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TXR#: 0054227

DATA EVALUATION RECORD

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

PC CODE: 000692 **DP BARCODE:** D335563

TEST MATERIAL (PURITY): AE 0317309 (95.7% w/w a.i.)

SYNONYMS: Pyrasulfotole technical

CITATION: Gilmore RG, Sheets LP, Hoss HE. (2006). A developmental neurotoxicity screening study with technical grade AE0317309 in Wistar rats. Bayer CropScience LP, Stilwell, KS. Laboratory Study No.: 04-D72-YE, February 2, 2006. MRID 46801917. Unpublished.

SPONSOR: Bayer CropScience LP, Research Triangle Park, NC

EXECUTIVE SUMMARY:

In a developmental neurotoxicity study (MRID 46801917), AE 0317309 (95.7% w/w a.i., batch Op. 1-4) was administered from gestation day 6 through postnatal day 21 to 30 female Wistar rats per dose in the diet at nominal concentrations of 0, 45, 450, or 4500 ppm during gestation and 0/0/0, 24/20/16, 237/196/161, or 2368/1957/1607 ppm during weeks 1/2/3 of lactation. These concentrations provided an average daily intake of 0, 3.8, 37, or 354 mg/kg bw/day over gestation and lactation. Offspring were not dosed directly in this study. Dams were observed for clinical signs at least once daily. FOB (functional observational battery) tests were conducted on GDs 13 and 20 and LDs 11 and 21. Body weight and food consumption were measured on GDs 6, 13, and 20 and on LDs 0, 7, 14, and 21. On LD 4 litters were culled to eight pups, with four male and four female pups wherever possible. Dams were sacrificed on LD 21 following weaning of their litters, and a gross necropsy examination was conducted. Offspring were allocated for FOB and assessment of motor activity, auditory startle reflex habituation, learning and memory (passive avoidance and watermaze testing), and neuropathology (including brain weights). Offspring were monitored daily throughout lactation for clinical signs or morbidity and were weighed individually on LDs 0, 4, 11, 17, and 21 and weekly thereafter. The age of sexual maturation (vaginal opening in females and preputial separation in males) was also recorded.

There were no treatment-related effects on mortality, clinical signs during gestation, or body weight in dams. During lactation, ocular opacities were observed in up to 5/21 dams from LD 9 at 37 mk/kg/day and in up to 14/20 females from LD 10 at 354 mg/kg/day. During the FOB, ocular opacities were observed on LD 11 in 3/10 dams at 37 mk/kg/day and in 7/10 dams at 354

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mg/kg/day; and on LD 21 in 2/10 and 7/10 dams at 37 and 354 mg/kg/day, respectively. Food consumption was reduced in dams during weeks 1-2 of lactation at 37 (12-19%) and 354 (9-20%) mg/kg/day, however without a corresponding effect on body weight. The fertility index was decreased (NSS) at 37 mg/kg/day (3%) and 354 mg/kg/day (13.3%); however, this observation was not considered treatment-related, since dosing began on GD 6. All other reproductive parameters were unaffected by treatment.

The maternal LOAEL is 37 mg/kg/day, based on ocular opacities during lactation. The maternal NOAEL is 3.8 mg/kg/day.

There were no treatment-related effects on litter size, viability/mortality, or other litter parameters in offspring. Clinical signs and body weight were unaffected during lactation. During post-weaning, ocular opacities were observed in 6/58 males at 354 mg/kg/day on or after PND 29, as well as in 2/63 females at 37 mg/kg/day and 1/60 females at 354 mg/kg/day on or after PND 30. Body weight was decreased in males and females by 6-9% and 4-8% each at 37 mg/kg/day and by 8-13% and 8-11% each at 354 mg/kg/day. Preputial separation was delayed at 37 mg/kg/day (46.0 days) and 354 mg/kg/day (46.7 days, $P< 0.01$), compared to controls (44.1 days). Vaginal patency was unaffected by treatment. During the FOB, ocular opacity was observed in 1/15 females at both 37 mg/kg/day and 354 mg/kg/day. These changes were first noted on postnatal days 45 and 35, respectively, and persisted in both cases through postnatal day 60.

