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Date: July 11, 2007OPP OFFICIAL REVIEW
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 801MEMORANDUMSUBJECT: Lambda-Cyhalothrin: Evaluation of a Developmental Neurotoxicity
Study in Rats (MRID 46449102). PC Code: 128897; DP Number:
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CONCLUSION: This memorandum transmits the evaluation of the definitive developmental neurotoxicity (DNT) study with lambda-cyhalothrin (MRID 46449102). In this study, female Alpk:AP_fSD (Wistar-derived) rats were administered lambda-cyhalothrin via the diet at nominal concentrations of 0, 25, 60, or 150 ppm from gestation day (GD) 7 through lactation day (LD) 23 [equivalent to 0, 1.8, 4.3, or 10.0 mg/kg/day, adjusted for purity, during gestation]. HED concluded that the maternal LOAEL is 10 mg/kg/day, based on decreased maternal body weight, body weight gain, and food consumption. The maternal NOAEL is 4.3 mg/kg/day. The offspring NOAEL/LOAEL could not be determined, and the study was classified unacceptable/guideline because the motor activity data were considered inadequate for assessment; the auditory startle response data in PND 61 females were considered inadequate for assessment; morphometric data at the mid and low doses were not available for the measurements in which effects were observed at the high dose; and statistical analyses of body weight, brain weight, and brain morphometric data inappropriately adjusted for body weights measured once dosing had begun.

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I. BACKGROUND

Syngenta Crop Protection, Inc. submitted results from preliminary and main developmental neurotoxicity (DNT) studies on lambda-cyhalothrin (MRIDs 46449102, 46449101, 46526802, 46526803, 46526804, and 46526805), which were conducted by Central Toxicology Laboratory (UK).

II. EVALUATION BY DNT WORK GROUP

The DNT Workgroup met on September 7, 2006 to review the definitive DNT study on lambda-cyhalothrin.

For maternal effects, the Workgroup concluded that the LOAEL is 10 mg/kg/day, based on decreased maternal body weight, body weight gain, and food consumption. The maternal NOAEL is 4.3 mg/kg/day.

In offspring, the Workgroup identified a number of treatment-related effects at 10 mg/kg/day. At this dose, a significant decrease (6%; $p \leq 0.01$) in the number of pups surviving from PNDs 1-5 (pre-cull) was observed, compared to controls. Pup body weights and body weight gains were consistently lower ($p \leq 0.01$) in both sexes at 10 mg/kg/day from PNDs 5-29, with a maximum decrease in body weight of 12%, compared to controls. In females exposed to 10 mg/kg/day, the mean time to completion of the water maze on PND 21 was longer, the proportion of successful trials on PND 21 was lower than controls for cut-off times ranging from 3-10 seconds, and the group mean success rate at 1.5 the straight channel swim time on PND 21 was decreased, although this change was not statistically significant. When memory was tested on PND 24, females in the 10 mg/kg/day group showed only a slight increase in the mean time per trial, compared to controls, but the proportion of successful trials for cut-off times from 3-9 seconds were still decreased. Finally, at the high dose, statistically significant decreases were seen in the molecular layer of the preculminate fissure of the cerebellum (13%), the overall width of the hippocampus (7%), and the level 3 dorsal cortex 1 (7%) of PND 12 males. In PND 12 females, statistically significant decreases were observed at 10 mg/kg/day in the level 5 dorsal cortex (6%), the level 4 dorsal cortex (7%), the thalamus width (4%), and the thalamus/cortex width (4%). At PND 63, a statistically significant decrease (7%) was observed in the level 3 piriform cortex of high-dose males.

Although treatment-related effects were identified in the offspring, several study deficiencies precluded the establishment of an offspring NOAEL and LOAEL:

- The motor activity data were considered inadequate for assessment. Of the control animals, habituation was only observed in PND 22 females. Although habituation might not be expected in PND 14 animals (e.g., the pups' eyes may still be closed, and their brains may not yet be developed enough so that habituation is possible), failure for all but one of the other control groups to

properly habituate indicates a lack of an adequate assessment of this parameter in this study.

- In PND 61 females, decreases in maximum auditory startle response were seen in all treated groups for repetitions 11-50, compared to controls. The magnitude of the decreases were similar across all doses (i.e., the dose-response was flat), and the decreases reached statistical significance at the low and high doses ($p \leq 0.01$). However, while the behavior of the treated PND 61 females is different from the controls, it is not possible to determine whether this difference is due to treatment or if it is because the PND 61 control females failed to exhibit the expected habituation. Failure for these animals to properly habituate indicates an inadequate assessment of auditory startle in the PND 61 females tested in this study. (Habituation was evident in PND 61 males.)
- For the brain morphometrics measurements in which significant changes were seen at the high dose (listed above), data was not available at the mid and low doses, but it should be provided to confirm whether or not the effects are limited to the high dose.
- Finally, body weights were analyzed by ANCOVA using GD 7 or LD 1 body weight for dams or PND 1 or 5 body weight for pups as the covariate, and brain weight and morphology data were considered by ANOVA and ANCOVA on final body weight. Since body weights should be randomized prior to the commencement of dosing, it is considered inappropriate to adjust for body weights measured once dosing has begun (i.e., on LD 1, PND 1, or PND 5) in statistical analyses of body weight, brain weight, and morphology data.

DATA EVALUATION RECORD**LAMBDA-CYHALOTHRIN**

**STUDY TYPE: DEVELOPMENTAL NEUROTOXICITY STUDY - RAT;
OPPTS 870.6300**

**MRID 46449102 (main study), MRID 46449101 (second preliminary study),
MRID 46526802 (comparison of systemic exposure in the pregnant and nonpregnant rat),
MRID 46526803 (determination of systemic exposure following dietary administration to female rats),
MRID 46526804 (comparison of systemic exposure in the female rat),
MRID 46526805 (preliminary study)**

Prepared for

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LAMBDA-CYHALOTHRIN/128897

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OPPT 870.6300

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DATA EVALUATION RECORD

STUDY TYPE: Developmental Neurotoxicity Study - Rat; OPPTS 870.6300 (883-6)**PC CODE:** 128897**DP BARCODE:** D312637**TEST MATERIAL (PURITY):** Technical Grade Lambda-cyhalothrin (87.7%)**SYNONYMS:** None provided

CITATION: Milburn, G. M. (2004) Lambda-Cyhalothrin: Developmental neurotoxicity study in rats. Syngenta Limited, Alderley Park, Macclesfield, Cheshire, UK SK 10 4TJ. Laboratory study number RR0969; November 3, 2004. MRID 46449102. Unpublished.

Williams, J. (2001) Lambda-Cyhalothrin: Second preliminary developmental neurotoxicity study in rats. Syngenta Limited, Fernhurst, Haslemere, Surrey, UK. Laboratory study number RR0812; May 4, 2001. MRID 46449101. Unpublished.

Hall, M.G. (2001) Lambda-Cyhalothrin: Comparison of systemic exposure in the pregnant and non-pregnant rat. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. CTL Number UR0594; April 30, 2001. MRID 46526802. Unpublished.

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Holme, P.C. (2001) Lambda-Cyhalothrin: Comparison of systemic exposure in the female rat. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. CTL Number UR0611; June 13, 2001. MRID 46526804. Unpublished.

Milburn, G.M. (2002) Lambda-Cyhalothrin: Preliminary developmental neurotoxicity study in rats. Central Toxicology Laboratory, Alderley Park,

LAMBDA-CYHALOTHRIN/128897

Macclesfield, Cheshire, UK; CTL Number RR0809; December 19, 2002. MRID 46526805. Unpublished.

SPONSOR: Syngenta Crop Protection, Inc., 410 Swing Road, PO Box 18300, Greensboro, NC 27419

EXECUTIVE SUMMARY: In a developmental neurotoxicity study (MRID 46449102), Lambda-cyhalothrin (87.7% a.i., batch #P31 (BX E624)) was administered in the diet to 30 mated female Alpk:AP_rSD (Wistar-derived) rats/group at nominal concentrations of 0, 25, 60 or 150 ppm from gestation day (GD) 7 through day 23 post partum. Average doses to the animals, adjusted for purity, were 1.8, 4.3, and 10.0 mg/kg/day, respectively, during gestation and 4.0, 9.4, and 23.1 mg/kg/day, respectively, during lactation. Dietary concentrations were based on the results of a preliminary developmental neurotoxicity study (MRID 46449101). A Functional Observational Battery (FOB) was performed on all dams on GDs 10 and 17 and on lactation days (LDs) 2 and 9. On postnatal day (PND) 5, litters were culled to yield four males and four females (as closely as possible). Offspring, representing at least 20 litters/dose, were allocated for detailed clinical observations and assessment of motor activity, auditory startle response, and learning and memory. Neural tissues were collected from selected offspring (10/sex/dose, representing 20 litters) on PND 12 and at study termination (PND 63). Pup body weights were recorded, and the age of sexual maturation was assessed (vaginal opening in females and preputial separation in males).

In the dams, no treatment-related effects were observed on mortality, reproductive performance, or gross pathology. Treatment-related maternal toxicity included decreased ($p \leq 0.05$ or 0.01) body weights, body weight gains, and food consumption during gestation and lactation at the high dose (150 ppm). At this dose, absolute maternal body weights were consistently decreased by 8-9%, compared to controls, throughout the treatment period and persisting through LD 15.

The maternal LOAEL is 150 ppm (10.0 mg/kg/day during gestation), based on decreased body weight, body weight gain, and food consumption. The maternal NOAEL is 60 ppm (4.3 mg/kg/day during gestation).

In offspring, no treatment-related effects were observed on clinical signs, developmental landmarks, the functional observational battery, brain weights, macroscopic neuropathology, or microscopic neuropathology.

A significant decrease (6%; $p \leq 0.01$) in the number of pups surviving from PNDs 1-5 (pre-cull), compared to controls, was observed at 150 ppm. Survival was unaffected by treatment with 25 or 60 ppm.

Pup body weights and body weight gains were consistently lower ($p \leq 0.01$) in both sexes at 150 ppm from PNDs 5-29, with a maximum decrease in body weight of 12%, compared to controls.

The motor activity data were considered inadequate for assessment. Of the control animals, habituation was only observed in PND 22 females. Although habituation might not be expected

in PND 14 animals (*e.g.*, the pups' eyes may still be closed, and their brains may not yet be developed enough so that habituation is possible), failure for all but one of the other control groups to properly habituate indicates a lack of an adequate assessment of this parameter in this study.

No treatment-related effects were seen in auditory startle response in PND 23 males or females or in PND 61 males. In PND 61 females, decreases in maximum auditory startle response were seen in all treated groups for repetitions 11-50, compared to controls. The magnitude of the decreases were similar across all doses (*i.e.*, the dose-response was flat), and the decreases reached statistical significance at the low and high doses ($p \leq 0.01$). However, while the behavior of the treated PND 61 females is different from the controls, it is not possible to determine whether this difference is due to treatment or if it is because the PND 61 control females failed to exhibit the expected habituation. Failure for these animals to properly habituate indicates an inadequate assessment of auditory startle in the PND 61 females tested in this study. Habituation was evident in PND 61 males.

High-dose females showed differences in water maze performance on PNDs 21 and 24. Learning was affected on PND 21, in that mean time to completion was longer, and the proportion of successful trials was lower than controls for cut-off times ranging from 3-10 seconds. When the cut-off was expressed in relation to the time taken to complete the straight channel, the group mean success rate at 1.5 the straight channel swim time on PND 21 was decreased, although this change was not statistically significant. When memory was tested on PND 24, high-dose females showed only a slight increase in the mean time per trial, compared to controls, but the proportion of successful trials for cut-off times from 3-9 seconds were still decreased. Treatment-related effects on learning and memory were not seen in PND 59/62 females or in males at either time point.

At the high dose, statistically significant decreases were seen in the molecular layer of the preculminate fissure of the cerebellum (13%), the overall width of the hippocampus (7%), and the level 3 dorsal cortex 1 (7%) of PND 12 males. In PND 12 females, statistically significant decreases were observed at 150 ppm in the level 5 dorsal cortex (6%), the level 4 dorsal cortex (7%), the thalamus width (4%), and the thalamus/cortex width (4%). At PND 63, a statistically significant decrease (7%) was observed in the level 3 piriform cortex of high-dose males. Data for these measurements at the mid and low doses should be provided to confirm whether or not the effects are limited to the high dose.

The offspring NOAEL/LOAEL cannot be determined due to the lack of brain morphometrics at the low and mid doses, as well as inadequate assessments of auditory startle response in PND 61 females and of motor activity.

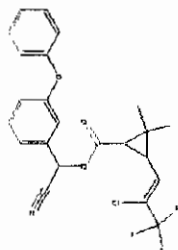
This study is classified **Unacceptable/Guideline** and does not satisfy the guideline requirement for a developmental neurotoxicity study in rats (OPPTS 870.6300, §83-6). The motor activity data were considered inadequate for assessment. It was not possible to determine whether the difference in auditory startle response between treated and control PND 61 females was due to treatment because the PND 61 control females failed to exhibit the expected habituation. Finally,

morphometric data at the mid and low doses were not available for the measurements in which effects were observed at the high dose.

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

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

1. **Test material:** Technical grade Lambda-cyhalothrin
Description: Dark brown solid
Lot/Batch #: P31 (BX E624)
Purity: 87.7 % a.i.
Compound Stability: Stable in the diet for 29 days at room temperature confirmed by re-analysis after the end of the in-life phase of the study. A certificate of analysis was not provided.
CAS # of TGA1: 91465-08-6
Structure:



2. **Vehicle and/or positive control:** The test article was dissolved in corn oil and mixed with basal diet. Appendix D provides time course data on the concentration of lambda-cyhalothrin in the plasma of adult female rats following a single oral gavage dose using three types of vehicle. No positive control was used in this study.

3. Test animals (P):

Species:	Rat
Strain:	Alpk:AP ₇ SD (Wistar-derived)
Age at study initiation (GD 1):	Females: 10-12 wks
Wt. at study initiation (GD 1):	217-296 g
Source:	Rodent Breeding Unit (RBU), Alderley Park, Macclesfield, Cheshire
Housing:	Individually or with litter in solid plastic cages with wood flake bedding; F ₁ animals 4/sex after weaning (GD 29) in wire mesh cages.
Diet:	Powdered CT1 diet, <i>ad libitum</i>
Water:	Tap water, <i>ad libitum</i>
Environmental conditions:	Temperature: 22±3°C Humidity: 39-75% Air changes: at least 15/hour Photoperiod: 12 hrs dark/12 hrs light
Acclimation period:	6 days before start of dosing

B. PROCEDURES AND STUDY DESIGN:

1. **In life dates:** Start: April 15, 2003; End: July 24, 2003
2. **Study schedule:** Time-mated females were delivered to the testing facility on gestation day (GD) 1 and assigned to the study. The test substance was administered to the maternal animals from GD 7 through day 23 post partum. Pups were weaned on postnatal day (PND) 29, after which time maternal animals were killed. The study included 30 parent

females/dose level. F₁ pups remained on study until scheduled termination on PND 12 or 63 (study termination).

3. **Mating procedure:** Mating was carried out at the Rodent Breeding Unit prior to delivery of the animals to the testing facility. The day on which sperm were detected in a vaginal smear was designated GD 1. The day on which parturition occurred was designated LD 1.
4. **Animal assignment:** Mated females and offspring were allocated as shown in Table 1. The study had a replicate (randomized block) design. Each replicate consisted of one cage/animal per treatment group. Cages were allocated to each group using an automatic method. The parental females were randomly allocated to cages/treatment groups on arrival at the testing facility. On PND 5, litters were culled to eight offspring, with sexes represented as equally as possible. Litters of 7 or 8 pups with at least 3 male and 3 female pups were used for selection of the F₁ generation.

Two pups/sex/litter were allocated on postnatal day 5 for testing of learning and memory; half were tested on PNDs 21 and 24, and the other half were tested on PNDs 59 and 62. One pup/litter was allocated on postnatal day 5 to each of the following examinations: functional observational battery, motor activity testing, auditory startle, sacrifice and fixation of the brain on PND 12, and sacrifice and fixation of the brain on PND 63. On day 63, an additional 10 animals/sex/group, different from those discussed above, were sacrificed by perfusion, and neural and muscle tissues were collected for microscopic examination.

