as reported in the range finding study above. Motor activity and rearing measurements were performed during habituation for a duration of 1 h (12 intervals of 5 minutes each) prior to dosing and for a duration of 1 h (12 intervals of 5 minutes each) at approximately 5 minutes after dosing.

There were no effects of the test material on total session distance values or total session rearing during habituation for either sex. For animals probed with saline (Subset 6) total session distance traveled and rearing decreased ≥ 50% after injection for both males and females, but there were no treatment-related differences. Similarly, for animals probed with 0.4 mg/kg nicotine (Subset 7), total session distance traveled and rearing decreased ≥ 50% after injection for both males and females, but there were no treatment-related differences.

However, it was noted that nicotine decreased horizontal activity at the beginning of the session and tended to increase activity towards the end of the session in all BAS 083W dose groups including controls. Rearing activity was decreased in the nicotine challenge animals at all doses of BAS 083W including controls compared to the saline challenge groups. Both measures of motor activity (distance traveled and number of rears) demonstrate that BAS 083W treated animals did not have differential sensitivity to nicotine treatment.

In conclusion, *in utero* and postnatal exposure to BAS 083W (Mepiquat chloride) up to 60 mg (a.i.)/kg/day did not result in differential effects to acute exposure to nicotine.

TABLE 1a. Mean (±SD) session distance traveled in Subset 6 (saline) and Subset 7 (nicotine) on PND 71±4. [a]

Test	Dose (mg/kg bw/day)			
	0	15	30	60
Males				
Before Saline	7110.9±1425.5	6805.9±1552.7	8426.9±1620.9	7611.7±855.4
Before Nicotine	7477.5±989.2	6937.5±977.3	7822.0±1824.6	7062.2±1438.2
After Saline	3001.3±819.1	2734.6±959.5	2538.3±598.1	2235.5±1059.1
After Nicotine	2269.8±708.5	2325.9±635.3	3198.7±697.1	2548.7±1097.4
Females				
Before Saline	9039.8±1704.7	8537.5±2019.7	8479.3±2121.4	7953.0±1338.6
Before Nicotine	8126.8±1716.0	8814.2±1919.9	7900.1±1787.2	8254.8±1579.8
After Saline	4096.8±1774.2	3118.5±1533.0	3499.7±1394.2	3506.0±770.3
After Nicotine	2840.3±1043.5	3831.3±3077.6	2838.9±895.3	3126.8±1061.9

a Data were extracted from Table 4.3.2.1 on page 105 of the study report; n=10.

TABLE 1b. Mean (±SD) session number of rears in Subset 6 (saline) and Subset 7 (nicotine) on PND 71±4. [a]

Test	Dose (mg/kg bw/day)			
	0	15	30	60
Males				
Before Saline	208.8±42.1	181.3±54.0	230.5±49.7	192.4±32.3
Before Nicotine	220.0±51.3	181.4±34.3	226.1±59.8	196.3±58.7
After Saline	85.2±36.5	65.9±21.5	69.3±22.7	49.4±27.8
After Nicotine	19.9±16.9	11.8±14.7	25.1±18.2	16.9±18.4
Females				
Before Saline	271.5±61.5	225.0±59.6	248.2±47.0	221.2±50.6
Before Nicotine	228.0±52.4	228.2±63.1	231.4±45.5	237.1±43.4
After Saline	109.3±68.9	74.1±31.5	88.5±37.7	87.4±28.1
After Nicotine	29.1±19.1	53.5±71.2	31.6±24.8	33.0±32.7

a Data were extracted from Table 4.3.2.2 on page 105 of the study report; n=10.

APPENDIX IV

The following are pages 260-291 of the study report

BASF
Project Number 66R0189/97018

BAS 083 W (MEPIQUAT CHLORIDE)

GROUP MEANS

MOTOR ACTIVITY DAY 13 p.p.
INTERSESSION DISTANCE TRAVELLED

PRINT DATE 13APR05

M A L E S

		Interv. 1 Distance cm	Interv. 2 Distance cm	Interv. 3 Distance cm	Interv. 4 Distance cm	Interv. 5 Distance cm	Interv. 6 Distance cm	Interv. 7 Distance cm	Interv. 8 Distance cm
GROUP 0									
0 MG/KG	M	389.2	430.5	485.7	535.8	575.7	420.0	280.8	382.6
	SD	178.6	347.8	389.1	404.9	548.9	365.3	310.5	481.7
	N	10	10	10	10	10	10	10	10
GROUP 1									
15 MG/KG	M	428.4	273.0	468.8	402.1	400.8	283.1	147.0	177.3
	SD	232.7	210.0	347.1	260.0	324.2	294.4	115.4	193.0
	N	10	10	10	10	10	10	10	10
GROUP 2									
30 MG/KG	M	377.0	461.4	415.7	495.1	556.8	568.2	538.6	344.8
	SD	260.3	408.4	354.5	448.3	325.9	484.0	576.8	252.2
	N	10	10	10	10	10	10	10	10
GROUP 3									
60 MG/KG	M	381.1	239.0	371.7	587.8	479.4	220.7	337.4	312.8
	SD	107.1	162.0	294.5	362.1	402.4	342.4	367.7	355.1
	N	10	10	10	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

BASF
Project Number 66R0189/97018

BAS 083 W (MEPIQUAT CHLORIDE)