TABLE 1. Study design				
Dose received (mg/kg/day)	Dose (ppm in diet)			
	0	25	60	150
Gestation	0	2.1	4.9	11.4
Gestation (adjusted for purity)	0	1.8	4.3	10.0
Lactation	0	4.6	10.7	26.3
Lactation (adjusted for purity)	0	4.0	9.4	23.1
Experimental parameter		No. of animals assigned		
Maternal animals				
FOB (GD 10, 17; LD 2, 9)	All	All	All	All
Offspring				
FOB (PND 5, 12, 22, 36, 46, 61)	≥10/sex	≥10/sex	≥10/sex	≥10/sex
Motor activity (PND 14, 18, 22, 60)	≥10/sex	≥10/sex	≥10/sex	≥10/sex
Auditory startle (PND 23, 61)	≥10/sex	≥10/sex	≥10/sex	≥10/sex
Passive Avoidance	not tested			
Water maze (PNDs 21 & 24)	≥20/sex	≥20/sex	≥20/sex	≥20/sex
Water maze (PNDs 59 & 62))	≥20/sex	≥20/sex	≥20/sex	≥20/sex
Gross necropsy and Brain Measurements (PND 12)	≥10/scx	≥10/sex	≥10/sex	≥10/sex
Gross necropsy and Brain Measurements (PND 63)	≥20/sex	≥20/sex	≥20/sex	≥20/sex

5. **Dose selection rationale:** Dose levels were chosen based on the results of a range-finding study in Alpk:AP₆SD rats (MRID 46449101). Details of this study are given in Appendix A. Briefly, groups of 10 female rats were administered 0, 25, 60, or 150 ppm in the diet from GD 7 through lactation day 22. Satellite groups of 6 females were also fed diets containing the test compound at 25, 60, or 150 ppm. During gestation, maternal animals in the 150 ppm group had body weights approximately 6% lower than controls; food consumption was also decreased during gestation. On PND 1, male and female pup body weights were lower in the 150 ppm group; however, growth was comparable to controls, thereafter. No other treatment-related effects were noted. As discussed in Appendix A of this DER, Lambda-cyhalothrin was detected in the plasma of maternal animals and pups at all time points evaluated, and plasma levels increased with increasing dietary concentration. Based on these results, the doses selected for the developmental neurotoxicity study were 0, 25, 60 and 150 ppm in the diet.
6. **Dosage administration:** The test article was administered in the diet to maternal animals on GD 7 through LD 23. Studies in which the plasma concentration of lambda cyhalothrin was measured following gavage or dietary exposure are discussed in Appendices B and C, respectively. The authors concluded that dietary administration was suitable, based on those studies.
7. **Dosage preparation and analysis:** For dosage calculations in units of ppm, purity of the test material was assumed to be 100%. The control and test article diets were prepared in 20 kg batches and stored at room temperature for up to 5 weeks. The appropriate amount of test article for each group was dissolved in warm corn oil to give a final weight of 50 g. The test article in corn oil was quantitatively transferred from the sample bottle into the grinder bowl with 950 g of finely ground CT1 diet. The premix was ground until the test substance was thoroughly mixed in the diet and was then added to another 19 kg of CT1 diet. The control diet was prepared in the same manner as the test article-treated diets without the addition of test article.

Homogeneity and stability of the test article in the diet were analyzed by gas chromatography. Samples for homogeneity were withdrawn from the top, middle and bottom of the low and high dose test diets prepared on April 16, 2003. Additional samples from these diets were stored for 29 days at room temperature and analyzed for stability. A sample from each dose group was taken prior to the start of and once during the main study for analysis of concentration.

Results:

Homogeneity analysis: Mean concentrations of lambda-cyhalothrin in the 25 ppm nominal dietary mixture were 24.0 ppm (top sample), 24.5 ppm (middle sample), and 24.5 ppm (bottom sample). Mean concentrations in the 150 ppm diet were 146 ppm (top sample), 152 ppm (middle sample), and 144 ppm (bottom sample).

Stability analysis: After 29 days at room temperature, the mean concentrations of the 25 and 150 ppm nominal dietary mixtures were 105.8% and 100.0%, respectively, of the initial measured concentrations.

Concentration analysis: Absence of test article was confirmed in the control diet. The mean concentrations of the 25, 60, and 150 ppm dietary mixtures ranged from 97.2-105.2%, 95.7-100.0%, and 98.0-104.0%, respectively, of nominal.

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

C. OBSERVATIONS:

1. In-life observations:

- a. **Maternal animals:** Females were observed twice daily for mortality and moribundity. Detailed clinical observations were recorded on arrival, on GDs 7, 15, and 22, on LDs 1, 5, 8, 12, 15, 22, and on the day of termination.

A Functional Observational Battery (FOB) was performed on all dams on GDs 10 and 17 and on LDs 2 and 9. It was not stated whether the observers were blind to the animals' treatment group. The method of ranking was not stated, and severity scores were described only as none (n), slight (s) or present (x). The following functional observations were recorded.

Functional observations—Maternal animals	
X	Signs of autonomic function, including: 1) Lacrimation and salivation 2) Presence or absence of piloerection and exophthalmus, 3) Urination and defecation 4) Pupillary function such as constriction of the pupil in response to light, or a measure of pupil size 5) Degree of palpebral closure, e.g., ptosis.
X	Description, incidence, and severity of any convulsions, tremors, or abnormal movements.
X	Description and incidence of posture and gait abnormalities.
X	Description and incidence of any unusual or abnormal behaviors, excessive or repetitive actions (stereotypies), emaciation, dehydration, hypotonia or hypertonia, altered fur appearance, red or crusty deposits around the eyes, nose, or mouth, and any other observations that may facilitate interpretation of the data.

The reviewer did not locate information regarding environmental conditions (e.g., noise level, etc.) during testing. However, this information was included with the positive control data submitted to EPA separately.

Individual maternal body weights were recorded on arrival, on GDs 7, 15, and 22, on LDs 1, 5, 8, 12, 15, 22, and on the day of termination. Food consumption was recorded throughout gestation and lactation and was calculated as g/rat/day.

b. Offspring:

1. **Litter observations:** Each litter was examined as soon as possible after completion of parturition (lactation day 1 or PND 1). On PNDs 1 and 5, the sex, weight, and clinical condition of each pup were recorded. Litters were checked daily for dead or abnormal pups.

On PND 5, litters were standardized to a maximum of 8 pups/litter (4/sex/litter, as nearly as possible); excess pups were killed and discarded.

2. **Developmental landmarks:** Beginning on PND 41, male offspring were examined daily for preputial separation. Beginning on PND 29, female offspring were examined daily for vaginal patency. The age of onset and the offspring body weight at that time were recorded.
3. **Detailed observations:** All pups were observed once daily for survival and clinical signs of toxicity. Individual offspring underwent detailed clinical observations and were weighed within 24 hours of birth, on PNDs 5, 12, 18, 22, 29, 36, 43, 50, and 57, and prior to termination on PND 63.
4. **Neurobehavioral evaluations:** Following litter standardization on PND 5, one male and/or one female from each litter were assigned to the following neurobehavioral tests.
 - i. **Functional observational battery (FOB):** On PNDs 5, 12, 22, 36, 46, and 61, approximately 10 offspring/sex/group (one male or one female from each litter) were examined outside the home cage in an FOB assessment by an observer blind to the animal's treatment group.

FUNCTIONAL OBSERVATIONS- Offspring	
X	Signs of autonomic function, including: 1) Lacrimation and salivation 2) Presence or absence of piloerection and exophthalmus, 3) Urination and defecation, including polyuria and diarrhea 4) Pupillary function such as constriction of the pupil in response to light, or a measure of pupil size 5) Degree of palpebral closure, e.g., ptosis.
X	Description, incidence, and severity of any convulsions, tremors, or abnormal movements.
X	Description and incidence of posture and gait abnormalities.
X	Description and incidence of any unusual or abnormal behaviors, excessive or repetitive actions (stereotypies), emaciation, dehydration, hypotonia or hypertonia, altered fur appearance, red or crusty deposits around the eyes, nose, or mouth, and any other observations that may facilitate interpretation of the data.

- ii. **Motor activity testing:** Motor activity was evaluated in approximately 10 offspring/sex/group (one male or one female from each litter) on PNDs 14, 18, 22, and 60. The report stated only that "the test was conducted in a separate room to minimize disturbance and used automated activity recording apparatus which

recorded small and large movements as an activity count." Each test was divided into 10 scans of five minutes each. No description of background noise or light intensity was provided.

iii. **Auditory startle habituation:** Auditory startle reflex habituation testing was performed on approximately 10 offspring/sex/group (one male or one female from each litter) on PNDs 23 and 61 using an automated system. The mean response maximum amplitude and the time to maximum amplitude on each block of 10 trials (5 blocks of 10 trials per session) were calculated. No description of the startle stimulus was given.

iv. **Learning and memory testing:**

Water maze: Learning and memory testing was performed in approximately 20 offspring/sex/dose (one male and one female from each litter) on PNDs 21 and 24 and in another approximately 20 offspring/sex/dose on PNDs 59 and 61 using a Y-water maze with one escape ladder. Different animals were used for each of the two testing periods. The time to find the escape ladder was recorded for each trial. The pups were given 6 trials on each of days 21 and 59 to test learning and three days later were retested using the same procedures. In addition, each animal was placed in a straight channel immediately after the six trials in the Y-maze on either PND 21 or 59 to evaluate swimming speed. No further description of the testing apparatus was given.

2. **Postmortem observations:**

- a. **Maternal animals:** Gross examination, including examination of the uterus to confirm pregnancy, was conducted on one female sacrificed for humane reasons on LD 2, four females that failed to litter and were sacrificed on PND 26, and on one female found dead on LD 6. The remaining animals, including those with total litter loss, were sacrificed by over-exposure to halothane Ph. Eur. vapor followed by exsanguination and discarded without examination. These animals included those with litters not required for selection of F₁ animals, which were sacrificed on LD 5, and those with litters selected for the study, which were sacrificed on day 29.
- b. **Offspring:** All pups found dead, those whose dam was found dead or sacrificed for humane reasons, those requiring euthanasia, those not selected for the F₁ generation on PND 5, and those not selected for brain weight or neuropathological evaluation as described below were not examined. The offspring selected for brain weight or neuropathological evaluation were sacrificed on postnatal day 12 or 63. These animals were subjected to postmortem examinations as described below.

PND 12: At postnatal day 12, one pup/litter (to give at least 10 pups/sex/dose) were sacrificed for gross necropsy and brain weight measurements. Animals were sacrificed by carbon dioxide inhalation, and the brain immediately removed and fixed in 10% neutral buffered formol saline. The brains were weighed after approximately 24 hours

fixation. The brains of animals in the control and high-dose group were processed for neuropathological examination.

After the gross brain measurements were recorded, brains from control and high-dose rats were embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Seven coronal sections from control and high-dose animals were examined microscopically. Brain morphometric measurements were made using a KS400 image analysis system.

The following brain morphometric measurements were made for control and high-dose animals:

Caudal edge of olfactory bulb (height and width)
Dorsal cortex parallel to midsagittal line (inner origin at most dorsal point of external capsule)
Dorsal cortex (inner origin at a point cut by a line drawn diagonally to midsagittal line)
Pyriform cortex at midpoint between rhinal and amygdaloid fissures
Hippocampus from midline to outer edge of most lateral pyramidal cells or from widest point from inner zone of dentate gyrus to outer edge of CA2
Dorsal cortex measurement made at right angles to a tangential line at surface of brain to run through the medial tip of the dentate gyrus
Thalamic height and width
Width of cerebral cortex and thalamus at widest point
Width of dentate gyrus at level of most medial part of lower limb of CA3 or widest point
Length of dentate gyrus
Cerebellum (height and length)
Perculminate and prepyramidal fissures (thickness of various layers)

PND 63: Ten animals/sex/group were euthanized by carbon dioxide asphyxiation, subjected to gross necropsy and the brains were removed, weighed (fresh weight), fixed, and stored. Another 10 rats/sex/dose were anesthetized by injection of sodium pentobarbitone and killed by perfusion fixation with a modified Karnovsky's fixative. The brain (weighed), vertebral column, spinal cord, peripheral nerves (sciatic, sural, and tibial), gasserian ganglion, and gastrocnemius muscle were preserved in an appropriate fixative.

The brain and muscle were embedded in paraffin wax, sectioned at 5 μ m, and stained with H&E. Transverse sections of the vertebral column containing samples from the lumbar and cervical regions of the spinal cord, with dorsal root ganglia and spinal roots attached, were decalcified, embedded in paraffin wax, sectioned at 5 μ m, and stained with H&E. The remaining tissues were embedded in resin and semi-thin sections cut and stained with toluidine blue.

The brain of 6 rats/sex from the control and high-dose groups were examined at seven levels. Spinal cord sections from the cervical and lumbar regions were examined in transverse section. Spinal roots and dorsal root ganglia from C3-C6 and L1-L4 levels and

the Gasserian ganglia were examined. Transverse and longitudinal sections of the sciatic nerve and transverse sections of the sural and tibial nerves were examined. The gastrocnemius muscle was examined in transverse plane. Detailed morphometric evaluation was conducted as described for day 12 animals.

D. DATA ANALYSIS:

1. **Statistical analyses:** Body weights were analyzed by ANCOVA using GD 7 or LD 1 body weight for dams or PND 1 or 5 body weight for pups as the covariate. Since body weights should be randomized prior to the commencement of dosing, however, statistical analyses that adjust for body weight once dosing begins are considered inappropriate. Food consumption during gestation, litter size, initial (day 1) pup weight, and total litter weight were analyzed by ANOVA. Proportion data were considered by Fisher's exact test. Percentages were analyzed by ANOVA followed by the double arcsine transformation of Freeman and Tukey. Statistical analyses were conducted on the adjusted mean (*i.e.*, mean adjusted for initial value/covariate).

Motor activity measurements, acoustic startle peak amplitude data, time to complete straight channel water maze, and mean day for attainment of developmental landmarks were analyzed by ANOVA. The mean time per water maze trial was analyzed by Student's t-test. Brain weight and morphology data were considered by ANOVA and ANCOVA on final body weight. Since body weights should be randomized prior to the commencement of dosing, statistical analyses of brain weight and morphology data that adjust for body weight once dosing begins are considered inappropriate.

2. **Indices:** Reproductive and offspring viability indices were not calculated. Proportions and percentages for group totals were given for pups live born, pup survival days 1-5, and sex distribution.
3. **Positive and historical control data:** Historical control data were submitted for whole litter losses, mean pup weight, proportion of successful water maze trials, pathology and brain morphometry. Positive control data have been submitted to EPA and are currently under review. The positive control studies include the following: Adult water maze- MRID 46012924; Pup motor activity- MRID 46336201; Young adult grip strength- MRID 46336202; Adult FOB and neuropathology- MRID 46336203; and Pup morphometry- MRID 46336204.

II. RESULTS:

A. PARENTAL ANIMALS:

1. **Mortality and clinical and functional observations:** No treatment-related maternal deaths occurred before scheduled termination. The number of females sacrificed prior to scheduled termination due to insufficient pups was 5, 3, 3, and 6 in the control, low-, mid-, and high-dose groups, respectively. (Sufficient pups were defined as at least 3 males and 3 females in

a litter of at least 7 pups on day 5.) An additional mid-dose female was sacrificed on day 2 postpartum for humane reasons, and an additional four females (1 control, 1 low-dose, and 2 mid-dose) were sacrificed because they failed to litter. One control female was found dead on day 6 postpartum.

One mid-dose and two high-dose females had hunched posture and piloerection during the early post partum period. The study authors considered these to be common non-specific observations and incidental to treatment. The mid-dose female killed for humane reasons on day 2 post partum had ataxia, was pale and dehydrated, and its sides were "pinched in." In the absence of a dose-response relationship, this finding is considered incidental to treatment. No other treatment-related clinical signs of toxicity were seen during general observations or the FOB.

2. **Body weight and food consumption:** Selected group mean absolute body weights and body weight gains for pregnant and lactating dams are summarized in Table 2. A treatment-related effect on maternal body weight and body weight gain was seen at the high dose. Decreases at the mid-dose were not considered biologically significant. Body weights were analyzed statistically by ANCOVA using GD 7 or LD 1 body weight for dams or as the covariate. Since body weights should be randomized prior to the commencement of dosing, however, statistical analyses that adjust for body weight once dosing has begun (*i.e.*, those that adjust for LD 1 body weight) are considered inappropriate.

During gestation, females in the 60 and 150 ppm groups had lower body weights ($p \leq 0.05$ or 0.01) than the controls on GDs 15 and 22. Maximum decreases in adjusted body weights were 3% in the 60 ppm group and 7% in the 150 ppm group. Overall body weight gain during gestation at the time when compound was administered (GD 7-22) was 10% and 24% lower than controls in the 60 and 150 ppm groups, respectively. There were no effects on body weight or body weight gain during gestation in the 25 ppm group.

During lactation days (LD) 1-15, mean body weight of females in the 150 ppm group was lower ($p \leq 0.01$) than that of controls; the maximum decrease was 9%. By LD 29, this body weight effect had resolved. Mean absolute body weight of 60 ppm dams was 5% lower ($p \leq 0.05$) than controls on LD 5, but it was comparable to controls thereafter. There were no effects on body weight or body weight gain during lactation in the 25 ppm group.

Selected group mean food consumption data for pregnant and lactating dams are summarized in Table 3. Food consumption by the mid- and high-dose groups was decreased by 6-9% and 13-23%, respectively, ($p \leq 0.05$ or 0.01) during weeks 2 and 3 of gestation. Food consumption was also decreased ($p \leq 0.01$) in 150 ppm dams throughout lactation. There were no effects on food consumption in the 25 ppm group.