GROUP MEANS

MOTOR ACTIVITY DAY 13 p.p.
INTERSESSION DISTANCE TRAVELLED

PRINT DATE 13APR05

M A L E S

		Interv. 9 Distance cm	Interv.10 Distance cm	Interv.11 Distance cm	Interv.12 Distance cm	Interv.1-12 Sum cm
GROUP 0						
0 MG/KG	M	346.0	270.7	299.0	232.2	4648.1
	SD	446.7	358.2	494.3	411.0	3674.4
	N	10	10	10	10	10
GROUP 1						
15 MG/KG	M	301.0	164.6	199.4	227.7	3473.3
	SD	367.7	218.5	272.8	330.4	2002.7
	N	10	10	10	10	10
GROUP 2						
30 MG/KG	M	328.2	313.0	280.5	188.2	4867.4
	SD	422.4	349.2	421.1	321.5	3526.3
	N	10	10	10	10	10
GROUP 3						
60 MG/KG	M	88.4	75.0	127.3	122.2	3342.6
	SD	108.0	77.8	138.4	227.5	1771.8
	N	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

BASF
Project Number 66R0189/97018

BAS 083 W (MEPIQUAT CHLORIDE)

GROUP MEANS

MOTOR ACTIVITY DAY 17 p.p.
INTERSESSION DISTANCE TRAVELLED

PRINT DATE 13APR05

M A L E S

		Interv. 1 Distance cm	Interv. 2 Distance cm	Interv. 3 Distance cm	Interv. 4 Distance cm	Interv. 5 Distance cm	Interv. 6 Distance cm	Interv. 7 Distance cm	Interv. 8 Distance cm
GROUP 0									
0 MG/KG	M	767.8	783.4	489.4	347.1	290.8	242.2	403.2	330.6
	SD	295.8	381.9	323.3	356.4	494.2	327.0	413.4	465.4
	N	10	10	10	10	10	10	10	10
GROUP 1									
15 MG/KG	M	848.3	583.0	469.3	329.0	442.6	352.6	277.0	324.4
	SD	243.8	350.1	417.2	328.3	382.6	374.3	471.7	497.2
	N	10	10	10	10	10	10	10	10
GROUP 2									
30 MG/KG	M	813.4	842.4	643.9	515.6	502.8	467.4	466.9	477.3
	SD	174.5	215.0	390.8	436.3	309.0	539.8	486.6	408.0
	N	10	10	10	10	10	10	10	10
GROUP 3									
60 MG/KG	M	1044.7	956.5	669.1	488.5	659.9	561.0	425.1	328.9
	SD	261.2	195.1	330.3	416.0	434.4	416.4	399.7	472.4
	N	10	10	10	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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BAS 083 W (MEPIQUAT CHLORIDE)

GROUP MEANS

MOTOR ACTIVITY DAY 17 p.p.
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PRINT DATE 13APR05

M A L E S

		Interv. 9 Distance cm	Interv.10 Distance cm	Interv.11 Distance cm	Interv.12 Distance cm	Interv.1-12 Sum cm
GROUP 0						
0 MG/KG	M	320.9	373.4	403.2	357.3	5109.3
	SD	489.5	388.0	396.9	428.9	3655.2
	N	10	10	10	10	10
GROUP 1						
15 MG/KG	M	318.4	307.1	247.4	309.3	4808.5
	SD	543.1	553.1	380.3	510.6	3629.7
	N	10	10	10	10	10
GROUP 2						
30 MG/KG	M	318.1	379.1	650.2	753.6	6830.5
	SD	411.2	440.1	480.8	494.7	2599.6
	N	10	10	10	10	10
GROUP 3						
60 MG/KG	M	453.6	410.0	588.1	689.7	7275.1
	SD	531.9	469.2	532.4	741.5	3456.0
	N	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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BAS 083 W (MEPIQUAT CHLORIDE)

GROUP MEANS

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M A L E S

		Interv. 1 Distance cm	Interv. 2 Distance cm	Interv. 3 Distance cm	Interv. 4 Distance cm	Interv. 5 Distance cm	Interv. 6 Distance cm	Interv. 7 Distance cm	Interv. 8 Distance cm
GROUP 0									
0 MG/KG	M	885.8	479.7	162.9	67.7	73.3	36.5	95.3	71.8
	SD	363.9	236.5	256.8	152.5	102.2	39.0	157.9	160.3
	N	10	10	10	10	10	10	10	10
GROUP 1									
15 MG/KG	M	1019.4	439.2	124.5	209.5	65.7	70.1	16.2	25.2
	SD	296.1	321.4	148.3	398.7	86.6	138.8	12.0	24.6
	N	10	10	10	10	10	10	10	10
GROUP 2									
30 MG/KG	M	944.8	426.8	218.9	93.9	49.5	49.4	55.7	91.3
	SD	246.0	195.3	231.8	152.2	92.0	79.9	98.1	193.8
	N	10	10	10	10	10	10	10	10
GROUP 3									
60 MG/KG	M	1026.4	602.3	368.5	219.6	141.0	77.5	49.4	65.9
	SD	142.3	176.4	231.1	171.2	243.1	115.8	52.8	146.1
	N	10	10	10	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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GROUP MEANS

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M A L E S

		Interv. 9 Distance cm	Interv.10 Distance cm	Interv.11 Distance cm	Interv.12 Distance cm	Interv.1-12 Sum cm
GROUP 0						
0 MG/KG	M	28.4	54.3	68.4	72.2	2096.2
	SD	10.9	104.5	138.3	120.1	1141.3
	N	10	10	10	10	10
GROUP 1						
15 MG/KG	M	16.1 * 143	31.9	80.6	82.8	2181.3
	SD	11.5	27.0	183.2	177.6	1110.7
	N	10	10	10	10	10
GROUP 2						
30 MG/KG	M	76.2	72.6	34.5	35.0	2148.4
	SD	133.2	75.5	27.4	40.2	1129.7
	N	10	10	10	10	10
GROUP 3						
60 MG/KG	M	29.8	24.6	31.9	27.2	2664.0
	SD	30.0	12.2	15.7	13.2	635.9
	N	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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BAS 083 W (MEPIQUAT CHLORIDE)

GROUP MEANS

MOTOR ACTIVITY DAY 60 p.p.
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M A L E S

		Interv. 1 Distance cm	Interv. 2 Distance cm	Interv. 3 Distance cm	Interv. 4 Distance cm	Interv. 5 Distance cm	Interv. 6 Distance cm	Interv. 7 Distance cm	Interv. 8 Distance cm
GROUP 0									
0 MG/KG	M	1169.9	945.9	814.2	694.5	639.3	554.5	464.2	378.6
	SD	154.7	143.7	171.5	242.4	183.2	124.1	222.6	185.9
	N	10	10	10	10	10	10	10	10
GROUP 1									
15 MG/KG	M	1318.8	1024.7	840.6	768.5	675.3	574.7	468.5	398.9
	SD	153.8	182.4	223.8	182.3	252.4	193.5	191.2	187.2
	N	10	10	10	10	10	10	10	10
GROUP 2									
30 MG/KG	M	1325.5	1033.1	902.8	691.9	669.8	489.2	535.2	497.7
	SD	219.1	149.7	247.2	217.5	236.0	214.1	205.2	230.0
	N	10	10	10	10	10	10	10	10
GROUP 3									
60 MG/KG	M	1284.2	1051.6	851.0	666.2	653.1	436.4	392.3	374.0
	SD	199.8	178.1	213.6	112.3	178.7	261.5	245.6	247.4
	N	10	10	10	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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BAS 083 W (MEPIQUAT CHLORIDE)

GROUP MEANS

MOTOR ACTIVITY DAY 60 p.p.
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M A L E S

		Interv. 9 Distance cm	Interv.10 Distance cm	Interv.11 Distance cm	Interv.12 Distance cm	Interv.1-12 Sum cm
GROUP 0						
0 MG/KG	M	358.4	245.7	245.7	300.1	6811.1
	SD	251.6	280.7	219.4	260.1	1154.8
	N	10	10	10	10	10
GROUP 1						
15 MG/KG	M	288.7	298.6	260.9	289.9	7208.3
	SD	207.5	232.1	275.8	305.9	1440.9
	N	10	10	10	10	10
GROUP 2						
30 MG/KG	M	425.3	389.5	278.1	232.4	7470.2
	SD	188.5	231.9	288.6	260.0	1395.3
	N	10	10	10	10	10
GROUP 3						
60 MG/KG	M	314.8	225.4	165.2	248.7	6662.9
	SD	233.2	324.2	279.1	386.9	1514.9
	N	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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BAS 083 W (MEPIQUAT CHLORIDE)

GROUP MEANS

MOTOR ACTIVITY DAY 13 p.p.
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F E M A L E S

		Interv. 1 Distance cm	Interv. 2 Distance cm	Interv. 3 Distance cm	Interv. 4 Distance cm	Interv. 5 Distance cm	Interv. 6 Distance cm	Interv. 7 Distance cm	Interv. 8 Distance cm
GROUP 0									
0 MG/KG	M	414.9	370.5	423.6	486.5	486.8	170.0	302.1	239.2
	SD	193.9	254.1	272.6	293.5	342.1	156.0	367.2	280.3
	N	10	10	10	10	10	10	10	10
GROUP 1									
15 MG/KG	M	647.6	567.3	644.6	597.4	352.2	127.5	185.5	212.6
	SD	499.1	519.7	426.3	363.8	343.6	122.5	212.9	290.8
	N	10	10	10	10	10	10	10	10
GROUP 2									
30 MG/KG	M	440.4	475.9	529.4	446.8	355.1	276.8	361.7	328.0
	SD	275.6	348.6	508.2	528.3	416.9	330.8	461.6	468.4
	N	10	10	10	10	10	10	10	10
GROUP 3									
60 MG/KG	M	322.0	224.4	414.8	336.2	374.9	195.2	130.8	156.2
	SD	182.8	263.7	427.7	232.3	458.1	277.1	202.3	153.0
	N	10	10	10	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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GROUP MEANS

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F E M A L E S

		Interv. 9 Distance cm	Interv.10 Distance cm	Interv.11 Distance cm	Interv.12 Distance cm	Interv.1-12 Sum cm
GROUP 0						
0 MG/KG	M	261.5	201.4	146.4	63.1	3565.8
	SD	264.1	365.5	214.6	50.2	1524.5
	N	10	10	10	10	10
GROUP 1						
15 MG/KG	M	175.3	130.9	212.4	88.0	3941.0
	SD	227.9	255.9	354.7	119.3	2244.7
	N	10	10	10	10	10
GROUP 2						
30 MG/KG	M	240.5	487.1	261.9	132.1	4335.7
	SD	466.5	723.3	403.8	209.2	4011.9
	N	10	10	10	10	10
GROUP 3						
60 MG/KG	M	234.0	130.8	71.1	129.7	2720.1
	SD	368.4	139.4	76.9	185.9	1711.1
	N	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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GROUP MEANS