TABLE 2. Selected maternal body weights (mean±SD; g) and weight gains (g) during gestation and lactation

Observation/study interval	0 ppm	25 ppm	60 ppm	150 ppm
Gestation (n= 28-30)				
Body wt. GD 1	251.9 ± 18.6	252.8 ± 18.8	249.6 ± 17.4	248.3 ± 20.4
Body wt. GD 7	284.3 ± 18.3	283.9 ± 19.4	279.5 ± 17.8	279.4 ± 19.0
Body wt. GD 15 (Absolute mean) (Adjusted mean)	328.9 ± 19.4 327.1	330.0 ± 18.3 327.9	320.9 ± 18.6 (98) 322.1* (98)	302.1 ± 17.8 (92) 304.1** (93)
Body wt. GD 22 (Absolute mean) (Adjusted mean)	399.4 ± 22.4 397.9	396.8 ± 18.2 394.9	382.9 ± 24.1 384.3** (97)	366.9 ± 23.9 (92) 368.8** (93)
Wt. gain GDs 1-7 ^a	32.4	31.1	29.9	31.1
Wt. gain GDs 7-15 ^a	44.6	46.1	41.4 (93)	22.7 (51)
Wt. gain GDs 15-22 ^a	70.5	66.8	62.0 (88)	64.8 (92)
Lactation (n=19-29)				
Body wt. LD 1	310.3 ± 28.7	298.7 ± 28.1	298.2 ± 28.7	283.5** ± 27.1 (91)
Body wt. LD 5 (Absolute mean) (Adjusted mean)	328.0 ± 23.9 319.9	319.3 ± 19.6 318.6	311.6 ± 30.8 (95) 310.0* (97)	297.5 ± 29.8 (91) 306.4** (96)
Body wt. LD 8 (Absolute mean) (Adjusted mean)	335.4 ± 21.0 331.9	327.6 ± 18.2 328.3	329.8 ± 24.9 327.4	304.2 ± 25.1 (91) 312.1** (94)
Body wt. LD 12 (Absolute mean) (Adjusted mean)	351.2 ± 19.5 347.2	345.9 ± 17.6 346.4	344.3 ± 23.6 342.9	319.0 ± 21.9 (91) 326.5** (94)
Body wt. LD 15 (Absolute mean) (Adjusted mean)	361.2 ± 23.1 357.8	359.9 ± 17.5 359.3	355.2 ± 22.1 353.8	328.3 ± 24.6 (91) 337.3** (94)
Body wt. LD 22 (Absolute mean) (Adjusted mean)	368.0 ± 22.2 364.8	367.0 ± 14.8 368.4	365.6 ± 21.0 363.2	347.2 ± 25.6 (94) 356.6 (98)
Body wt. LD 29 (Absolute mean) (Adjusted mean)	345.1 ± 25.6 341.5	344.2 ± 25.0 345.1	345.4 ± 22.1 343.3	338.4 ± 26.0 346.7
Wt. gain LDs 1-22 ^a	57.7	68.3 (118)	67.4 (117)	63.7 (110)

Data taken from Tables 6 & 7, pp. 74-75, MRID 46449102.

^a Calculated by reviewer from group absolute means.

* p≤0.05, ** p≤0.01

Values in parentheses are percent of controls, calculated by reviewer.

TABLE 3. Selected maternal food consumption (mean±SD; g/rat/day) data during gestation and lactation

Observation/study interval	0 ppm	25 ppm	60 ppm	150 ppm
Gestation (n= 28-30)				
GDs 1-7	21.1 ± 2.5	21.2 ± 2.3	20.9 ± 2.0	21.4 ± 2.1
GDs 7-15	27.4 ± 2.5	26.5 ± 1.9	24.8** ± 2.3 (91)	21.2** ± 5.1 (77)
GDs 15-22	30.7 ± 2.9	30.0 ± 3.2	28.8* ± 3.4 (94)	26.6** ± 4.7 (87)

TABLE 3. Selected maternal food consumption (mean±SD; g/rat/day) data during gestation and lactation				
Observation/study interval	0 ppm	25 ppm	60 ppm	150 ppm
Lactation (n=21-29)				
LDs 1-5	35.5± 6.8	36.3 ± 9.1	33.4 ± 8.2	29.2** ± 9.0 (82)
LDs 5-8	45.9 ± 9.0	46.5 ± 13.9	44.2 ± 10.7	43.3 ± 10.7 (94)
LDs 8-12	58.0 ± 9.1	59.3 ± 12.6	56.6 ± 6.7	51.8 ± 13.8 (89)
LDs 12-15	65.3 ± 6.0	67.0 ± 8.9	64.7 ± 7.2	58.9** ± 9.5 (90)
LDs 15-18	70.6 ± 4.8	70.1 ± 5.9	69.9 ± 8.0	63.4** ± 7.7 (90)
LDs 18-21	80.1 ± 6.6	79.2 ± 6.4	79.6 ± 7.2	72.0** ± 6.1 (90)
LDs 21-23	88.5 ± 8.4	85.5 ± 8.0	86.3 ± 5.6	80.7** ± 6.6 (91)

Data taken from Tables 8 & 9, pp. 76-77, MRID 46449102.

* p≤0.05, ** p≤0.01

Values in parentheses are percentages of controls, calculated by reviewer.

3. **Reproductive performance:** Results for the maternal animals are summarized in Table 4. No treatment-related effects were noted for the number of animals that delivered or in the mean gestation length. One control, one 25 ppm female, and one 60 ppm female had no implantation sites, and another 60 ppm female was sacrificed for humane reasons.

TABLE 4. Reproductive performance				
Observation	0 ppm	25 ppm	60 ppm	150 ppm
Number Mated	30	30	30	30
Number Delivered	29	29	28	30
Mean (±SD) gestation length (days)	22.0 ± 0.2	22.0 ± 0.0	22.0 ± 0.2	22.0 ± 0.0

Data taken from Tables 10 & 11, pp. 78-79, MRID 46449102.

4. **Maternal postmortem results:** One 60 ppm female had a pale liver. Otherwise, no abnormalities were detected.

B. OFFSPRING:

1. **Viability and clinical signs:** Litter size and viability results from pups during postnatal days (PNDs) 1-5 are summarized in Table 5. Mean live litter size at birth was not affected by treatment. There was no treatment-related effect on the incidence of whole litter loss. Pup survival from PNDs 1-5 was significantly decreased ($p \leq 0.01$) at the high dose. There was no effect on survival in the 25 or 60 ppm groups. The numbers of pups missing and presumed dead and of those found dead were higher in the 25 and 150 ppm groups, compared to controls. This reflects total litter losses in the 25 ppm group and increased pup mortality in the 150 ppm group. One litter of pups from the 60 ppm group was sacrificed for humane reasons when their dam was killed.

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Post-cull, from PND 5-63, animals that were found dead include 1 male in the control group and 1 male at the 25 ppm group. Animals missing that were presumed dead include 3 controls (1 male and 2 females), 3 animals in the 25 ppm group (1 male and 2 females), and 3 females in the 60 ppm group.

No treatment-related clinical signs of toxicity were observed in pups.

TABLE 5. Litter size and viability				
Observation	0 ppm	25 ppm	60 ppm	150 ppm
Number of live litters	29	29	28	30
Mean no. pups born	11.4	12.5	11.0	11.8
Mean live litter size (PND 1) ^a	11.3 ± 3.3	12.0 ± 3.4	10.9 ± 3.2	11.7 ± 3.4
No. of dams with total litter loss	0	2	0	3
Live Birth Index (PND 1; % per litter) ^a	98.6 ± 4.7	97.6 ± 6.8	98.6 ± 5.0	98.8 ± 3.3
Sex ratio on PND 1(% males/litter)	55.2 ± 16.3	50.4 ± 14.8	55.1 ± 13.5	52.8 ± 14.8
Viability Index [PNDs 1-5 (precull); % per litter] ^a	97.2 ± 5.8	95.2 ± 11.3	94.6 ± 12.3	90.9 ± 19.3** (94)
Number pups missing, which were presumed dead, on PNDs 1-5 (litters), including whole litter loss	11 (8)	45 (9)	19 (7)	65 (13)
Number pups missing, which were presumed dead, on PNDs 1-5 (litters), excluding whole litter loss ^b	11 (8)	14 (7)	19 (7)	31 (10)
Number pups found dead on PNDs 1-5 (litters)	5 (3)	7 (6)	3 (3)	10 (6)

Data taken from Tables 11-15, pages 79-84, and Table 18, p. 87, MRID 46449102.

^a Excludes whole litter losses.

^b Calculated by reviewer.

Significantly different from control: *p ≤ 0.05; **p ≤ 0.01.

Values in parentheses are percentages of controls, calculated by reviewer.

- 2. Body weight:** Selected mean pre-weaning pup body weight data are presented in Table 6, and selected post-weaning body weights are summarized in Table 7. Statistical analyses are requested for the unadjusted (absolute) body weight data. There were no treatment-related body weight effects at birth. At the high dose, a treatment-related decrease (p ≤ 0.01) in male and female pup body weights was seen during lactation, beginning on PND 5. Body weights of these high dose animals continued to be slightly lower than controls post-weaning, from PNDs 36-63. Body weight gains were decreased to 76% of control values in both males and females during PNDs 1-5 (pre-cull) and to 91-92% over PNDs 5-29. Low- and mid-dose males showed slight decreases (p ≤ 0.05) in body weight from PNDs 36 or 43 through 57; however, in the absence of a dose-response relationship and considering that the values were similar to control values in other studies, these effects are not considered biologically significant.

TABLE 6: Offspring body weight and body weight gain (g) during lactation				
Postnatal day	0 ppm	25 ppm	60 ppm	150 ppm
Males (n=27-30, pre-cull; n=21-24, post-cull)				
1	6.3 ± 0.6	6.1 ± 0.7	6.2 ± 0.6	6.2 ± 0.8
5 (pre-cull) (Absolute mean) (Adjusted mean)	10.5 ± 1.3 10.4	9.8 ± 1.5 9.9*	10.1 ± 1.3 10.1	9.4 ± 2.0 (90) 9.6* (92)
5 (post-cull)	10.2 ± 0.9	9.8 ± 1.4	10.2 ± 1.2	9.2* ± 1.5 (90)
12 (Absolute mean) (Adjusted mean)	24.7 ± 1.7 24.3	24.0 ± 2.1 24.1	24.7 ± 1.9 24.2	21.8 ± 3.4 (88) 22.7** (93)
18 (Absolute mean) (Adjusted mean)	39.8 ± 2.5 39.5	39.4 ± 1.9 39.5	40.0 ± 2.4 39.5	35.9 ± 3.8 (90) 36.7** (93)
22 (Absolute mean) (Adjusted mean)	54.1 ± 3.0 53.7	53.1 ± 2.2 53.2	54.0 ± 3.1 53.5	48.3 ± 4.6 (89) 49.2** (92)
29 (Absolute mean) (Adjusted mean)	94.1 ± 4.3 93.5	92.3 ± 3.6 92.5	93.9 ± 5.2 93.0	86.6 ± 7.5 (92) 88.2** (94)
Wt. gain days 1-5 ^b (pre-cull)	4.2	3.7	3.9	3.2 (76)
Wt. gain days 5-29 ^b	83.9	82.5	83.7	77.4 (92)
Females (n=26-30, pre-cull; n=21-24, post-cull)				
1	5.9 ± 0.7	5.8 ± 0.7	5.9 ± 0.5	5.7 ± 0.8
5 (pre-cull) (Absolute mean) (Adjusted mean)	10.1 ± 1.3 10.0	9.5 ± 1.5 9.5* (95)	9.7 ± 1.3 9.5* (95)	8.9 ± 1.8 (88) 9.1** (91)
5 (post-cull)	9.7 ± 1.0	9.4 ± 1.4	9.9 ± 1.2	8.5** ± 1.4 (88)
12 (Absolute mean) (Adjusted mean)	23.8 ± 1.7 23.5	23.4 ± 2.1 23.4	23.9 ± 2.0 23.3	20.5 ± 3.3 (86) 21.6** (92)
18 (Absolute mean) (Adjusted mean)	38.2 ± 2.6 37.9	38.1 ± 1.8 38.1	38.5 ± 2.3 37.9	33.9 ± 3.8 (89) 35.0** (92)
22 (Absolute mean) (Adjusted mean)	52.2 ± 3.2 51.8	51.6 ± 2.2 51.6	52.2 ± 2.8 51.4	45.8 ± 4.7 (88) 47.1** (91)
29 (Absolute mean) (Adjusted mean)	89.1 ± 5.0 88.4	87.5 ± 3.4 87.4	88.4 ± 4.8 87.2	80.4 ± 7.6 (90) 82.6** (93)
Wt. gain days 1-5 ^b	4.2	3.7	3.8	3.2 (76)
Wt. gain days 5-29 ^b	79.4	78.1	78.5	71.9 (91)

Data taken from Tables 16 and 20, pp. 85 and 125-128, respectively, MRID 46449102.

^a Values in parentheses are percentages of controls; calculated by reviewer.

^b Calculated by reviewer from group absolute means.

Significantly different from control: *p ≤ 0.05 or **p ≤ 0.01.

TABLE 7: Offspring body weights (g) during the post-weaning interval				
Postnatal day	0 ppm	25 ppm	60 ppm	150 ppm
Males (n=21-24)				
36 (Absolute mean) (Adjusted mean)	151.6 ± 6.6 150.4	147.1 ± 7.1 147.5	148.5 ± 8.6 146.8* (98)	139.2 ± 10.5 142.0** (94)
43 (Absolute mean) (Adjusted mean)	212.1 ± 9.1 210.6	204.4 ± 10.4 204.8* (97)	206.2 ± 11.8 204.1* (97)	194.4 ± 13.4 198.0** (94)
50 (Absolute mean) (Adjusted mean)	270.7 ± 12.3 269.1	261.5 ± 10.1 261.9* (97)	264.9 ± 12.7 262.5* (98)	249.9 ± 15.4 253.9** (94)
57 (Absolute mean) (Adjusted mean)	326.6 ± 13.9 324.8	316.6 ± 11.3 317.1* (98)	319.8 ± 15.6 317.3* (98)	303.0 ± 17.9 307.3** (95)
63 (Absolute mean) (Adjusted mean)	361.8 ± 16.2 360.0	352.8 ± 18.0 353.3	355.5 ± 18.9 352.9	338.5 ± 18.6 343.0** (95)
Females (n=21-24)				
36 (Absolute mean) (Adjusted mean)	131.0 ± 6.6 130.1	128.0 ± 6.0 128.0	129.4 ± 6.5 127.7	120.5 ± 9.2 123.5** (95)
43 (Absolute mean) (Adjusted mean)	164.6 ± 8.2 163.7	160.8 ± 7.6 160.7	161.1 ± 9.5 159.4	150.1 ± 11.0 153.2** (94)
50 (Absolute mean) (Adjusted mean)	189.8 ± 10.3 188.7	183.3 ± 8.4 183.2*	186.1 ± 8.3 184.2	173.2 ± 12.4 176.6** (94)
57 (Absolute mean) (Adjusted mean)	210.7 ± 11.7 209.7	207.5 ± 7.7 207.4	207.7 ± 12.4 205.8	194.7 ± 13.1 198.0** (94)
63 (Absolute mean) (Adjusted mean)	220.0 ± 13.0 219.0	216.0 ± 9.4 215.9	216.2 ± 11.9 214.3	203.8 ± 13.5 207.1** (95)

Data taken from Table 20, pp. 125-128, MRID 46449102.

^a Values in parentheses are percentages of controls; calculated by reviewer.

Significantly different from control: *p ≤ 0.05 or **p ≤ 0.01.

3. Developmental landmarks:

- a. **Sexual maturation:** Age and body weight at sexual maturation are given in Table 8. Mean body weights of high dose males and females on the day of attainment were 94% and 92%, respectively, of controls. The mean age of preputial separation for males was ½ day older for the 150 ppm males, compared to controls, but that change is slight and reflects decreased body weight. Thus, it is not considered adverse. In females, no treatment-related effect on the mean age of vaginal opening was observed.

TABLE 8. Mean ($\pm$ SD) age of sexual maturation (days)				
Endpoint	0 ppm	25 ppm	60 ppm	150 ppm
N (M/F)	23/23	24/24	24/24	21/21
Body weight (g $\pm$ SD) at attainment				
Males	228.3 $\pm$ 14.6	223.4 $\pm$ 11.0	222.5 $\pm$ 11.8	215.68** $\pm$ 12.0 (94)
Females	120.8 $\pm$ 12.8	117.7 $\pm$ 7.5	118.8 $\pm$ 8.5	110.8** $\pm$ 10.7 (92)
Postnatal Day of preputial separation (males)	45.0 $\pm$ 1.2	45.3 $\pm$ 1.2	45.1 $\pm$ 1.2	45.8* $\pm$ 1.0
Postnatal Day of vaginal opening (females)	34.6 $\pm$ 1.5	34.5 $\pm$ 1.4	34.3 $\pm$ 0.9	34.5 $\pm$ 1.4

Data taken from Table 21, pp. 129-130, MRID 46449102.

Significantly different from control: * $p \leq 0.05$; ** $p \leq 0.01$.