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F E M A L E S

		Interv. 1 Distance cm	Interv. 2 Distance cm	Interv. 3 Distance cm	Interv. 4 Distance cm	Interv. 5 Distance cm	Interv. 6 Distance cm	Interv. 7 Distance cm	Interv. 8 Distance cm
GROUP 0									
0 MG/KG	M	823.8	577.2	584.2	544.7	541.5	401.5	225.2	289.8
	SD	300.3	298.4	293.2	317.7	531.7	423.4	271.4	307.3
	N	10	10	10	10	10	10	10	10
GROUP 1									
15 MG/KG	M	1062.4	732.4	513.1	487.9	374.1	430.1	347.9	291.7
	SD	376.3	401.9	352.7	464.6	421.9	479.5	442.5	416.1
	N	10	10	10	10	10	10	10	10
GROUP 2									
30 MG/KG	M	762.2	734.6	609.3	514.7	492.8	222.6	72.0	246.8
	SD	320.0	403.9	542.5	364.8	577.1	393.4	118.3	552.4
	N	10	10	10	10	10	10	10	10
GROUP 3									
60 MG/KG	M	720.5	742.8	549.8	532.7	680.3	521.7	431.3	499.6
	SD	383.9	335.7	310.1	415.2	319.4	345.0	430.6	424.6
	N	10	10	10	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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GROUP MEANS

MOTOR ACTIVITY DAY 17 p.p.
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F E M A L E S

		Interv. 9 Distance cm	Interv.10 Distance cm	Interv.11 Distance cm	Interv.12 Distance cm	Interv.1-12 Sum cm
GROUP 0						
0 MG/KG	M	448.4	428.7	249.2	334.3	5448.3
	SD	453.4	407.2	430.1	440.8	3089.0
	N	10	10	10	10	10
GROUP 1						
15 MG/KG	M	454.8	439.5	360.9	451.8	5946.6
	SD	489.2	521.1	477.6	557.0	4212.7
	N	10	10	10	10	10
GROUP 2						
30 MG/KG	M	390.3	656.6	504.4	502.9	5709.1
	SD	429.2	634.8	545.3	471.7	3608.1
	N	10	10	10	10	10
GROUP 3						
60 MG/KG	M	522.3	518.7	406.5	387.9	6514.1
	SD	464.1	421.9	414.7	462.0	2664.2
	N	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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GROUP MEANS

MOTOR ACTIVITY DAY 22 p.p.
INTERSESSION DISTANCE TRAVELLED

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F E M A L E S

		Interv. 1 Distance cm	Interv. 2 Distance cm	Interv. 3 Distance cm	Interv. 4 Distance cm	Interv. 5 Distance cm	Interv. 6 Distance cm	Interv. 7 Distance cm	Interv. 8 Distance cm
GROUP 0									
0 MG/KG	M	929.8	496.5	303.8	144.4	54.9	86.8	72.0	82.0
	SD	224.8	173.5	260.7	222.4	48.6	132.6	95.4	159.2
	N	10	10	10	10	10	10	10	10
GROUP 1									
15 MG/KG	M	1158.3	569.8	233.9	188.8	207.9	115.9	74.8	95.2
	SD	217.6	191.1	232.3	212.7	282.7	157.3	79.7	188.4
	N	10	10	10	10	10	10	10	10
GROUP 2									
30 MG/KG	M	1052.1	513.7	202.7	184.3	47.9	21.1	32.5	30.9
	SD	429.8	227.9	143.2	244.9	75.6	15.2	20.0	29.8
	N	10	10	10	10	10	10	10	10
GROUP 3									
60 MG/KG	M	1217.6	614.7	303.1	128.7	85.8	32.7	20.1	22.0
	SD	473.6	255.8	222.4	201.7	134.5	25.3	14.3	9.2
	N	10	10	10	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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GROUP MEANS

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F E M A L E S

		Interv. 9 Distance cm	Interv.10 Distance cm	Interv.11 Distance cm	Interv.12 Distance cm	Interv.1-12 Sum cm
GROUP 0						
0 MG/KG	M	24.2	19.4	77.5	37.4	2328.6
	SD	24.7	12.4	171.1	47.8	1163.8
	N	10	10	10	10	10
GROUP 1						
15 MG/KG	M	28.7	23.3	22.2	20.6	2739.4
	SD	22.2	11.5	19.7	10.7	695.2
	N	10	10	10	10	10
GROUP 2						
30 MG/KG	M	64.4	86.6	40.3	61.2	2337.5
	SD	126.8	174.4	41.7	114.0	805.7
	N	10	10	10	10	10
GROUP 3						
60 MG/KG	M	25.4	32.6	22.2	27.2	2531.9
	SD	14.2	19.7	17.6	17.9	864.2
	N	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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GROUP MEANS

MOTOR ACTIVITY DAY 60 p.p.
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F E M A L E S