4. Behavioral assessments:

- a. **Functional observational battery:** No treatment-related effects were observed at any dose level on any test day (PND 5, 12, 22, 36, 46, or 61). Chromodacryorrhea was seen in 1, 3, 2, and 0 of the control, low, mid, and high-dose males, as well as in 0, 0, 1, and 1 of the control, low, mid, and high-dose females, but this finding was considered incidental.
- b. **Motor and locomotor activity:** Subsession and total motor activity counts are given in Table 9. Data for motor and locomotor activity were not separated. At the mid-dose on PND 14, a statistically significant increase in overall activity (minutes 1-50) was seen in males, and statistically significant increases were seen various subsession data for females; however, in the absence of a dose-response relationship, these observations are considered incidental to treatment. In high-dose males and females on PND 18, decreases in motor activity were observed for multiple subsessions; however, due to the high variability and the lack of habituation in PND 18 controls, the data are considered equivocal. Of the control animals, habituation was only observed in PND 22 females. Although habituation might not be expected in PND 14 animals (e.g., the pups' eyes may still be closed, and their brains may not yet be developed enough so that habituation is possible), failure for all but one of the other control groups to properly habituate indicates a lack of an adequate assessment of this parameter in this study.

TABLE 9: Mean ($\pm$ S.D.) motor activity data (total activity counts)								
Interval (minutes)	0 ppm	25 ppm	60 ppm	150 ppm	0 ppm	25 ppm	60 ppm	150 ppm
	Males (n=10-12)				Females (n=10-12)			
PND 14								
1-5	13.2 $\pm$ 17.2	25.4 $\pm$ 26.9	42.3** $\pm$ 26.3	22.7 $\pm$ 23.1	24.9 $\pm$ 21.0	33.2 $\pm$ 26.5	41.3 $\pm$ 25.4	30.4 $\pm$ 32.4
6-10	12.5 $\pm$ 17.1	16.8 $\pm$ 22.4	28.9 $\pm$ 28.4	19.2 $\pm$ 17.2	23.8 $\pm$ 28.2	30.8 $\pm$ 27.2	28.5 $\pm$ 22.8	17.1 $\pm$ 21.2
11-15	15.0 $\pm$ 21.2	16.4 $\pm$ 19.9	25.4 $\pm$ 22.1	11.2 $\pm$ 15.1	7.7 $\pm$ 11.1	24.0 $\pm$ 22.2	28.4* $\pm$ 27.4	10.3 $\pm$ 15.2

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TABLE 9: Mean ($\pm$ S.D.) motor activity data (total activity counts)								
Interval (minutes)	0 ppm	25 ppm	60 ppm	150 ppm	0 ppm	25 ppm	60 ppm	150 ppm
16-20	8.2 $\pm$ 21.8	9.2 $\pm$ 15.5	23.5 $\pm$ 23.1	7.3 $\pm$ 12.6	18.8 $\pm$ 27.3	25.5 $\pm$ 26.9	26.8 $\pm$ 23.5	17.2 $\pm$ 21.0
21-25	17.2 $\pm$ 19.0	3.1* $\pm$ 4.5	16.8 $\pm$ 16.5	10.5 $\pm$ 15.6	24.3 $\pm$ 29.0	22.0 $\pm$ 22.5	28.3 $\pm$ 25.5	8.2 $\pm$ 9.8
26-30	9.2 $\pm$ 16.0	16.3 $\pm$ 22.3	14.8 $\pm$ 17.7	13.3 $\pm$ 22.3	19.3 $\pm$ 21.0	20.9 $\pm$ 22.8	20.9 $\pm$ 22.9	8.8 $\pm$ 12.7
31-35	6.2 $\pm$ 12.8	6.0 $\pm$ 10.7	18.0 $\pm$ 19.6	11.2 $\pm$ 18.2	8.4 $\pm$ 10.5	16.7 $\pm$ 23.5	24.4* $\pm$ 22.3	2.1 $\pm$ 3.0
36-40	3.5 $\pm$ 6.5	11.9 $\pm$ 19.0	17.6 $\pm$ 23.3	11.3 $\pm$ 20.1	8.7 $\pm$ 12.1	17.0 $\pm$ 22.1	28.5* $\pm$ 24.2	6.1 $\pm$ 12.0
41-45	9.3 $\pm$ 18.7	9.2 $\pm$ 14.9	16.7 $\pm$ 13.8	8.1 $\pm$ 10.3	14.1 $\pm$ 25.6	22.0 $\pm$ 27.0	19.7 $\pm$ 20.0	5.6 $\pm$ 6.7
46-50	5.8 $\pm$ 11.9	11.8 $\pm$ 14.5	12.6 $\pm$ 19.9	8.4 $\pm$ 11.9	11.3 $\pm$ 15.8	8.6 $\pm$ 9.8	22.2 $\pm$ 20.2	13.0 $\pm$ 16.2
Overall: 1-50	100.1 $\pm$ 92.6	126.0 $\pm$ 111.4	216.5* $\pm$ 145.7 ($\uparrow$ 116%)	123.1 $\pm$ 113.7	161.2 $\pm$ 154.9	220.7 $\pm$ 160.4	269.1 $\pm$ 164.9	118.8 $\pm$ 94.7
PND 18								
1-5	5.3 $\pm$ 4.9	19.2 $\pm$ 19.4	21.3* $\pm$ 18.6	19.4 $\pm$ 23.5	17.8 $\pm$ 20.1	29.0 $\pm$ 27.7	19.7 $\pm$ 24.9	29.5 $\pm$ 20.1
6-10	18.3 $\pm$ 19.1	16.8 $\pm$ 20.4	21.8 $\pm$ 25.8	17.8 $\pm$ 22.1	31.3 $\pm$ 22.3	33.2 $\pm$ 22.7	19.2 $\pm$ 19.9	23.5 $\pm$ 22.1
11-15	24.6 $\pm$ 25.0	16.7 $\pm$ 22.7	24.6 $\pm$ 25.2	10.1 $\pm$ 15.5	21.9 $\pm$ 19.6	30.9 $\pm$ 26.4	16.8 $\pm$ 20.5	10.2 $\pm$ 14.8
16-20	22.2 $\pm$ 23.1	16.3 $\pm$ 26.3	18.0 $\pm$ 18.5	8.1 $\pm$ 18.4	20.8 $\pm$ 23.8	35.7 $\pm$ 24.3	25.9 $\pm$ 24.0	19.5 $\pm$ 19.1
21-25	29.6 $\pm$ 32.6	21.5 $\pm$ 17.7	23.3 $\pm$ 22.6	9.3* $\pm$ 17.2	29.1 $\pm$ 21.1	30.1 $\pm$ 24.6	19.2 $\pm$ 24.4	7.2* $\pm$ 10.8
26-30	18.6 $\pm$ 20.4	20.3 $\pm$ 22.4	19.1 $\pm$ 20.4	13.9 $\pm$ 17.8	30.8 $\pm$ 24.0	30.1 $\pm$ 24.5	20.3 $\pm$ 23.7	13.8 $\pm$ 17.3
31-35	23.2 $\pm$ 26.2	32.0 $\pm$ 25.9	18.1 $\pm$ 21.4	16.1 $\pm$ 18.5	30.0 $\pm$ 21.6	25.5 $\pm$ 22.1	22.0 $\pm$ 22.6	22.4 $\pm$ 21.9
36-40	10.0 $\pm$ 15.0	31.9* $\pm$ 28.9	17.8 $\pm$ 29.2	6.7 $\pm$ 13.6	19.8 $\pm$ 22.1	41.8* $\pm$ 18.3	12.0 $\pm$ 19.7	13.3 $\pm$ 17.6
41-45	14.1 $\pm$ 21.0	34.5* $\pm$ 22.4	19.7 $\pm$ 26.0	0.3 $\pm$ 0.6	14.3 $\pm$ 21.3	35.3 $\pm$ 27.2	33.9 $\pm$ 35.5	21.0 $\pm$ 25.9
46-50	14.0 $\pm$ 22.4	27.5 $\pm$ 22.6	10.8 $\pm$ 18.5	3.4 $\pm$ 8.0	20.3 $\pm$ 19.4	22.7 $\pm$ 23.1	19.0 $\pm$ 23.1	7.9 $\pm$ 8.9
Overall: 1-50	179.9 $\pm$ 152.7	236.7 $\pm$ 115.7	194.3 $\pm$ 172.7	105.0 $\pm$ 117.7	236.3 $\pm$ 132.0	314.4 $\pm$ 181.3	207.8 $\pm$ 181.3	168.3 $\pm$ 116.2
PND 22								
1-5	36.9 $\pm$ 27.2	48.1 $\pm$ 14.4	49.8 $\pm$ 23.8	43.5 $\pm$ 24.8	41.6 $\pm$ 21.9	40.0 $\pm$ 26.1	34.2 $\pm$ 20.7	43.3 $\pm$ 20.5
6-10	34.3 $\pm$ 22.0	41.6 $\pm$ 17.6	40.5 $\pm$ 24.7	44.5 $\pm$ 28.6	33.2 $\pm$ 26.2	41.0 $\pm$ 23.6	39.3 $\pm$ 22.5	36.4 $\pm$ 25.7
11-15	26.8 $\pm$ 27.6	28.0 $\pm$ 20.4	25.1 $\pm$ 27.7	26.9 $\pm$ 21.3	17.5 $\pm$ 22.7	27.1 $\pm$ 31.8	25.3 $\pm$ 21.8	36.6 $\pm$ 24.7
16-20	23.2 $\pm$ 29.2	27.1 $\pm$ 18.2	28.4 $\pm$ 28.9	24.2 $\pm$ 24.9	30.1 $\pm$ 26.5	39.5 $\pm$ 27.1	28.9 $\pm$ 29.8	39.6 $\pm$ 27.5
21-25	29.0 $\pm$ 23.7	31.2 $\pm$ 25.8	23.5 $\pm$ 22.4	27.7 $\pm$ 22.6	32.7 $\pm$ 26.7	25.3 $\pm$ 23.9	28.8 $\pm$ 29.9	32.7 $\pm$ 21.0
26-30	35.6 $\pm$ 31.0	44.8 $\pm$ 26.1	35.5 $\pm$ 20.9	25.2 $\pm$ 24.9	35.3 $\pm$ 30.2	12.6 $\pm$ 19.3	27.8 $\pm$ 28.0	40.7 $\pm$ 30.6
31-35	31.7 $\pm$ 27.7	47.4 $\pm$ 22.4	25.4 $\pm$ 22.4	25.3 $\pm$ 19.8	38.0 $\pm$ 31.5	35.3 $\pm$ 32.7	16.3 $\pm$ 16.8	31.3 $\pm$ 27.7
36-40	29.5 $\pm$ 30.6	29.7 $\pm$ 26.2	29.1 $\pm$ 31.2	14.1 $\pm$ 19.3	27.8 $\pm$ 22.6	44.1 $\pm$ 25.1	20.4 $\pm$ 20.8	24.7 $\pm$ 25.8
41-45	25.7 $\pm$ 28.4	25.8 $\pm$ 25.5	25.4 $\pm$ 26.2	15.1 $\pm$ 18.4	14.0 $\pm$ 19.4	19.0 $\pm$ 19.5	26.0 $\pm$ 31.2	21.3 $\pm$ 27.6
46-50	34.6 $\pm$ 29.8	44.7 $\pm$ 20.3	26.9 $\pm$ 35.8	23.8 $\pm$ 25.6	14.3 $\pm$ 18.2	20.1 $\pm$ 21.8	20.6 $\pm$ 22.7	18.6 $\pm$ 23.5
Overall: 1-50	307.3 $\pm$ 202.8	368.3 $\pm$ 104.2	309.7 $\pm$ 194.7	270.3 $\pm$ 168.3	284.4 $\pm$ 148.0	303.9 $\pm$ 164.7	267.6 $\pm$ 162.7	325.2 $\pm$ 168.1

TABLE 9: Mean ($\pm$ S.D.) motor activity data (total activity counts)								
Interval (minutes)	0 ppm	25 ppm	60 ppm	150 ppm	0 ppm	25 ppm	60 ppm	150 ppm
PND 60								
1-5	62.7 $\pm$ 12.1	58.6 $\pm$ 10.3	68.8 $\pm$ 8.4	66.6 $\pm$ 7.4	61.8 $\pm$ 10.2	57.4 $\pm$ 10.4	54.8 $\pm$ 11.9	61.7 $\pm$ 13.1
6-10	66.0 $\pm$ 11.7	66.5 $\pm$ 10.8	66.8 $\pm$ 7.1	68.0 $\pm$ 11.3	62.4 $\pm$ 6.4	61.6 $\pm$ 10.4	59.8 $\pm$ 9.9	58.7 $\pm$ 13.4
11-15	61.9 $\pm$ 17.2	55.8 $\pm$ 17.5	61.9 $\pm$ 20.4	60.5 $\pm$ 20.2	61.7 $\pm$ 9.8	65.9 $\pm$ 11.1	59.3 $\pm$ 17.1	62.7 $\pm$ 9.5
16-20	48.3 $\pm$ 17.7	51.3 $\pm$ 21.7	47.9 $\pm$ 24.5	48.3 $\pm$ 19.1	56.1 $\pm$ 14.0	58.5 $\pm$ 14.5	54.3 $\pm$ 17.7	57.1 $\pm$ 13.9
21-25	37.0 $\pm$ 18.5	39.1 $\pm$ 23.8	43.3 $\pm$ 27.5	44.8 $\pm$ 24.8	58.1 $\pm$ 14.2	55.9 $\pm$ 22.5	57.3 $\pm$ 14.0	56.5 $\pm$ 12.9
26-30	47.8 $\pm$ 20.7	36.3 $\pm$ 28.0	44.7 $\pm$ 28.6	34.3 $\pm$ 24.1	52.8 $\pm$ 13.0	49.5 $\pm$ 23.2	54.3 $\pm$ 14.7	53.6 $\pm$ 19.1
31-35	33.0 $\pm$ 23.5	29.5 $\pm$ 26.1	38.2 $\pm$ 30.8	41.1 $\pm$ 26.3	47.3 $\pm$ 26.0	45.5 $\pm$ 19.3	58.2 $\pm$ 9.1	54.4 $\pm$ 14.2
36-40	29.3 $\pm$ 19.1	25.6 $\pm$ 25.1	38.3 $\pm$ 32.0	39.6 $\pm$ 25.1	50.4 $\pm$ 23.6	55.6 $\pm$ 25.4	58.3 $\pm$ 13.3	55.5 $\pm$ 12.6
41-45	42.3 $\pm$ 26.1	35.3 $\pm$ 27.9	44.6 $\pm$ 29.1	33.2 $\pm$ 29.7	53.2 $\pm$ 17.9	54.1 $\pm$ 24.5	50.4 $\pm$ 19.0	61.5 $\pm$ 15.5
46-50	45.6 $\pm$ 21.9	44.9 $\pm$ 27.4	40.9 $\pm$ 33.1	34.6 $\pm$ 27.8	57.8 $\pm$ 8.3	53.2 $\pm$ 13.8	50.8 $\pm$ 18.7	53.6 $\pm$ 13.8
Overall: 1-50	473.9 $\pm$ 77.3	442.8 $\pm$ 158.9	495.4 $\pm$ 187.3	471.0 $\pm$ 138.0	561.7 $\pm$ 76.3	557.3 $\pm$ 100.4	557.5 $\pm$ 78.5	575.3 $\pm$ 88.4

Data taken from Table 22, pp. 131-138, MRID 46449102. * $p \leq 0.05$.

- c. **Auditory startle reflex**: Data for startle amplitude and latency are given in Tables 10 and 11, respectively. Data for both endpoints were provided for each of 5 blocks; however, overall mean values were not calculated.

No treatment-related effects were seen in auditory startle response in PND 23 males or females or in PND 61 males. In PND 61 females, decreases in maximum auditory startle response were seen in all treated groups for repetitions 11-50, compared to controls. The magnitude of the decreases were similar across all doses (*i.e.*, the dose-response was flat), and the decreases reached statistical significance at the low and high doses ($p \leq 0.01$). However, while the behavior of the treated PND 61 females is different from the controls, it is not possible to determine whether this difference is due to treatment or if it is because the PND 61 control females failed to exhibit the expected habituation. Failure for these animals to properly habituate indicates an inadequate assessment of auditory startle in the PND 61 females tested in this study. Habituation was evident in PND 61 males.

TABLE 10: Auditory startle peak amplitude (Vmax)					
Day	Repetition	0 ppm	25 ppm	60 ppm	150 ppm
Males (n = 10-14)					
PND 23	1-10	333.3 $\pm$ 95.1	335.1 $\pm$ 98.5	357.4 $\pm$ 129.5	280.5 $\pm$ 93.9
	11-20	237.9 $\pm$ 55.6	221.8 $\pm$ 71.0	259.6 $\pm$ 111.2	219.7 $\pm$ 73.7
	21-30	216.6 $\pm$ 43.5	205.8 $\pm$ 63.1	248.2 $\pm$ 71.8	186.7 $\pm$ 57.1
	31-40	208.7 $\pm$ 52.9	201.1 $\pm$ 64.9	215.5 $\pm$ 78.1	176.1 $\pm$ 52.3

	41-50	191.2 ± 67.5	184.6 ± 57.2	230.4 ± 69.9	176.8 ± 41.5
PND 61	1-10	1338.6 ± 569.5	1214.8 ± 440.3	1146.0 ± 732.8	1261.0 ± 318.2
	11-20	959.1 ± 363.1	1015.6 ± 256.6	907.6 ± 646.8	993.5 ± 455.7
	21-30	832.7 ± 370.0	797.4 ± 368.6	846.0 ± 495.4	738.2 ± 248.5
	31-40	854.3 ± 444.9	778.9 ± 303.6	610.1 ± 383.6	636.1 ± 254.5
	41-50	751.0 ± 284.4	671.6 ± 247.5	613.3 ± 503.1	620.9 ± 232.6
Females (n = 10-14)					
PND 23	1-10	343.2 ± 113.6	292.6 ± 75.8	266.0 ± 74.7	298.8 ± 93.3
	11-20	234.2 ± 106.8	255.6 ± 52.4	232.8 ± 56.0	208.0 ± 60.3
	21-30	245.8 ± 99.9	216.1 ± 54.2	186.5 ± 72.9	201.2 ± 56.2
	31-40	216.8 ± 92.0	214.8 ± 50.8	195.3 ± 45.4	186.3 ± 63.8
	41-50	211.4 ± 89.0	203.5 ± 61.1	195.8 ± 55.2	200.4 ± 53.9
PND 61	1-10	860.9 ± 224.1	837.1 ± 360.9 (97)	819.5 ± 215.4 (95)	800.2 ± 212.1 (93)
	11-20	858.2 ± 247.3	730.8 ± 398.0 (85)	715.7 ± 271.9 (83)	654.7 ± 175.3 (76)
	21-30	894.4 ± 292.6	559.4** ± 392.2 (63)	661.1 ± 215.7 (74)	598.8* ± 175.8 (67)
	31-40	810.9 ± 345.7	443.2** ± 276.7 (55)	635.0 ± 297.0 (78)	469.0** ± 146.2 (58)
	41-50	619.8 ± 242.1	428.2* ± 185.1 (69)	564.9 ± 249.7 (91)	435.8 ± 151.9 (70)

Data taken from Table 23, pp. 139-142, MRID 46449102.

Significantly different from control: *p ≤ 0.05; **p ≤ 0.01.

TABLE 11: Auditory startle time to maximum amplitude (ms)					
Day	Repetition	0 ppm	25 ppm	60 ppm	150 ppm
Males (n = 10-14)					
PND 23	1-10	24.5 ± 5.5	26.8 ± 4.6	27.0 ± 4.7	24.9 ± 4.4
	11-20	21.5 ± 3.4	21.0 ± 2.4	21.9 ± 3.2	22.1 ± 3.7
	21-30	20.7 ± 2.0	20.9 ± 2.7	19.6 ± 1.0	20.5 ± 2.3
	31-40	21.3 ± 3.7	20.5 ± 1.6	19.7 ± 1.9	20.7 ± 2.6
	41-50	20.0 ± 1.3	20.0 ± 1.6	19.2 ± 1.2	20.1 ± 1.1
PND 61	1-10	26.7 ± 5.3	26.0 ± 5.2	26.7 ± 6.9	26.9 ± 4.4
	11-20	22.9 ± 2.5	23.3 ± 3.6	25.3 ± 5.8	26.6 ± 4.8
	21-30	24.3 ± 3.5	26.0 ± 3.0	25.6 ± 6.6	24.8 ± 3.9
	31-40	24.4 ± 3.3	26.0 ± 4.2	26.4 ± 5.6	26.1 ± 4.7

	41-50	24.7 ± 5.5	26.9 ± 3.6	27.2 ± 7.2	25.4 ± 2.6
Females (n = 10-11)					
PND 23	1-10	25.7 ± 5.1	25.3 ± 2.6	25.4 ± 4.5	27.8 ± 6.8
	11-20	21.4 ± 3.0	21.4 ± 4.5	21.0 ± 1.8	25.5 ± 8.3
	21-30	19.9 ± 2.4	20.2 ± 1.5	20.9 ± 2.0	22.3* ± 4.2
	31-40	20.8 ± 2.6	21.0 ± 2.3	20.7 ± 2.2	21.9 ± 3.9
	41-50	21.7 ± 3.7	20.3 ± 2.1	21.4 ± 2.3	22.0 ± 3.6
PND 61	1-10	24.1 ± 2.8	24.6 ± 7.0	25.1 ± 5.0	24.7 ± 4.4
	11-20	22.5 ± 3.7	26.5 ± 8.7	23.2 ± 4.9	24.7 ± 3.2
	21-30	22.3 ± 3.1	27.4* ± 9.1	23.3 ± 3.5	23.8 ± 4.1
	31-40	23.2 ± 2.2	26.3 ± 7.3	22.9 ± 4.3	24.5 ± 5.5
	41-50	24.4 ± 2.5	26.6 ± 7.5	26.1 ± 6.2	23.9 ± 3.3

Data taken from Table 24, pp. 143-146, MRID 46449102.

Significantly different from control: *p ≤ 0.05.

d. Learning and memory testing:

Water maze: Data are summarized in Tables 12, 13, and 14.

As shown in Table 14, learning was demonstrated at both time points (PNDs 21 and 59) in all groups by a decrease in the time required to complete the water maze between trials 1 and 6. Memory was demonstrated by the difference in time taken to complete trial 1 between the learning and memory phases. Straight channel swimming speeds were similar between treated and control animals.

High-dose females showed differences in performance on PNDs 21 and 24. Learning was affected on day 21, in that mean time to completion was longer (Table 12), and the proportion of successful trials was lower than controls for cut-off times ranging from 3-10 seconds (Table 13). When the cut-off was expressed in relation to the time taken to complete the straight channel, the group mean success rate at 1.5 the straight channel swim time on PND 21 was decreased (Table 14), although this was not statistically significant. When memory was tested on PND 24, these high-dose females showed only a slight increase in the mean time per trial, compared to controls, but the proportion of successful trials for cut-off times from 3-9 seconds were still decreased.

Similar effects were not seen in PND 59/62 females or in males at either time point.

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TABLE 12: Water maze mean time to completion per trial (sec)								
Trial	0 ppm	25 ppm	60 ppm	150 ppm	0 ppm	25 ppm	60 ppm	150 ppm
Males					Females			
PND 21 - Learning phase								
Straight channel	4.39± 1.39	5.67*± 3.30	4.49±1.60	4.77±1.59	5.28± 3.39	6.13± 3.09	4.96± 2.91	6.92± 6.11
Trial 1	10.96± 7.71	11.53 ± 7.26	15.01 ± 7.99	15.73* ± 7.62	12.78 ± 5.04	11.27 ± 6.38	15.31 ± 9.25	15.07 ± 6.47
Trial 2	8.90 ± 3.83	10.58 ± 7.96	9.57 ± 6.08	9.56 ± 6.67	6.77 ± 4.11	12.23* ± 10.12	9.28 ± 7.02	12.63* ± 7.88
Trial 3	7.94 ± 5.17	8.66 ± 8.21	8.74 ±5.36	8.91±5.13	6.25 ± 2.96	7.87 ± 5.22	8.42 ± 6.05	10.17* ± 6.65
Trial 4	9.58 ± 6.59	8.35±6.46	8.02±3.17	10.63 ± 7.88	7.09 ± 5.41	6.11 ± 3.01	7.49 ± 4.69	8.77 ± 6.33
Trial 5	6.92 ± 4.21	8.60±6.37	10.21± 7.24	6.83 ± 3.67	7.42 ± 5.00	7.29 ± 5.43	8.37 ± 7.59	11.83* ± 7.97
Trial 6	7.59 ± 4.96	7.69 ± 4.14	7.22 ± 3.00	6.80 ± 3.39	6.11 ± 3.91	7.32 ± 3.42	6.83 ± 5.09	8.13 ± 4.61
PND 24 - Memory phase								
Straight channel	3.44± 1.42	3.81± 1.15	3.56±1.12	4.03±1.49	3.69± 1.26	3.47± 0.77	4.00± 1.27	3.76±0.85
Trial 1	6.42 ± 4.05	8.59 ± 6.51	7.70±3.94	6.72 ± 3.52	7.79 ± 5.22	8.34 ± 4.53	7.53 ± 4.57	10.09 ± 5.77
Trial 2	5.31 ± 4.30	6.62 ± 4.66	4.78 ± 2.60	4.77 ± 2.37	5.21 ± 2.83	5.58 ± 4.48	4.44 ± 4.05	6.24 ± 2.63
Trial 3	3.92 ± 1.27	4.97 ± 3.31	5.58 ± 4.03	4.15 ± 2.06	4.46 ± 2.67	5.00 ±3.08	3.69 ± 1.68	4.83 ± 3.02
Trial 4	4.01 ± 1.87	5.07 ± 4.46	4.75 ± 2.69	4.79 ± 2.88	3.94 ± 1.52	5.94* ± 3.51	4.65 ± 2.31	5.14 ± 2.59
Trial 5	4.01 ± 1.83	5.06 ± 3.25	5.10 ± 3.23	5.58 ± 3.69	4.23 ± 3.60	4.86 ± 2.68	4.31 ± 2.62	6.86* ± 5.76
Trial 6	5.69 ± 4.31	4.82 ± 3.14	6.13 ± 4.65	5.18 ± 2.92	4.31± 2.40	5.99 ± 3.60	4.20 ± 2.24	5.33 ± 3.03
PND 59 - Learning phase								
Straight channel	3.26± 1.26	3.62± 1.68	3.47±1.30	2.80±0.58	3.18± 1.55	2.83± 1.09	3.15± 1.69	2.77±0.64
Trial 1	15.53 ± 5.80	13.78 ± 5.38	11.89* ± 4.52	12.40 ± 4.99	13.80 ± 5.70	14.98 ± 7.49	14.62 ± 6.28	14.92 ± 6.32
Trial 2	7.45 ± 5.65	8.39 ± 7.59	5.72 ± 2.13	6.29 ± 2.38	7.73 ± 5.36	5.99 ± 3.68	8.05 ± 5.46	5.99 ± 2.11
Trial 3	5.33 ± 3.62	5.62 ± 2.69	6.04 ± 3.08	6.08 ± 5.30	5.35 ± 2.70	6.29 ± 4.38	5.25 ± 2.27	5.31 ± 4.17
Trial 4	5.62 ± 4.55	3.85 ± 1.71	5.69 ± 4.16	4.94 ± 3.84	4.54 ± 2.36	4.51 ± 2.70	4.12 ± 1.71	4.14 ± 1.39
Trial 5	4.02 ± 2.09	5.60 ± 3.53	4.76 ± 3.12	3.74 ± 1.26	5.12 ± 3.13	5.37 ± 3.53	4.32 ± 2.37	4.41 ± 2.60
Trial 6	3.76 ± 1.07	3.67 ± 2.30	4.07 ± 2.06	4.62 ± 4.83	4.84 ± 3.35	3.77 ± 1.69	4.51 ± 4.35	4.86 ± 4.83
PND 62 - Memory phase								
Straight channel	2.78± 0.56	2.94± 0.68	3.07±0.98	2.76±0.80	2.87± 0.94	2.70± 0.96	2.59± 0.58	2.79±0.93
Trial 1	5.00 ± 2.00	6.79 ± 5.41	5.93 ± 3.12	7.43 ± 5.91	5.91 ± 3.90	4.24 ± 2.64	4.92 ± 2.49	4.22 ± 1.63
Trial 2	4.72 ± 2.76	4.47 ± 2.15	3.61 ± 1.34	3.60 ± 1.46	4.09 ± 2.72	4.19 ± 3.13	4.39 ± 3.67	4.17 ± 3.80
Trial 3	5.72 ± 4.00	4.45 ± 2.44	5.99 ± 4.96	4.89 ± 2.72	6.05 ± 4.80	4.16 ± 2.47	4.93 ± 2.94	5.44 ± 4.03
Trial 4	7.37 ± 3.71	5.19* ± 2.57	6.22 ± 3.38	6.72 ± 4.01	6.07 ± 4.61	7.31±5.12	5.86 ± 5.22	9.92* ± 7.55
Trial 5	6.36 ± 4.47	6.98 ± 4.60	5.97 ± 4.39	5.83 ±3.88	7.35 ± 5.99	7.17±5.19	7.10 ± 3.85	7.82 ± 6.25
Trial 6	5.40 ± 2.69	5.26 ± 3.00	6.82 ± 6.11	4.91 ±2.76	7.09 ± 5.79	7.57 ± 5.16	6.15 ± 5.41	8.26± 6.76

Data taken from Table 25, pp. 147-154, MRID 46449102.

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OPPT 870.6300/ OECD 426Significantly different from control: * $p \leq 0.05$; ** $p \leq 0.01$.

TABLE 13: Water maze percentage of successful trials ^a								
Cut-off	0 ppm	25 ppm	60 ppm	150 ppm	0 ppm	25 ppm	60 ppm	150 ppm
	Males				Females			
PND 21 - Learning phase								
3 sec	3.8 ± 8.8	2.8 ± 6.3	2.1 ± 7.5	0.0 ± 0.0	4.8 ± 7.7	3.5 ± 6.9	5.1 ± 12.7	1.6 ± 5.0
4 sec	17.4 ± 18.2	24.3 ± 19.6	11.9 ± 18.8	10.3 ± 17.1	29.4 ± 25.2	24.4 ± 19.6	23.2 ± 27.4	15.4* ± 16.2
5 sec	31.1 ± 18.0	34.0 ± 21.1	23.9 ± 22.1	24.6 ± 24.5	43.7 ± 23.8	34.3 ± 21.7	35.5 ± 28.1	22.5* ± 21.5
6 sec	42.4 ± 21.7	41.7 ± 23.6	30.3 ± 22.5	36.5 ± 27.2	50.0 ± 24.2	44.3 ± 22.6	43.5 ± 30.5	29.8* ± 22.9
7 sec	50.8 ± 18.9	50.0 ± 23.6	41.5 ± 25.8	43.7 ± 25.5	57.9 ± 23.3	55.4 ± 17.3	49.3 ± 29.1	37.8* ± 21.4
8 sec	57.6 ± 20.4	55.6 ± 23.9	49.2 ± 25.1	54.0 ± 22.3	61.1 ± 23.8	61.0 ± 15.9	57.2 ± 25.0	44.9* ± 20.9
9 sec	65.2 ± 19.2	65.3 ± 25.0	58.3 ± 25.5	61.9 ± 19.1	68.3 ± 19.7	66.5 ± 16.2	63.0 ± 21.3	48.9** ± 19.1
10 sec	70.5 ± 17.8	70.1 ± 22.5	66.7 ± 24.6	67.5 ± 19.3	73.0 ± 15.3	70.7 ± 16.4	69.6 ± 17.9	51.3** ± 18.7
PND 24 - Memory phase								
3 sec	21.2 ± 20.7	22.9 ± 25.9	20.8 ± 26.1	16.7 ± 22.4	28.9 ± 26.5	13.9* ± 16.1	24.6 ± 20.6	13.5* ± 18.0
4 sec	60.6 ± 27.0	47.2 ± 27.7	47.2 ± 24.9	45.2* ± 25.4	57.0 ± 27.5	43.8 ± 23.0	58.7 ± 15.0	36.5** ± 27.2
5 sec	69.7 ± 25.0	63.2 ± 24.6	59.0 ± 23.0	64.3 ± 19.9	69.7 ± 23.8	59.0 ± 20.8	73.9 ± 18.0	51.6** ± 23.5
6 sec	80.3 ± 19.7	70.8 ± 27.0	68.8 ± 19.2	74.6 ± 22.1	75.4 ± 22.7	68.1 ± 20.8	81.2 ± 16.1	64.3* ± 18.5
7 sec	85.6 ± 15.7	75.0 ± 23.1	73.6* ± 17.7	81.7 ± 22.9	82.5 ± 20.7	72.9* ± 16.9	85.5 ± 13.6	68.3** ± 18.9
8 sec	88.6 ± 14.0	77.8* ± 22.3	79.9 ± 14.7	87.3 ± 19.7	88.1 ± 16.8	77.1** ± 14.6	87.0 ± 13.3	74.6** ± 16.3
9 sec	90.9 ± 11.2	80.6* ± 20.1	85.4 ± 12.3	88.1 ± 19.8	90.5 ± 13.5	79.9** ± 14.7	91.3 ± 11.1	77.8** ± 12.2
10 sec	92.4 ± 9.9	86.8 ± 19.0	87.5 ± 13.2	89.7 ± 19.3	90.5 ± 13.5	82.6* ± 15.1	93.5 ± 8.3	84.9 ± 14.8
PND 59 - Learning phase								
3 sec	26.1 ± 26.2	25.8 ± 24.5	18.8 ± 20.9	20.2 ± 23.9	20.5 ± 22.4	28.0 ± 28.4	26.1 ± 24.0	18.3 ± 18.7
4 sec	45.8 ± 26.2	46.2 ± 29.5	37.0 ± 26.1	46.3 ± 25.6	40.9 ± 25.6	46.2 ± 30.8	41.3 ± 27.0	43.3 ± 24.4
5 sec	54.8 ± 23.4	54.5 ± 25.3	48.6 ± 23.0	62.1 ± 21.2	47.7 ± 22.6	52.3 ± 29.2	50.7 ± 25.4	56.7 ± 22.6
6 sec	62.4 ± 18.9	60.6 ± 20.3	58.0 ± 20.0	69.1 ± 19.3	55.3 ± 20.2	59.8 ± 24.5	63.8 ± 17.9	65.0 ± 16.1
7 sec	70.3 ± 15.3	66.7 ± 17.1	65.2 ± 19.4	75.3 ± 11.5	62.1 ± 17.2	66.7 ± 19.2	66.7 ± 18.1	70.0 ± 17.6
8 sec	70.3 ± 15.3	72.7 ± 13.2	73.2 ± 15.7	78.8 ± 10.8	68.9 ± 14.8	71.2 ± 20.0	72.5 ± 16.4	76.7 ± 17.4
9 sec	74.1 ± 16.8	75.8 ± 14.3	79.0 ± 16.1	82.3 ± 10.4	76.5 ± 14.2	75.0 ± 19.1	77.5 ± 15.6	82.5 ± 12.7
10 sec	74.8 ± 15.1	79.5 ± 13.5	82.6* ± 14.6	83.2 ± 11.1	79.5 ± 15.4	77.3 ± 15.9	81.2 ± 13.6	83.3 ± 10.8
Day 62 - Memory phase								
3 sec	22.7 ± 27.0	17.4 ± 22.1	21.7 ± 28.6	28.9 ± 31.3	32.6 ± 29.3	32.6 ± 26.5	34.8 ± 25.1	26.7 ± 21.2
4 sec	39.4 ± 28.0	47.0 ± 28.5	42.8 ± 32.9	46.5 ± 24.6	53.8 ± 27.2	53.0 ± 22.2	50.7 ± 28.6	44.2 ± 20.4