		Interv. 1 Distance cm	Interv. 2 Distance cm	Interv. 3 Distance cm	Interv. 4 Distance cm	Interv. 5 Distance cm	Interv. 6 Distance cm	Interv. 7 Distance cm	Interv. 8 Distance cm
GROUP 0									
0 MG/KG	M	1397.9	1143.1	991.4	934.1	745.1	627.5	686.6	581.6
	SD	176.0	153.7	210.8	151.5	302.7	373.3	332.1	333.7
	N	10	10	10	10	10	10	10	10
GROUP 1									
15 MG/KG	M	1554.8	1267.6	1092.2	1002.8	910.0	732.4	655.3	545.4
	SD	219.1	129.8	170.9	208.1	266.8	240.1	319.7	380.7
	N	10	10	10	10	10	10	10	10
GROUP 2									
30 MG/KG	M	1368.8	1129.4	970.1	882.7	775.4	708.0	658.9	450.9
	SD	244.5	192.3	186.3	162.9	234.1	223.2	109.9	231.1
	N	10	10	10	10	10	10	10	10
GROUP 3									
60 MG/KG	M	1439.9	1334.4 *	1185.8	1017.2	962.9	820.5	685.9	443.6
	SD	195.1	181.4	175.1	252.4	151.9	259.7	302.4	296.7
	N	10	10	10	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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GROUP MEANS

MOTOR ACTIVITY DAY 60 p.p.
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F E M A L E S

		Interv. 9 Distance cm	Interv.10 Distance cm	Interv.11 Distance cm	Interv.12 Distance cm	Interv.1-12 Sum cm
GROUP 0						
0 MG/KG	M	594.2	556.9	526.5	269.4	9054.2
	SD	245.3	306.6	343.9	239.4	1853.9
	N	10	10	10	10	10
GROUP 1						
15 MG/KG	M	436.7	555.7	400.9	358.8	9512.7
	SD	335.9	386.5	331.3	395.3	1646.2
	N	10	10	10	10	10
GROUP 2						
30 MG/KG	M	664.4	457.5	298.5	326.8	8691.2
	SD	304.7	209.7	290.3	287.8	1404.0
	N	10	10	10	10	10
GROUP 3						
60 MG/KG	M	607.9	445.0	546.7	352.6	9842.3
	SD	400.6	328.8	284.8	344.3	1793.7
	N	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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GROUP MEANS

MOTOR ACTIVITY DAY 13 p.p.
REARING

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M A L E S

		Interv. 1 Rearing	Interv. 2 Rearing	Interv. 3 Rearing	Interv. 4 Rearing	Interv. 5 Rearing	Interv. 6 Rearing	Interv. 7 Rearing	Interv. 8 Rearing
GROUP 0									
0 MG/KG	M	17.5	12.5	11.9	17.6	12.6	7.5	8.6	9.6
	SD	10.7	8.0	10.2	13.3	9.7	6.8	12.0	12.5
	N	10	10	10	10	10	10	10	10
GROUP 1									
15 MG/KG	M	17.8	14.5	17.6	17.7	12.4	8.0	5.5	6.1
	SD	14.6	10.0	11.8	9.8	11.2	8.2	9.6	8.0
	N	10	10	10	10	10	10	10	10
GROUP 2									
30 MG/KG	M	13.6	19.2	18.3	13.5	17.2	14.9	14.2	12.5
	SD	11.1	15.9	17.6	13.5	11.5	17.7	18.4	14.9
	N	10	10	10	10	10	10	10	10
GROUP 3									
60 MG/KG	M	13.9	7.7	10.7	13.5	11.2	4.9	9.1	5.0
	SD	8.0	7.9	11.3	6.2	6.2	6.8	11.1	6.2
	N	10	10	10	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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GROUP MEANS

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M A L E S

		Interv. 9 Rearing	Interv.10 Rearing	Interv.11 Rearing	Interv.12 Rearing	Interv.1-12 Sum
GROUP 0						
0 MG/KG	M	6.3	3.7	3.3	2.7	113.8
	SD	9.5	4.8	6.5	4.1	66.1
	N	10	10	10	10	10
GROUP 1						
15 MG/KG	M	9.2	4.9	5.2	6.7	125.6
	SD	12.6	8.1	8.2	8.2	73.7
	N	10	10	10	10	10
GROUP 2						
30 MG/KG	M	7.1	13.5	9.2	4.9	158.1
	SD	11.4	15.4	15.8	10.7	126.7
	N	10	10	10	10	10
GROUP 3						
60 MG/KG	M	1.4	0.8	2.5	2.7	83.4
	SD	3.4	1.6	4.4	6.3	49.9
	N	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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GROUP MEANS

MOTOR ACTIVITY DAY 17 p.p.
REARING

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M A L E S

		Interv. 1 Rearing	Interv. 2 Rearing	Interv. 3 Rearing	Interv. 4 Rearing	Interv. 5 Rearing	Interv. 6 Rearing	Interv. 7 Rearing	Interv. 8 Rearing
GROUP 0									
0 MG/KG	M	34.0	33.3	22.6	14.5	9.0	9.0	13.8	9.0
	SD	12.7	14.1	12.4	15.2	14.7	13.2	14.6	12.7
	N	10	10	10	10	10	10	10	10
GROUP 1									
15 MG/KG	M	38.9	28.8	16.9	9.2	15.4	11.0	6.9	8.5
	SD	8.8	12.0	11.9	9.4	11.7	14.9	10.4	14.1
	N	10	10	10	10	10	10	10	10
GROUP 2									
30 MG/KG	M	34.6	34.9	26.5	16.1	19.0	12.6	11.1	11.0
	SD	11.8	9.5	14.7	14.6	10.5	13.4	13.2	10.9
	N	10	10	10	10	10	10	10	10
GROUP 3									
60 MG/KG	M	35.9	33.6	30.0	15.3	22.6	20.2	12.5	7.7
	SD	7.9	9.9	11.2	12.5	14.7	14.8	14.7	9.7
	N	10	10	10	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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Project Number 66R0189/97018