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TABLE 13: Water maze percentage of successful trials ^a								
Cut-off	0 ppm	25 ppm	60 ppm	150 ppm	0 ppm	25 ppm	60 ppm	150 ppm
5 sec	50.8 ± 28.9	62.9 ± 26.2	60.1 ± 24.5	57.0 ± 28.0	60.6 ± 22.7	58.3 ± 21.7	58.7 ± 26.5	57.5 ± 18.3
6 sec	65.2 ± 30.0	72.7 ± 18.9	71.7 ± 24.3	68.4 ± 26.6	63.6 ± 22.8	67.4 ± 17.4	63.0 ± 25.6	62.5 ± 20.9
7 sec	70.5 ± 26.7	79.5 ± 15.4	77.5 ± 18.5	76.3 ± 23.1	70.5 ± 19.9	74.2 ± 19.1	75.4 ± 24.0	68.3 ± 20.9
8 sec	76.5 ± 21.0	81.4 ± 15.4	81.2 ± 16.9	79.8 ± 21.9	75.0 ± 15.2	76.5 ± 18.3	81.2 ± 17.6	74.2 ± 20.6
9 sec	86.4 ± 16.0	85.6 ± 12.9	85.5 ± 16.1	85.1 ± 19.2	77.3 ± 16.7	80.3 ± 19.7	86.2 ± 17.2	77.5 ± 21.8
10 sec	90.9 ± 12.3	88.6 ± 11.9	86.2 ± 15.6	88.6 ± 17.6	79.5 ± 17.0	83.3 ± 19.2	89.9 * ± 14.0	80.0 ± 21.4

Data taken from Table 26, pp. 155-170, MRID 46449102.

^aA successful trial is one completed in less than the cut-off time.

Significantly different from control: *p ≤ 0.05; **p ≤ 0.01.

TABLE 14. Mean percentage of successful trials at 1.5× straight channel swim time				
Interval (phase)	0 ppm	25 ppm	60 ppm	150 ppm
Males (n=19-24)				
PND 21 (learning)	43.9 ± 25.0	51.4 ± 33.3	39.3 ± 25.2	44.4 ± 29.5
PND 24 (memory)	68.9 ± 22.6	66.0 ± 29.3	62.5 ± 24.7	68.3 ± 25.2
PND 59 (learning)	51.1 ± 24.2	57.6 ± 26.1	53.6 ± 28.0	49.8 ± 28.1
PND 62 (memory)	40.9 ± 26.1	50.8 ± 31.5	54.3 ± 34.2	44.7 ± 26.1
Females (n=20-24)				
PND 21 (learning)	60.3 ± 27.1	59.6 ± 25.8	50.7 ± 26.3	45.7 ± 28.6
PND 24 (memory)	72.1 ± 29.0	59.7* ± 20.8	73.9 ± 18.0	60.3 ± 21.4
PND 59 (learning)	44.7 ± 23.2	45.5 ± 32.6	44.9 ± 28.6	45.8 ± 25.3
PND 62 (memory)	55.3 ± 26.9	53.0 ± 19.0	50.0 ± 28.0	46.7 ± 24.5

Data taken from Table 26, pp. 155-170, MRID 46449102.

A successful trial is one completed in less than the cut-off time.

Significantly different from control: *p ≤ 0.05; **p ≤ 0.01.

5. Postmortem results:

- a. **Brain weights:** Mean brain weight data are given in Table 15. Absolute brain weights of male and female offspring were similar between the treated and control groups on PND 12 and at study termination. Note that statistical analyses on absolute brain weight data (unadjusted for body weight) were not conducted.

TABLE 15. Mean (g ± SD) absolute brain weight data for offspring				
Parameter	0 ppm	25 ppm	60 ppm	150 ppm
Males				
PND 12 (n=10)	1.15 ± 0.07	1.13 ± 0.08	1.16 ± 0.07	1.12 ± 0.15 (97)
PND 63 (n=20)	2.00 ± 0.05	2.02 ± 0.07	2.03 ± 0.07	2.01 ± 0.10
Females				
PND 12 (n=9-10)	1.12 ± 0.04	1.14 ± 0.05	1.14 ± 0.06	1.10 ± 0.08 (98)
PND 63 (n=20)	1.84 ± 0.07	1.86 ± 0.05	1.86 ± 0.06	1.81 ± 0.08 (98)

Data taken from Table 29, pp. 175-176, MRID 46449102.

Values in parentheses are percentages of controls; calculated by reviewer.

b. Neuropathology:

- 1. Macroscopic examination:** No treatment-related gross lesions were reported for male or female offspring at postnatal day 12 or at study termination.
- 2. Microscopic examination:** Selected microscopic findings are presented in Table 16; data are not available at the mid or low doses. On PND 12, 1/9 of the high dose males had a brain cyst, compared to 0/10 control males that were examined. None of the treated or control females examined on PND 12 had this effect. On PND 63, increased incidences of demyelination in the distal tibial (0/10 control, 3/10 high-dose) and proximal sciatic (3/10 control, 8/10 high-dose) nerves were observed in 150 ppm males. In PND 63 females, the incidences of demyelination in these nerves were comparable between controls and treated animals. Historical control data are available for proximal sciatic and distal tibial nerves in males from 9 studies with start dates of March 2002 – April 2003. In these studies, the incidences of minimal demyelination of distal tibial nerve ranged from 10-40% (mean = 24%), and the incidences of minimal and slight demyelination of proximal sciatic nerve ranged from 30-73% (mean = 54%) and 0-20% (mean = 6%), respectively. Thus, these are common spontaneous observations that fall within historical control ranges and are not considered treatment-related.

TABLE 16: Selected histopathological findings in PND 63 offspring					
Measurement	0 ppm	150 ppm	Historical data (n=9 studies)	0 ppm	150 ppm
	Males (n = 10)			Females (n = 10)	
Demyelination of distal tibial nerve minimal	0	3	24% (1/10 – 4/10)	2	1
Demyelination of proximal sciatic nerve minimal	3	7	54% (3/10 – 8/11)	3	4

slight	0	1	6% (0/11 - 2/10)	2	0
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Data taken from Table 28, pp. 173-174, MRID 46449102.

3. **Brain morphometry:** Brain measurement data for PNDs 12 and 63 are given in Tables 17 and 18, respectively. In PND 12 males, statistically significant decreases were seen in the molecular layer of the preculminate fissure of the cerebellum (13%), the overall width of the hippocampus (7%), and the level 3 dorsal cortex 1 (7%). In PND 12 females, statistically significant decreases were observed in the level 5 dorsal cortex (6%), the level 4 dorsal cortex (7%), the thalamus width (4%), and the thalamus/cortex width (4%). At PND 63, a statistically significant decrease (7%) was observed in the level 3 piriform cortex of high-dose males. No statistically significant differences were seen in PND 63 females.

Data for these measurements at the mid and low doses should be provided to confirm whether or not the effects are limited to the high dose.

TABLE 17: Offspring brain morphometry on PND 12				
Measurement	0 ppm	150 ppm	0 ppm	150 ppm
	Males (n = 7-10)		Females (n = 9-10)	
Cerebellum				
Height (mm)	3.84 ± 0.20	3.76 ± 0.37	3.92 ± 0.18	3.82 ± 0.26
Length (mm)	4.18 ± 0.23	3.99 ± 0.43	4.27 ± 0.18	4.24 ± 0.34
Preculminate Fissure				
Outer granular layer (µm)	40.6 ± 6.9	36.2 ± 7.7	37.8 ± 4.4	38.2 ± 3.5
Inner granular layer (µm)	147 ± 16	140 ± 24	146 ± 19	128 ± 24
Molecular layer (µm)	78.4 ± 7.6	68.0* ± 11.1 (87)	73.9 ± 4.4	74.6 ± 13.3
Prepyramidal Fissure				
Outer granular layer (µm)	43.5 ± 7.0	46.3 ± 5.3	42.5 ± 6.1	45.6 ± 3.8
Inner granular layer (µm)	132 ± 23	127 ± 17 (96)	139 ± 15	126 ± 14 (91)
Molecular layer (µm)	60.5 ± 7.3	54.9 ± 8.3 (91)	63.0 ± 8.6	58.2 ± 9.8 (92)
Level 5				
Dorsal cortex (mm)	1.14 ± 0.08	1.07 ± 0.08 (94)	1.13 ± 0.09	1.06* ± 0.03 (94)
Piriform cortex (mm)	1.07 ± 0.05	1.05 ± 0.12	1.10 ± 0.08	1.05 ± 0.09
Thalamus width (mm)	6.98 ± 0.43	6.86 ± 0.43	7.04 ± 0.26	7.03 ± 0.22
Hippocampus - width dentate gyrus (mm)	0.75 ± 0.08	0.68 ± 0.07	0.70 ± 0.04	0.70 ± 0.05
Hippocampus width overall (mm)	1.39 ± 0.09	1.29* ± 0.09 (93)	1.34 ± 0.08	1.34 ± 0.06
Level 4				
Dorsal cortex (mm)	1.17 ± 0.07	1.15 ± 0.10	1.19 ± 0.06	1.11** ± 0.04 (93)
Piriform cortex (mm)	0.94 ± 0.05	0.90 ± 0.10	0.95 ± 0.06	0.91 ± 0.11
Corpus callosum (mm)	0.69 ± 0.12	0.60 ± 0.10	0.64 ± 0.09	0.64 ± 0.06
Thalamus height (mm)	5.35 ± 0.24	5.32 ± 0.42	5.23 ± 0.20	5.08 ± 0.29

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Thalamus width (mm)	8.14 ± 0.31	7.88 ± 0.59	8.02 ± 0.20	7.71* ± 0.31 (96)
Thalamus/cortex width (mm)	13.11 ± 0.50	12.52 ± 0.98	12.91 ± 0.38	12.41* ± 0.42 (96)
Hippocampus - length from midline (mm)	4.22 ± 0.20	4.19 ± 0.29	4.21 ± 0.18	4.06 ± 0.18
Hippocampus - width dentate gyrus (mm)	0.51 ± 0.04	0.47 ± 0.06	0.50 ± 0.03	0.49 ± 0.05
Hippocampus - length dentate gyrus (mm)	1.48 ± 0.11	1.37 ± 0.18	1.43 ± 0.14	1.39 ± 0.14
Level 3				
Dorsal cortex 1 (mm)	1.30 ± 0.08	1.21* ± 0.10 (93)	1.26 ± 0.08	1.26 ± 0.02
Dorsal cortex 2 (mm)	1.44 ± 0.08	1.38 ± 0.11	1.45 ± 0.10	1.42 ± 0.10
Piriform cortex (mm)	1.00 ± 0.07	0.97 ± 0.09	1.00 ± 0.07	0.97 ± 0.05
Hippocampus - length from midline (mm)	3.03 ± 0.15	3.09 ± 0.35	3.06 ± 0.19	3.04 ± 0.32
Level 2				
Frontal cortex height (mm)	5.95 ± 0.47	5.86 ± 0.65	5.99 ± 0.37	5.89 ± 0.54
Frontal cortex width (mm)	4.65 ± 0.32	4.65 ± 0.37	4.76 ± 0.27	4.74 ± 0.31

Data taken from Table 30, pp. 178-193, MRID 46449102.

Significantly different from control: *p ≤ 0.05; **p ≤ 0.01.

TABLE 18. Offspring brain morphometry on PND 63				
Measurement	0 ppm	150 ppm	0 ppm	150 ppm
	Males (n = 9-10)		Females (n = 9-10)	
Cerebellum				
Height (mm)	5.55 ± 0.31	5.42 ± 0.35	5.22 ± 0.27	5.31 ± 0.16
Length (mm)	7.12 ± 0.45	6.83 ± 0.17	6.56 ± 0.54	6.71 ± 0.25
Preculminate Fissure				
Inner granular layer (µm)	178 ± 26	166 ± 32	177 ± 22	177 ± 24
Molecular layer (µm)	217.2 ± 17.5	211.8 ± 16.8	211.5 ± 16.1	208.9 ± 12.5
Prepyramidal Fissure				
Inner granular layer (µm)	153 ± 23	158 ± 26	151 ± 22	162 ± 36
Molecular layer (µm)	210.7 ± 13.7	200.9 ± 8.8	198.9 ± 16.4	206.2 ± 12.5
Level 5				
Dorsal cortex (mm)	1.19 ± 0.10	1.24 ± 0.12	1.19 ± 0.11	1.24 ± 0.05
Piriform cortex (mm)	1.14 ± 0.10	1.12 ± 0.09	1.17 ± 0.10	1.16 ± 0.08
Thalamus width (mm)	7.83 ± 0.36	7.72 ± 0.19	7.70 ± 0.40	7.62 ± 0.39
Hippocampus - width dentate gyrus (mm)	0.68 ± 0.05	0.68 ± 0.05	0.66 ± 0.04	0.67 ± 0.08
Hippocampus width overall (mm)	1.42 ± 0.09	1.45 ± 0.04	1.45 ± 0.04	1.43 ± 0.07
Level 4				
Dorsal cortex (mm)	1.16 ± 0.05	1.24 ± 0.16	1.16 ± 0.09	1.23 ± 0.14

Piriform cortex (mm)	1.20 ± 0.11	1.19 ± 0.09	1.20 ± 0.08	1.20 ± 0.15
Corpus callosum (mm)	0.43 ± 0.08	0.41 ± 0.07	0.37 ± 0.06	0.35 ± 0.09
Thalamus height (mm)	5.32 ± 0.34	5.42 ± 0.37	5.36 ± 0.35	5.27 ± 0.43
Thalamus width (mm)	8.84 ± 0.35	8.71 ± 0.47	8.49 ± 0.30	8.41 ± 0.49
Thalamus/cortex width (mm)	14.22 ± 0.53	14.45 ± 0.51	14.00 ± 0.51	14.06 ± 0.67
Hippocampus - length from midline (mm)	3.43 ± 0.32	3.43 ± 0.30	3.44 ± 0.27	3.46 ± 0.32
Hippocampus - width dentate gyrus (mm)	0.57 ± 0.06	0.61 ± 0.08	0.58 ± 0.06	0.60 ± 0.06
Hippocampus - length dentate gyrus (mm)	1.45 ± 0.19	1.46 ± 0.25	1.51 ± 0.22	1.58 ± 0.23
Level 3				
Dorsal cortex 1 (mm)	1.26 ± 0.09	1.26 ± 0.12	1.22 ± 0.10	1.27 ± 0.06
Dorsal cortex 2 (mm)	1.48 ± 0.09	1.53 ± 0.21	1.47 ± 0.06	1.49 ± 0.10
Piriform cortex (mm)	1.30 ± 0.11	1.21* ± 0.06 (93)	1.25 ± 0.13	1.20 ± 0.17
Hippocampus - length from midline (mm)	2.45 ± 0.32	2.44 ± 0.27	2.49 ± 0.24	2.33 ± 0.16
Level 2				
Frontal cortex height (mm)	6.93 ± 0.45	6.90 ± 0.47	6.89 ± 0.40	6.76 ± 0.40
Frontal cortex width (mm)	5.18 ± 0.22	5.13 ± 0.22	5.07 ± 0.26	5.06 ± 0.23

Data taken from Table 30, pp. 186-193, MRID 46449102.

Significantly different from control: *p ≤ 0.05.

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS: The investigators concluded that the no effect levels are 150 ppm in the diet for developmental neurotoxicity and 25 ppm for toxicity based on maternal effects. Maternal toxicity was evident at 60 and 150 ppm as reduced body weight and food consumption during gestation. Body weight and food consumption were also reduced post partum in the 150 ppm group. There were no effects in dams receiving 25 ppm. Offspring in the 150 ppm group had reduced survival to day 5 and decreased body weight from day 5 until the end of the study. Slower swimming speed on day 21 was noted in female offspring in the 150 ppm group; however, the effect was not considered an effect on learning or memory.

B. REVIEWER COMMENTS:

In the dams, no treatment-related effects were observed on mortality, reproductive performance, or gross pathology. Treatment-related maternal toxicity included decreased (p ≤ 0.05 or 0.01) body weights, body weight gains, and food consumption during gestation and lactation at the high dose (150 ppm). At this dose, absolute maternal body weights were consistently decreased by 8-9%, compared to controls, throughout the treatment period and persisting through LD 15. Although statistically significant decreases in maternal body

weights (2-5%) were also seen at the mid-dose, these slight decreases were not considered adverse.

The maternal LOAEL is 150 ppm (10.0 mg/kg/day during gestation), based on decreased body weight, body weight gain, and food consumption. The maternal NOAEL is 60 ppm (4.3 mg/kg/day during gestation).

In offspring, no treatment-related effects were observed on clinical signs, developmental landmarks, the functional observational battery, brain weights, macroscopic neuropathology, or microscopic neuropathology.

A significant decrease (6%; $p \leq 0.01$) in the number of pups surviving from PNDs 1-5 (pre-cull), compared to controls, was observed at 150 ppm. Survival was unaffected by treatment with 25 or 60 ppm.

Pup body weights and body weight gains were consistently decreased ($p \leq 0.01$) in both sexes at 150 ppm from PNDs 5-29, with a maximum decrease in body weight of 12%, compared to controls. Although statistically significant decreases in pup body weights (2-5%) were also seen at the mid-dose, these slight decreases were not considered adverse.

The motor activity data were considered inadequate for assessment. Of the control animals, habituation was only observed in PND 22 females. Although habituation might not be expected in PND 14 animals (*e.g.*, the pups' eyes may still be closed, and their brains may not yet be developed enough so that habituation is possible), failure for all but one of the other control groups to properly habituate indicates a lack of an adequate assessment of this parameter in this study.

No treatment-related effects were seen in auditory startle response in PND 23 males or females or in PND 61 males. In PND 61 females, decreases in maximum auditory startle response were seen in all treated groups for repetitions 11-50, compared to controls. The magnitude of the decreases were similar across all doses (*i.e.*, the dose-response was flat), and the decreases reached statistical significance at the low and high doses ($p \leq 0.01$). However, while the behavior of the treated PND 61 females is different from the controls, it is not possible to determine whether this difference is due to treatment or if it is because the PND 61 control females failed to exhibit the expected habituation. Failure for these animals to properly habituate indicates an inadequate assessment of auditory startle in the PND 61 females tested in this study. Habituation was evident in PND 61 males.

High-dose females showed differences in water maze performance on PNDs 21 and 24. Learning was affected on PND 21, in that mean time to completion was longer, and the proportion of successful trials was lower than controls for cut-off times ranging from 3-10 seconds. When the cut-off was expressed in relation to the time taken to complete the straight channel, the group mean success rate at 1.5 the straight channel swim time on PND 21 was decreased, although this change was not statistically significant. When memory was tested on PND 24, high-dose females showed only a slight increase in the mean time per trial,

compared to controls, but the proportion of successful trials for cut-off times from 3-9 seconds were still decreased.

At the high dose, statistically significant decreases were seen in the molecular layer of the preculminate fissure (13%), the overall width of the hippocampus (7%), and the level 3 dorsal cortex 1 (7%) of PND 12 males. In PND 12 females, statistically significant decreases were observed at 150 ppm in the level 5 dorsal cortex (6%), the level 4 dorsal cortex (7%), the thalamus width (4%), and the thalamus/cortex width (4%). At PND 63, a statistically significant decrease (7%) was observed in the level 3 piriform cortex of high-dose males. Data for these measurements at the mid and low doses should be provided to confirm whether or not the effects are limited to the high dose.

The offspring NOAEL/LOAEL cannot be determined due to the lack of brain morphometrics at the low and mid doses, as well as inadequate assessments of auditory startle response in PND 61 females and of motor activity.

Note that pup survival was affected at 4, 6, and 8 mg/kg/day, when dams were exposed via gavage (vehicle = corn oil) in a preliminary study (Appendix E). Dams in the 6 mg/kg/day dose group were administered a single initial dose of 12 mg/kg/day, and dams in the 8 mg/kg/day group were administered a single initial dose of 15 mg/kg/day.

C. STUDY DEFICIENCIES:

- The motor activity data were considered inadequate for assessment.
- Although the auditory startle response in the treated PND 61 females is different from the controls, it is not possible to determine whether this difference is due to treatment because the PND 61 control females failed to exhibit the expected habituation.
- Brain morphometric data at the mid and low dose should be submitted for those measurements in which statistically significant changes were seen at the high dose.
- The scoring method and blinding for the FOB should be provided.
- The equipment used for the motor activity and auditory assessments should be provided.
- The statistical analyses for unadjusted data should be submitted.

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APPENDIX A : DOSE SELECTION RATIONALE
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STUDY TYPE: Developmental Neurotoxicity Study - Rat; OPPTS 870.6300 (§83-6); OECD 426 (draft)

PC CODE: 128897

DP BARCODE: D312637

TEST MATERIAL (PURITY): Technical Grade Lambda-cyhalothrin (87.7%)

SYNONYMS: None provided

CITATION: Williams, J. (2001) Lambda-Cyhalothrin: Second preliminary developmental neurotoxicity study in rats. Syngenta Limited, Fernhurst, Haslemere, Surrey, UK. Laboratory study number RR0812; May 4, 2001. MRID 46449101. Unpublished

SPONSOR: Syngenta Crop Protection, Inc., 410 Swing Road, PO Box 18300, Greensboro, NC 27419

EXECUTIVE SUMMARY: In a developmental neurotoxicity range-finding study (MRID 46449101), Lambda-Cyhalothrin (87.7% a.i., batch #P31 (BX E624) R119321) was administered to 10 female Alpk:AP₁SD (Wistar-derived) rats/group in the diet at doses of 0, 25, 60 or 150 ppm from gestation day 7 through lactation day 22. During gestation, mean doses received were 2.0, 4.7, and 10.7 mg/kg/day at dietary levels of 25, 60, and 150 ppm, respectively. During lactation, mean doses received were 4.0, 9.4, and 27.7 mg/kg/day at dietary levels of 25, 60, and 150 ppm, respectively. Maternal animals were assessed for clinical signs of toxicity, body weight changes, and food consumption. All maternal animals were killed on lactation day 22 without examination. Terminal blood samples were collected from dams for analysis of lambda-cyhalothrin in the blood. Litter data consisted of survival, sex, weight, and clinical condition of each pup. Terminal blood samples were collected from pups on lactation days 1, 5, 11, and 22 for analysis of lambda-cyhalothrin in the blood. Pups were killed at lactation days 1, 5, 11, or 22 without examination.

There were no treatment-related maternal clinical signs. Group mean body weight of dams in the 150 ppm group was decreased ($p \leq 0.05$ or 0.01) approximately 6% from the start of treatment throughout gestation. High-dose dams lost 6% of their body weight between gestation days 7 and 8. There were no treatment-related effects on body weight during gestation in dams in the 25 or 60 ppm groups. There were no statistically significant maternal body weight effects at any dose during lactation. Food consumption was decreased ($p \leq 0.05$ or 0.01) from the start of treatment throughout gestation in high-dose dams. Food consumption for the 60 ppm group was decreased ($p \leq 0.01$) only on gestation day 7. There were no food consumption effects during lactation.

There were no treatment-related effects on proportion of pups born alive, litter size at birth, or sex ratio.

There were no treatment-related effects on whole litter losses. Incidence of whole litter loss was 1, 0, 0, and 1 for control, low- mid- and high-dose groups, respectively. Pup survival was decreased in all dose groups from days 1-5 post partum (Appendix Table 1A). However, the observation of pups "missing-presumed dead" was also noted in all treatment groups and is reflected in pup survival data. Thus, in the absence of a clear dose-response relationship, the apparent effect on pup survival is of questionable toxicological significance. There was no effect on pup survival after litter standardization on PND 5. There were no treatment-related clinical signs in pups. Group mean body weights were decreased ($p \leq 0.01$) 9.8% in male and 8.8% in female pups in the 150 ppm group on PND 1. There were no effects on pup body weight thereafter, and there were no effects on total litter weight.

Toxicokinetic data are summarized in Appendix Table 2A. For all time points, there was considerable inter-animal variation in plasma levels of lambda-cyhalothrin in parent females and in pups. No considerable differences were noted between male and female pups. Generally, the plasma concentrations of lambda-cyhalothrin increased in both dams and pups with increasing concentrations of test material in the maternal diets.

In maternal animals in the 25 and 60 ppm groups, the concentrations of lambda-cyhalothrin in plasma on either days 15 and 22 of gestation were similar to those on day 8 of gestation. However, in the 150 ppm group, dams had higher plasma concentrations on day 15 than on day 8; by gestation day 22, plasma concentrations were similar to those measured on day 8. For all dose groups, mean plasma concentrations of test material in maternal plasma were lower on lactation day 1 than on gestation day 22. Mean plasma concentrations in dams in all dose groups increased between days 1 and 5 of lactation and remained similar thereafter.

At all dose levels, mean concentration of plasma lambda-cyhalothrin in pups increased between days 1 and 22 of lactation, and concentrations in pup plasma were similar to levels in corresponding maternal plasma.

Doses for the main study were chosen as 0, 25, 60, and 150 ppm in the diet.

TABLE 1A: Pup survival					
		0 ppm	25 ppm	60 ppm	150 ppm
(n=9-10)					
Day 1- Day 5 (pre cull)	Proportion of litters with all pups surviving	9/9	6/10	7/10	7/9
	Proportion of pups surviving	97/97	107/123**	111/118**	108/117**
	Percentage (mean $\pm$ SD)	100.0 $\pm$ 0.0	88.0 $\pm$ 22.5	94.8 $\pm$ 8.7	93.4 $\pm$ 14.8
Day 5	Proportion of litters with all	9/9	10/10	9/10	8/9

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(post cull)- Day 8	pups surviving				
	Proportion of pups surviving	69/69	76/76	78/79	71/72
	Percentage (mean $\pm$ SD)	100.0 $\pm$ 0.0	100.0 $\pm$ 0.0	98.8 $\pm$ 4.0	98.6 $\pm$ 4.2
Day 5 (post cull)- Day 11	Proportion of litters with all pups surviving	9/9	10/10	9/10	8/9
	Proportion of pups surviving	69/69	76/76	78/79	71/72
	Percentage (mean $\pm$ SD)	100.0 $\pm$ 0.0	100.00 $\pm$ 0.0	98.8 $\pm$ 4.0	98.6 $\pm$ 4.2
Day 5 (post cull)- Day 15	Proportion of litters with all pups surviving	9/9	10/10	9/10	8/9
	Proportion of pups surviving	69/69	76/76	78/79	71/72
	Percentage (mean $\pm$ SD)	100.0 $\pm$ 0.0	100.00 $\pm$ 0.0	98.8 $\pm$ 4.0	98.6 $\pm$ 4.2
Day 5 (post cull)- Day 22	Proportion of litters with all pups surviving	9/9	10/10	9/10	8/9
	Proportion of pups surviving	69/69	76/76	78/79	71/72
	Percentage (mean $\pm$ SD)	100.0 $\pm$ 0.0	100.00 $\pm$ 0.0	98.8 $\pm$ 4.0	98.6 $\pm$ 4.2
Missing-presumed dead	Number of pups	0	17	8	25
	Number of Litters	0	4	4	4
	Days: from- to	N/A	5-5	5-8	5-8

Data taken from Tables 13 & 14, pp. 56 & 57, MRID 46449101.

Significantly different from control: **p $\leq$ 0.01.

TABLE 2A. Mean plasma lambda-cyhalothrin concentrations (μ g lambda-cyhalothrin/ml plasma $\pm$ SD)						
	25 ppm		60 ppm		150 ppm	
	Dam	Pup	Dam	Pup	Dam	Pup
GD 8	0.035 $\pm$ 0.002	—	0.070 $\pm$ 0.013	—	0.062 $\pm$ 0.042	—
GD 15	0.051 $\pm$ 0.016	—	0.165 $\pm$ 0.108	—	0.406 $\pm$ 0.118	—
GD 22	0.052 $\pm$ 0.043	—	0.069 $\pm$ 0.041	—	0.155 $\pm$ 0.071	—
LD 1	0.014 $\pm$ 0.006	0.017 $\pm$ 0.009	0.030 $\pm$ 0.023	0.069 $\pm$ 0.076	0.137 $\pm$ 0.119	0.115 $\pm$ 0.061
LD 5	0.054 $\pm$ 0.014	0.070 $\pm$ 0.037	0.115 $\pm$ 0.042	0.095 $\pm$ 0.048	0.261 $\pm$ 0.097	0.241 $\pm$ 0.104
LD 11	0.180 $\pm$ 0.216	0.028 $\pm$ 0.008	0.131 $\pm$ 0.041	0.057 $\pm$ 0.019	0.226 $\pm$ 0.137	0.117 $\pm$ 0.025
LD 22	0.071 $\pm$ 0.035	0.124 $\pm$ 0.036	0.101 $\pm$ 0.024	0.244 $\pm$ 0.082	0.229 $\pm$ 0.090	0.301 $\pm$ 0.234

Data taken from Table 17 p. 62, MRID 46449101.

APPENDIX B:
Comparison of exposure in pregnant
and nonpregnant rats

STUDY TYPE: Comparison of exposure in pregnant and nonpregnant rats

PC CODE: 128897

DP BARCODE: D316318

TEST MATERIAL (PURITY): Technical Grade Lambda-cyhalothrin (87.7%)

SYNONYMS: None provided

CITATION: Hall, M.G. (2001) Lambda-Cyhalothrin: Comparison of systemic exposure in the pregnant and non-pregnant rat. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. CTL Number UR0594; April 30, 2001. MRID 46526802. Unpublished.

SPONSOR: Syngenta Crop Protection, Inc., 410 Swing Road, PO Box 18300, Greensboro, NC 27419

EXECUTIVE SUMMARY: In order to compare systemic exposure to Lambda-cyhalothrin in pregnant and non-pregnant rats, groups of 27 pregnant and 27 non-pregnant female Alpk:AP₁SD rats, were administered a single oral gavage dose of ¹⁴C-Lambda-Cyhalothrin (87.7% a.i. Test substance reference No. Y02537/321) in corn oil at 4 mg/kg on day 7 of gestation (MRID 46526802). An additional group of 27 non-pregnant rats received 4 mg/kg ¹⁴C-Lambda-Cyhalothrin as a diet slurry. Blood was collected by cardiac puncture under terminal anesthesia. Systemic exposure was estimated by determining the concentration of Lambda-Cyhalothrin in plasma (via gas chromatography) and total radioactivity in whole blood and plasma (via direct liquid scintillation counting). The profile of radiolabeled metabolites present in plasma was determined by liquid chromatography.

Data are summarized in Appendix Table 1B. Mean plasma concentrations of lambda-cyhalothrin were similar in pregnant and non-pregnant rats administered test compound in corn oil. Maximum peak concentrations occurred at 8 or 12 hours post-dosing in corn oil and had decreased to non-detectable levels by 24-hours post-dosing. Animals administered lambda-cyhalothrin in diet slurry showed the highest plasma concentration 2 hours post-dosing, but also decreased to nondetectable levels by 24-hours post-dosing. The AUC values were similar for all test groups. Even though the AUC values were reported as 2.64 µg/h/ml for non-pregnant rats and 4.41 µg/h/ml for pregnant rats, the AUC was calculated only over the 0-12 hour period for the non-pregnant rats because there was no measured lambda-cyhalothrin after 12 hours. When

AUCs for both pregnant and non-pregnant rats were calculated for the 0-12 hour period, the AUC for non-pregnant rats was 2.64 $\mu\text{g}/\text{h}/\text{ml}$ and the AUC for pregnant rats was 2.22 $\mu\text{g}/\text{h}/\text{ml}$. Mean concentrations of radioactivity for pregnant and non-pregnant rats administered lambda-cyhalothrin in corn oil were similar. Maximum concentrations were observed between 8 and 12 hours after dosing and had decreased to 0.05 to 0.1 $\mu\text{g}/\text{g}$ in plasma and 0.03 to 0.06 $\mu\text{g}/\text{g}$ in blood by 48-hours post-dosing. Animals given the diet slurry showed higher radioactivity concentrations earlier in both plasma and blood. There was no difference in metabolite profile between the test groups.

The authors concluded that there was no difference in systemic absorption between pregnant and non-pregnant rats.