BAS 083 W (MEPIQUAT CHLORIDE)

GROUP MEANS

MOTOR ACTIVITY DAY 17 p.p.
REARING

PRINT DATE 13APR05

M A L E S

		Interv. 9 Rearing	Interv.10 Rearing	Interv.11 Rearing	Interv.12 Rearing	Interv.1-12 Sum
GROUP 0						
0 MG/KG	M	9.6	12.2	13.3	13.9	194.2
	SD	15.9	15.7	16.5	17.3	131.3
	N	10	10	10	10	10
GROUP 1						
15 MG/KG	M	8.5	9.2	8.5	9.1	170.9
	SD	14.4	19.0	16.4	14.3	90.5
	N	10	10	10	10	10
GROUP 2						
30 MG/KG	M	12.3	14.2	18.2	20.0	230.5
	SD	14.7	16.4	17.0	13.8	82.9
	N	10	10	10	10	10
GROUP 3						
60 MG/KG	M	14.5	13.9	17.4	15.5	239.1
	SD	19.4	17.4	15.8	14.2	95.6
	N	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

BASF
Project Number 66R0189/97018 BAS 083 W (MEPIQUAT CHLORIDE)

GROUP MEANS MOTOR ACTIVITY DAY 22 p.p. PRINT DATE 13APR05
REARING

M A L E S

		Interv. 1 Rearing	Interv. 2 Rearing	Interv. 3 Rearing	Interv. 4 Rearing	Interv. 5 Rearing	Interv. 6 Rearing	Interv. 7 Rearing	Interv. 8 Rearing
GROUP 0									
0 MG/KG	M	33.3	20.9	5.3	1.8	3.7	2.0	2.2	1.8
	SD	10.2	10.4	9.8	5.0	8.0	4.8	4.4	5.7
	N	10	10	10	10	10	10	10	10
GROUP 1									
15 MG/KG	M	40.5	18.1	4.5	4.8	1.4	1.7	0.0	0.0
	SD	9.1	14.7	7.0	10.6	3.1	4.7	0.0	0.0
	N	10	10	10	10	10	10	10	10
GROUP 2									
30 MG/KG	M	36.6	17.5	8.6	3.8	1.6	1.2	1.1	1.3
	SD	13.5	8.4	10.1	7.8	5.1	3.9	3.5	4.1
	N	10	10	10	10	10	10	10	10
GROUP 3									
60 MG/KG	M	40.6	27.5	16.7	8.3	3.9	2.0	0.8	2.2
	SD	11.2	11.1	12.2	8.2	7.5	4.2	1.6	7.0
	N	10	10	10	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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BAS 083 W (MEPIQUAT CHLORIDE)

GROUP MEANS

MOTOR ACTIVITY DAY 22 p.p.
REARING

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M A L E S

		Interv. 9 Rearing	Interv.10 Rearing	Interv.11 Rearing	Interv.12 Rearing	Interv.1-12 Sum
GROUP 0						
0 MG/KG	M	0.0	0.7	0.8	1.2	73.7
	SD	0.0	2.2	2.5	3.2	43.8
	N	10	10	10	10	10
GROUP 1						
15 MG/KG	M	0.0	0.4	1.1	1.2	73.7
	SD	0.0	1.3	3.1	3.8	42.7
	N	10	10	10	10	10
GROUP 2						
30 MG/KG	M	0.3	1.5	0.4	0.1	74.0
	SD	0.7	3.7	1.3	0.3	43.0
	N	10	10	10	10	10
GROUP 3						
60 MG/KG	M	0.1	0.1	0.1	0.1	102.4
	SD	0.3	0.3	0.3	0.3	42.1
	N	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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BAS 083 W (MEPIQUAT CHLORIDE)

GROUP MEANS

MOTOR ACTIVITY DAY 60 p.p.
REARING

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M A L E S

		Interv. 1 Rearing	Interv. 2 Rearing	Interv. 3 Rearing	Interv. 4 Rearing	Interv. 5 Rearing	Interv. 6 Rearing	Interv. 7 Rearing	Interv. 8 Rearing
GROUP 0									
0 MG/KG	M	36.9	27.8	23.2	15.0	13.0	12.4	10.9	8.5
	SD	5.2	8.7	7.7	6.0	6.0	6.0	7.1	4.4
	N	10	10	10	10	10	10	10	10
GROUP 1									
15 MG/KG	M	38.2	27.7	23.7	21.8	19.0	15.8	12.8	8.5
	SD	6.8	6.3	8.7	6.4	8.5	5.6	7.7	4.8
	N	10	10	10	10	10	10	10	10
GROUP 2									
30 MG/KG	M	38.8	32.7	26.4	21.6	16.7	13.6	14.7	11.9
	SD	6.8	9.8	9.2	8.8	9.6	7.8	7.5	6.6
	N	10	10	10	10	10	10	10	10
GROUP 3									
60 MG/KG	M	40.5	30.2	23.4	17.1	17.0	10.2	8.9	8.2
	SD	6.7	7.8	7.6	6.1	7.1	6.8	8.7	7.3
	N	10	10	10	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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BAS 083 W (MEPIQUAT CHLORIDE)