TABLE 1B.			
Time (hours)	4 mg/kg in corn oil, non-pregnant rats	4 mg/kg in corn oil, pregnant rats	4 mg/kg in diet slurry, non-pregnant rats
Mean concentrations of lambda-cyhalothrin in plasma ($\mu\text{g}/\text{ml} \pm \text{SD}$)			
1	0.04 $\pm$ <0.01	0.05 $\pm$ 0.01	1.16 $\pm$ 0.18
2	0.08 $\pm$ 0.05	0.09 $\pm$ 0.01	0.67 $\pm$ 0.07
4	0.16 $\pm$ 0.14	0.23 $\pm$ 0.06	0.31 $\pm$ 0.08
6	0.22 $\pm$ 0.09	0.11 $\pm$ 0.10	0.25 $\pm$ 0.20
8	0.36 $\pm$ 0.08	0.26 $\pm$ 0.10	0.19 $\pm$ 0.12
12	0.32 $\pm$ 0.17	0.30 $\pm$ 0.17	0.07 $\pm$ 0.03
24	<LOQ	0.06 $\pm$ 0.03	NC
30	<LOQ	NC	<LOQ
48	<LOQ	<LOQ	<LOQ
C_{max} ($\mu\text{g}/\text{ml}$)	0.36	0.30	1.16
T_{max} (hours)	8	12	1
AUC ₍₀₋₄₈₎ ($\mu\text{g}\cdot\text{h}/\text{ml}$)	2.64	4.41	4.00
Mean concentrations of total radioactivity in plasma (μg equivalents/g $\pm \text{SD}$)			
1	0.16 $\pm$ 0.01	0.16 $\pm$ 0.02	3.29 $\pm$ 0.18
2	0.28 $\pm$ 0.07	0.30 $\pm$ 0.01	2.92 $\pm$ 0.41
4	0.47 $\pm$ 0.27	0.62 $\pm$ 0.17	2.90 $\pm$ 0.56
6	0.75 $\pm$ 0.19	0.56 $\pm$ 0.26	2.52 $\pm$ 0.56
8	1.26 $\pm$ 0.31	1.06 $\pm$ 0.04	2.01 $\pm$ 0.41
12	1.05 $\pm$ 0.43	1.08 $\pm$ 0.14	1.16 $\pm$ 0.52
24	0.51 $\pm$ 0.20	0.65 $\pm$ 0.10	0.60 $\pm$ 0.13
30	0.39 $\pm$ 0.12	0.29 $\pm$ 0.15	0.20 $\pm$ 0.05
48	0.11 $\pm$ 0.02	0.05 $\pm$ 0.01	0.08 $\pm$ 0.01

C_{max} (µg/ml)	1.26	1.08	3.29
T_{max} (hours)	8	12	1
AUC₍₀₋₄₈₎ (µg equiv.h/ml)	24.5	24.6	42.3
Mean concentrations of total radioactivity in blood (µg equivalents/g ±SD)			
1	0.10 ± 0.01	0.09 ± 0.01	1.82 ± 0.14
2	0.17 ± 0.05	0.16 ± 0.01	1.60 ± 0.28
4	0.33 ± 0.21	0.36 ± 0.10	1.50 ± 0.30
6	0.37 ± 0.07	0.30 ± 0.14	1.30 ± 0.30
8	0.79 ± 0.14	0.57 ± 0.02	0.97 ± 0.18
12	0.57 ± 0.24	0.61 ± 0.09	0.60 ± 0.22
24	0.29 ± 0.12	0.37 ± 0.06	0.34 ± 0.07
30	0.24 ± 0.08	0.16 ± 0.08	0.12 ± 0.03
48	0.06 ± 0.01	0.03 ± 0.01	0.04 ± 0.01
C_{max} (µg/ml)	0.79	0.61	1.82
T_{max} (hours)	8	12	1
AUC₍₀₋₄₈₎ (µg equiv.h/ml)	14.7	13.8	22.4

Data taken from Tables 2-4, pp. 30-32, MRID 46526802.

<LOQ- Less than the limit of quantitation (0.04µg/ml).

NC- Not calculated.

APPENDIX C:
Systemic exposure following dietary administration

STUDY TYPE: Systemic exposure following dietary administration in female rats

PC CODE: 128897

DP BARCODE: D316318

TEST MATERIAL (PURITY): Technical Grade Lambda-cyhalothrin (87.7%)

SYNONYMS: None provided

CITATION: Duerden, A. (2001) Lambda-Cyhalothrin: Determination of systemic exposure following dietary administration to female rats. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. CTL Number UR0615; May 30, 2001. MRID 46526803. Unpublished.

SPONSOR: Syngenta Crop Protection, Inc., 410 Swing Road, PO Box 18300, Greensboro, NC 27419

EXECUTIVE SUMMARY: In order to determine systemic exposure of Lambda-cyhalothrin in female rats via dietary exposure, 24 female Alpk:AP₁SD rats were administered 50 ppm of ¹⁴C-Lambda-Cyhalothrin (87.7% a.i.; Test substance reference No. Y02537/321) in the diet over a 24-hour period (MRID 46526803). The achieved dose was 3.6 mg/kg body weight. Blood was collected from each of three rats at 0.5, 1, 2, 4, 6, 8, 12, and 24 hours after the start of feeding by cardiac puncture under terminal halothane anesthesia. Systemic exposure was estimated by determining the concentrations of Lambda-Cyhalothrin in plasma (via gas chromatography) and total radioactivity in plasma (via direct liquid scintillation counting).

Data are summarized in Appendix Table 1C. The maximum mean plasma concentration of lambda-cyhalothrin (0.11 µg/ml) occurred 4 hours after the start of feeding and declined to 0.06 µg/ml by 24-hours after the start of feeding. Mean concentrations of radioactivity increased rapidly over the first 8 hours, reaching a maximum of 1.91 µg equivalents/ml at 24-hours after the start of feeding. The AUC value was 37.2 µg equivalents.hr/ml.

The authors concluded that a steady state plasma concentration of lambda-cyhalothrin was rapidly attained; thus, dietary administration is suitable as a dosing method.

TABLE 1C.	
Time (hours)	

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Mean concentrations of lambda-cyhalothrin in plasma ($\mu\text{g/ml} \pm \text{SD}$)	
0.5	NC
1	0.02 ± 0.01
2	0.03 ± 0.02
4	0.11 ± 0.02
6	0.07 ± 0.03
8	0.08 ± 0.03
12	0.09 ± 0.03
24	0.06 ± 0.01
C_{max} ($\mu\text{g/ml}$)	0.11
T_{max} (hours)	4
$AUC_{(0-24)}$ ($\mu\text{g.h/ml}$)	1.78
Mean concentrations of total radioactivity in plasma ($\mu\text{g equivalents/ml} \pm \text{SD}$)	
0.5	0.03 ± 0.03
1	0.17 ± 0.06
2	0.31 ± 0.10
4	1.20 ± 0.12
6	1.34 ± 0.34
8	1.70 ± 0.02
12	1.87 ± 0.16
24	1.91 ± 0.13
C_{max} ($\mu\text{g/ml}$)	1.91
T_{max} (hours)	24
$AUC_{(0-24)}$ ($\mu\text{g equiv.h/ml}$)	37.2

Data taken from Tables 1 & 2, pp. 25-26, MRID 46526803.

NC: Not Calculated

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APPENDIX D:
Comparison of exposure in female rats

STUDY TYPE: Comparison of exposure in female rats

PC CODE: 128897

DP BARCODE: D316318

TEST MATERIAL (PURITY): Technical Grade Lambda-cyhalothrin (87.7%)

SYNONYMS: None provided

CITATION: Holme, P.C. (2001) Lambda-Cyhalothrin: Comparison of systemic exposure in the female rat. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. CTL Number UR0611; June 13, 2001. MRID 46526804. Unpublished.

SPONSOR: Syngenta Crop Protection, Inc., 410 Swing Road, PO Box 18300, Greensboro, NC 27419

EXECUTIVE SUMMARY: This study was designed to compare systemic exposure to Lambda-cyhalothrin and metabolites in female rats following a single oral dose in either corn oil, 1% carboxy methyl cellulose (CMC) (+1% Tween) or a 1% CMC (+1% Tween) diet slurry. Groups of 27 female Alpk:AP₁SD rats, were administered a single oral gavage dose of ¹⁴C-Lambda-Cyhalothrin (87.7% a.i. Test substance reference No. Y02537/321) in corn oil, 1% CMC (+1% Tween), or a 1% CM (+1% Tween) diet slurry at a dose of 4 mg/kg (MRID 46526804). Blood was collected by cardiac puncture under terminal anesthesia. Systemic exposure was estimated by determining the concentrations of Lambda-Cyhalothrin in plasma (via gas chromatography) and total radioactivity in plasma (via direct liquid scintillation counting).

Data are summarized in Appendix Table 1D. Mean plasma concentrations of lambda-cyhalothrin were different for each dosing regimen. Maximum peak concentrations were lower and occurred later after dosing with the corn oil formulation compared to the 1% CMC formulations. Peak concentrations were the greatest and occurred earliest for the 1% CMC diet slurry formulation. The AUC values were similar for all dose groups despite the differences in patterns of exposure.

Mean peak radioactivity was also different for each dosing regimen. Maximum peak radioactivity was lower and occurred later after dosing with the corn oil formulation compared to the 1% CMC formulations. Peak radioactivity was the greatest and occurred earliest for the 1% CMC diet slurry formulation. The AUC values were similar for all dose groups despite the differences in patterns of exposure. However, the AUC values were normalized for the determined achieved radioactivity content in the dose formulations for each group because recovery was 116% of the radioactivity administered.

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TABLE 1D.			
Time (hours)	4 mg/kg in corn oil	4 mg/kg in 1% CMC	4 mg/kg in 1% CMC diet slurry
Mean concentrations of lambda-cyhalothrin in plasma ($\mu\text{g/ml} \pm \text{SD}$)			
1	0.064 $\pm$ 0.032	0.286 $\pm$ 0.073	1.168 $\pm$ 0.090
2	0.102 $\pm$ 0.000	0.732 $\pm$ 0.140	0.745 $\pm$ 0.139
4	0.303 $\pm$ 0.100	0.333 $\pm$ 0.096	0.506 $\pm$ 0.167
6	0.325 $\pm$ 0.146	0.152 $\pm$ 0.067	0.320 $\pm$ 0.068
8	0.353 $\pm$ 0.125	0.133 $\pm$ 0.091	0.262 $\pm$ 0.133
12	0.292 $\pm$ 0.068	0.039 $\pm$ 0.034	0.048 $\pm$ 0.034
24	0.017 $\pm$ 0.005	0.013 $\pm$ 0.000	0.013 $\pm$ 0.001
30	0.026 $\pm$ 0.014	0.013 $\pm$ 0.000	0.013 $\pm$ 0.000
48	0.013 $\pm$ 0.000	0.013 $\pm$ 0.000	0.013 $\pm$ 0.000
C_{max} ($\mu\text{g/ml}$)	0.353	0.732	1.168
T_{max} (hours)	8	2	1
AUC₍₀₋₄₈₎ ($\mu\text{g}\cdot\text{h/ml}$)	5.45	3.46	5.50
Mean concentrations of total radioactivity in plasma ($\mu\text{g equivalents/ml} \pm \text{SD}$)			
1	0.561 $\pm$ 0.039	3.245 $\pm$ 0.675	6.398 $\pm$ 0.871
2	0.785 $\pm$ 0.089	5.657 $\pm$ 0.407	6.315 $\pm$ 0.420
4	1.628 $\pm$ 0.321	4.445 $\pm$ 0.714	6.630 $\pm$ 1.447
6	1.789 $\pm$ 0.478	3.058 $\pm$ 1.354	5.688 $\pm$ 0.640
8	2.109 $\pm$ 0.255	2.159 $\pm$ 0.783	4.618 $\pm$ 1.178
12	2.446 $\pm$ 0.318	1.094 $\pm$ 0.170	2.513 $\pm$ 1.135
24	0.808 $\pm$ 0.659	0.298 $\pm$ 0.074	0.485 $\pm$ 0.176
30	0.697 $\pm$ 0.391	0.390 $\pm$ 0.126	0.238 $\pm$ 0.018
48	0.086 $\pm$ 0.004	0.085 $\pm$ 0.014	0.172 $\pm$ 0.20
C_{max} ($\mu\text{g/ml}$)	2.446	5.657	6.630
T_{max} (hours)	12	2	4
AUC₍₀₋₄₈₎ ($\mu\text{g equiv}\cdot\text{h/ml}$)	43.8 ^a	47.0 ^a	75.6 ^a

Data taken from Tables 2-7, pp. 27-32, MRID 46526804.

^a Value normalized for determined achieved radioactivity content in the dose formulation for the group.

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OPPT 870.6300/ OECD 426**APPENDIX E:
Preliminary Study****STUDY TYPE:** Preliminary Developmental Neurotoxicity Study**PC CODE:** 128897**DP BARCODE:** D316318**TEST MATERIAL (PURITY):** Technical Grade Lambda-cyhalothrin (87.7%)**SYNONYMS:** None provided**CITATION:** Milburn, G.M. (2002) Lambda-Cyhalothrin: Preliminary developmental neurotoxicity study in rats. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK; CTL Number RR0809; December 19, 2002. MRID 46526805. Unpublished.**SPONSOR:** Syngenta Crop Protection, Inc., 410 Swing Road, PO Box 18300, Greensboro, NC 27419

EXECUTIVE SUMMARY: In a developmental neurotoxicity range-finding study (MRID 46526805), Lambda-Cyhalothrin (87.7% a.i., Batch No. P31 (BX E624) R119321)) was administered to 10 female Alpk:AP₁SD rats/group by gavage in corn oil at doses of 0, 4, 6 or 8 mg/kg/day. Five animals in the 4 mg/kg/day group were given a single initial dose of 15 mg/kg/day, and five animals in the 6 mg/kg/day groups were given a single initial dose of 12 mg/kg/day. Rats were dosed from gestation day 7 until dosing was discontinued either for humane reasons, at the time of littering, or at study termination on days 6-7 post-partum. Maternal animals were assessed for clinical signs of toxicity, body weight changes, and food consumption. Maternal animals sacrificed for humane reasons or found dead were subjected to post mortum examination, including examination of the uterus for the presence of implantation sites. Maternal animals killed on post partum day 6 or 7 were not examined. Litter data consisted of survival, sex, weight, and clinical condition of each pup.

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Clinical signs were observed in maternal animals from all treatment groups. Single doses of 12 or 15 mg/kg on gestation day 7 produced ataxia, decreased limb function, piloerection, salivation, urinary staining, and staining around the mouth or nose. Effects were noted in 3/5 animals at 12 mg/kg and 4/5 animals at 15 mg/kg; three animals in the 15 mg/kg group were sacrificed due to severe toxicity and dose levels were reduced. Rats in the 8 mg/kg/day dose exhibited salivation, urinary staining, and staining around the mouth or nose, and one animal in this group was sacrificed after the initial dose because of severe toxicity. At the expected time of parturition, two 8 mg/kg dams were found dead, two other animals were sacrificed due to severe toxicity, and one animal was killed due to parturition difficulties. Dams in the 4 or 6 mg/kg group did not exhibit signs of toxicity until the expected time of parturition. Signs noted at 6 mg/kg included piloerection, salivation, urinary staining, staining around the mouth or nose, and suspected parturition difficulties. Signs noted at 4 mg/kg included piloerection, cold and pale. Two animals in the 6 mg/kg group and one animal in the 4 mg/kg group were sacrificed due to severe clinical signs and/or parturition difficulties. Group mean body weight of dams in the 8 mg/kg group was decreased ($p \leq 0.05$) throughout treatment, and were approximately 13% below control weight at the end of gestation. Weight gain was decreased ($p \leq 0.05$) at 8 mg/kg from the start of dosing through the end of gestation and was approximately 4% below controls at the end of gestation. A 3-6% decrease ($p \leq 0.05$ or $p \leq 0.01$) in body weight and body weight gain was also noted at 6 mg/kg. No body weight effects were noted at 4 mg/kg.

There were no treatment-related effects on proportion of pups born live or on sex ratio. A treatment-related increase in pup mortality was noted in all dose groups and was evidenced by increased total litter loss and loss of many pups in surviving litters. By day 5, there were only 2 litters remaining in the 8 mg/kg group, and 1 litter each remaining in the 6 and 4 mg/kg groups, compared to 9 in the control group (Table 1E). There were no treatment-related clinical signs noted in pups.

It was concluded that daily gavage doses of 4, 6, or 8 mg/kg are too high for use in a subsequent developmental neurotoxicity in the rat.

TABLE 1E. Summary of reproductive performance

	0 mg/kg	4 mg/kg	6 mg/kg	8 mg/kg
Number of Dams	10	7	10	9
Number of litters	10	7	10	5
Viable litters	10	6	9	4
Day 1- % born live	95	75	90	90
Day 1- live/dead	103/6	49/16	100/10	38/4
Day 1- pups/litter	10.9	9.29 g	11.0	8.4
Day 5- live pups	85	9	4 ^a	16
Mean Pup weight (day 1)	5.69 g	5.44	5.39 g	5.52 g
Litters at day 5 (suitable for	9 (7)	1 (1)	1 (0) ^a	2 (1)

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developmental neurotoxicity study)				
Litter losses	1/10	5/6	7/8 ^a	2/4

Data taken from Table 5, p. 32. MRID 46526805.

^aOne litter killed as dam killed for humane reasons; data from this litter excluded.

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13544

R150939

Chemical: lambda-Cyhalothrin

PC Code:
128897

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