GROUP MEANS

MOTOR ACTIVITY DAY 60 p.p.
REARING

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M A L E S

		Interv. 9 Rearing	Interv.10 Rearing	Interv.11 Rearing	Interv.12 Rearing	Interv.1-12 Sum
GROUP 0						
0 MG/KG	M	6.2	5.8	5.4	5.8	170.9
	SD	6.9	8.6	6.6	7.5	46.9
	N	10	10	10	10	10
GROUP 1						
15 MG/KG	M	7.0	6.0	6.2	5.4	192.1
	SD	6.2	6.5	8.3	8.4	48.5
	N	10	10	10	10	10
GROUP 2						
30 MG/KG	M	8.7	9.1	4.7	5.3	204.2
	SD	5.5	7.7	6.3	7.3	55.0
	N	10	10	10	10	10
GROUP 3						
60 MG/KG	M	5.0	4.7	1.8	5.7	172.7
	SD	5.4	8.2	3.2	9.8	48.8
	N	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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BAS 083 W (MEPIQUAT CHLORIDE)

GROUP MEANS

MOTOR ACTIVITY DAY 13 p.p.
REARING

PRINT DATE 13APR05

F E M A L E S

		Interv. 1 Rearing	Interv. 2 Rearing	Interv. 3 Rearing	Interv. 4 Rearing	Interv. 5 Rearing	Interv. 6 Rearing	Interv. 7 Rearing	Interv. 8 Rearing
GROUP 0									
0 MG/KG	M	19.7	16.3	16.3	16.2	17.3	6.5	9.5	6.7
	SD	10.3	8.4	12.1	15.3	11.5	10.0	11.9	8.9
	N	10	10	10	10	10	10	10	10
GROUP 1									
15 MG/KG	M	26.2	19.1	25.4	24.5	9.8	2.4	6.4	7.0
	SD	14.9	12.5	15.2	16.8	7.4	3.4	10.8	14.6
	N	10	10	10	10	10	10	10	10
GROUP 2									
30 MG/KG	M	20.2	19.7	18.5	10.8	9.7	11.0	13.5	10.7
	SD	12.0	13.0	18.2	12.9	15.9	14.1	16.8	16.6
	N	10	10	10	10	10	10	10	10
GROUP 3									
60 MG/KG	M	9.0 **↓54	6.0 **↓43	11.8	8.9	7.1	7.7	5.3	6.3
	SD	11.5	9.3	12.6	6.9	9.9	14.4	12.2	8.5
	N	10	10	10	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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BAS 083 W (MEPIQUAT CHLORIDE)

GROUP MEANS
MOTOR ACTIVITY DAY 13 p.p.
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F E M A L E S

		Interv. 9 Rearing	Interv.10 Rearing	Interv.11 Rearing	Interv.12 Rearing	Interv.1-12 Sum
GROUP 0						
0 MG/KG	M	5.6	4.7	5.2	2.3	126.3
	SD	6.8	7.5	8.6	4.8	53.4
	N	10	10	10	10	10
GROUP 1						
15 MG/KG	M	6.7	3.7	7.7	4.7	143.6
	SD	13.7	9.6	17.8	8.2	105.9
	N	10	10	10	10	10
GROUP 2						
30 MG/KG	M	6.9	10.1	8.4	3.5	143.0
	SD	17.9	14.6	16.8	8.9	127.5
	N	10	10	10	10	10
GROUP 3						
60 MG/KG	M	5.5	2.6	2.0	1.2	73.4
	SD	8.0	4.0	5.0	2.0	77.3
	N	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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BAS 083 W (MEPIQUAT CHLORIDE)

GROUP MEANS

MOTOR ACTIVITY DAY 17 p.p.
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F E M A L E S

		Interv. 1 Rearing	Interv. 2 Rearing	Interv. 3 Rearing	Interv. 4 Rearing	Interv. 5 Rearing	Interv. 6 Rearing	Interv. 7 Rearing	Interv. 8 Rearing
GROUP 0									
0 MG/KG	M	29.7	27.9	21.6	21.9	19.0	14.9	10.7	9.2
	SD	13.5	14.7	12.1	15.7	16.2	13.4	15.9	10.0
	N	10	10	10	10	10	10	10	10
GROUP 1									
15 MG/KG	M	41.9 *	30.2	22.8	17.3	14.0	13.5	11.2	7.5
	SD	6.3	13.2	14.7	14.8	15.3	14.7	12.0	10.1
	N	10	10	10	10	10	10	10	10
GROUP 2									
30 MG/KG	M	31.1	25.5	19.7	17.3	14.7	7.9	2.2	4.9
	SD	11.8	12.4	12.8	14.9	15.4	12.7	4.6	9.5
	N	10	10	10	10	10	10	10	10
GROUP 3									
60 MG/KG	M	25.7	28.6	23.5	18.4	23.5	16.0	16.5	18.0
	SD	9.9	11.2	9.4	7.4	11.5	8.1	16.4	17.2
	N	10	10	10	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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GROUP MEANS MOTOR ACTIVITY DAY 17 p.p. PRINT DATE 13APR05
REARING

F E M A L E S

		Interv. 9 Rearing	Interv.10 Rearing	Interv.11 Rearing	Interv.12 Rearing	Interv.1-12 Sum
GROUP 0						
0 MG/KG	M	12.0	13.9	8.5	11.3	200.6
	SD	14.1	14.9	10.5	13.6	123.0
	N	10	10	10	10	10
GROUP 1						
15 MG/KG	M	14.6	14.1	9.1	12.8	209.0
	SD	13.3	17.8	11.7	17.7	114.3
	N	10	10	10	10	10
GROUP 2						
30 MG/KG	M	8.1	13.6	15.0	14.5	174.5
	SD	10.4	13.0	15.3	13.6	69.0
	N	10	10	10	10	10
GROUP 3						
60 MG/KG	M	12.3	17.5	13.1	10.4	223.5
	SD	12.5	16.3	13.4	11.0	79.7
	N	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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BAS 083 W (MEPIQUAT CHLORIDE)

GROUP MEANS

MOTOR ACTIVITY DAY 22 p.p.
REARING

PRINT DATE 13APR05

F E M A L E S

		Interv. 1 Rearing	Interv. 2 Rearing	Interv. 3 Rearing	Interv. 4 Rearing	Interv. 5 Rearing	Interv. 6 Rearing	Interv. 7 Rearing	Interv. 8 Rearing
GROUP 0									
0 MG/KG	M	37.0	20.8	11.2	5.5	0.9	2.7	2.4	1.5
	SD	9.6	11.5	9.9	10.3	2.5	5.8	5.1	3.5
	N	10	10	10	10	10	10	10	10
GROUP 1									
15 MG/KG	M	40.4	23.1	10.2	6.0	5.0	2.9	1.3	2.1
	SD	10.6	10.7	11.6	7.4	7.2	4.9	2.1	4.7
	N	10	10	10	10	10	10	10	10
GROUP 2									
30 MG/KG	M	39.8	22.4	9.4	4.3	0.6	0.0	0.2	0.2
	SD	11.4	10.2	8.5	6.0	1.6	0.0	0.4	0.6
	N	10	10	10	10	10	10	10	10
GROUP 3									
60 MG/KG	M	35.6	23.7	9.7	3.5	1.8	0.1	0.0	0.0
	SD	12.1	12.8	8.1	4.6	3.8	0.3	0.0	0.0
	N	10	10	10	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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GROUP MEANS

MOTOR ACTIVITY DAY 22 p.p.
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F E M A L E S

		Interv. 9 Rearing	Interv.10 Rearing	Interv.11 Rearing	Interv.12 Rearing	Interv.1-12 Sum
GROUP 0						
0 MG/KG	M	0.0	0.0	1.8	0.8	84.6
	SD	0.0	0.0	5.7	1.9	52.3
	N	10	10	10	10	10
GROUP 1						
15 MG/KG	M	0.2	0.0	0.0	0.0	91.2
	SD	0.6	0.0	0.0	0.0	27.3
	N	10	10	10	10	10
GROUP 2						
30 MG/KG	M	1.9	1.6	0.5	0.7	81.6
	SD	5.7	5.1	1.3	2.2	31.0
	N	10	10	10	10	10
GROUP 3						
60 MG/KG	M	0.0	0.0	0.0	0.2	74.6
	SD	0.0	0.0	0.0	0.4	28.2
	N	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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BAS 083 W (MEPIQUAT CHLORIDE)

GROUP MEANS

MOTOR ACTIVITY DAY 60 p.p.
REARING

PRINT DATE 24MAY05

F E M A L E S

		Interv. 1 Rearing	Interv. 2 Rearing	Interv. 3 Rearing	Interv. 4 Rearing	Interv. 5 Rearing	Interv. 6 Rearing	Interv. 7 Rearing	Interv. 8 Rearing
GROUP 0									
0 MG/KG	M	40.7	33.3	29.3	25.9	18.0	14.3	16.4	10.1
	SD	5.4	11.5	4.7	7.7	7.9	10.0	7.2	4.4
	N	10	10	10	10	10	10	10	10
GROUP 1									
15 MG/KG	M	51.7 ** ↑2,3	40.5	29.3	29.4	23.7	18.1	14.3	11.8
	SD	6.5	5.8	7.2	6.7	13.1	7.5	9.4	11.4
	N	10	10	10	10	10	10	10	10
GROUP 2									
30 MG/KG	M	41.0	34.9	32.0	25.8	23.5	19.1	16.7	12.8
	SD	7.5	10.2	8.0	7.0	7.6	6.6	6.0	9.5
	N	10	10	10	10	10	10	10	10
GROUP 3									
60 MG/KG	M	44.6 * ↑1,0	36.6	35.0	22.5	21.8	15.9	18.5	9.4
	SD	11.2	7.2	6.8	5.5	6.9	7.0	11.5	7.0
	N	10	10	10	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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GROUP MEANS

MOTOR ACTIVITY DAY 60 p.p.
REARING

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F E M A L E S

		Interv. 9 Rearing	Interv.10 Rearing	Interv.11 Rearing	Interv.12 Rearing	Interv.1-12 Sum
GROUP 0						
0 MG/KG	M	12.7	11.4	10.5	4.9	227.5
	SD	7.1	8.8	8.0	5.7	39.2
	N	10	10	10	10	10
GROUP 1						
15 MG/KG	M	9.5	10.2	8.7	7.4	254.6
	SD	7.5	11.1	8.7	8.3	51.6
	N	10	10	10	10	10
GROUP 2						
30 MG/KG	M	14.8	9.4	6.1	6.1	242.2
	SD	8.1	6.1	8.0	6.8	58.0
	N	10	10	10	10	10
GROUP 3						
60 MG/KG	M	12.9	8.7	9.8	7.8	243.5
	SD	10.1	8.0	9.1	9.8	56.9
	N	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)