No treatment-related effects were observed on motor activity or auditory startle response. For PND 22 animals tested for passive avoidance, an increase ($P<0.05$) in the number of trials to criterion, as well as dose-dependent decreases in trials 1 and 2 latencies, were observed at ≥37 mg/kg/day during the learning session. During the retention session, an increase ($P<0.05$) in the number of trials to criterion and reduced latency at trial 1 were observed at 354 mg/kg/day. There were no treatment-related effects on acquisition and retention in either adult males or females during the water maze testing. An increase in the mean time required to complete trial 1 was observed in the retention phase in males at 37 mg/kg/day; however, the result was not considered treatment-related in the absence of dose response and treatment-related effects on the number of trials to reach criterion.

During ophthalmoscopic examinations, retinal degeneration was observed in 4/10 males at 354 mg/kg/day. Retinal degeneration was also observed in 0/13, 1/13, 3/11, and 4/10 females at 0, 3.8, 37, and 354 ($P<0.05$) mg/kg/day, respectively. The increase in one female animal at the low dose was not considered treatment-related based on the low incidence and lack of statistical significance in the current study and since retinal degeneration was not observed at a similar dose in F1 or F2 offspring in the 2-generation reproduction study. Absolute fixed brain weight on PND 21 was statistically significantly decreased for males (8%) at 354 mg/kg/day and for females at 37 mg/kg/day (6%) and 354 mg/kg/day (11%). Absolute fixed brain weight on PND 75 was also decreased for females at 354 mg/kg/day (5%). At necropsy, an increased incidence of opacity was observed in the eyes of 3/10 PND 75 males at 354 mg/kg/day. During macroscopic morphometry at PND 21, cerebellum length was decreased ($P<0.05$) in perfused males (6%) and females (7%) at 354 mg/kg/day. Cerebrum length was also decreased ($P<0.05$) in females at 37 (4%) and 354 (5%) mg/kg/day. At PND 75, cerebellum length was decreased in males (5%, $P<0.05$) and females (4%, NSS) at 354 mg/kg/day. During microscopic morphometry on PND 21, cerebellum height was decreased ($P<0.05$) in males at 37 mg/kg/day

(7%) and 354 mg/kg/day (8%) and in females at 354 mg/kg/day (10%). The hippocampal gyrus was decreased ($P<0.05$) by 11% and 9% in males and females, respectively, at 354 mg/kg/day on PND 21. On PND 75, cerebellum height was changed at the mid and high doses in males (↑14% and ↓6%, respectively) and females (↑13% and ↓6%); however, in the absence of a consistent change across dose, the findings were not considered toxicologically significant.

The offspring LOAEL is 37 mg/kg/day, based on ocular opacity (post-weaning), decreased body weight, delayed preputial separation (males), increase in the number of trials to criterion and decreases in trial latencies (passive avoidance; PND 22 males), retinal degeneration at ophthalmoscopy (females), decreased brain weight (PND 21 females), decreased cerebrum length (PND 21 females), and decreased cerebellum height (PND 21 males). The offspring NOAEL was 3.8 mg/kg/day.

This study is classified **Acceptable/Non-guideline** and may be used for regulatory purposes. It does not, however, satisfy the guideline requirement for a developmental neurotoxicity study in rats [OPPTS 870.6300, §83-6; OECD 426 (draft)] due to the pending review of the positive control data. The following deficiencies were noted in the report: 1) litter data were reported for only 20-23 dams/group. An explanation as to why litter data were not reported for the remaining 6-8 dams/group (after accounting for non-pregnant animals) that underwent "elective sacrifice" is requested; 2) SE (rather than SD) was used as the measure of variability around sample means.

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

This Executive Summary was prepared for United States Environmental Protection Agency, Office of Pesticides Programs, Health Effects Division use.

The following text was generated by the Australian Pesticides and Veterinary Medicines Authority. However, this document has undergone critical scientific analysis and been modified as appropriate.

Report:	**KIIA 5.7.5/01, Gilmore, R. G.; Sheets, L. P.; Hoss, H. E.; 2006**
Title:	A developmental neurotoxicity screening study with technical grade AE0317309 in Wistar rats
Laboratory	Bayer CropScience LP Toxicology, 17745 South Metcalf Ave, Stilwell, KS 66085-9104, USA
Study duration	7 December 2004 – 18 March 2005
Report No.:	201439
Document No.:	M-266434-01-1
Guidelines:	**U.S. EPA, OPPTS 870.6300** **Health Canada PMRA DACO No. 4.5.14**
GLP/QA	**Yes**

Materials and Methods

AE 0317309 (batch Op. 1-4, purity 95.7%) was incorporated into rodent diet by suspending the test substance in acetone and mixing the suspension into the meal-form chow. Diet was prepared at concentrations of 0, 45, 450, and 4500 ppm (during gestation) and administered to groups of 30 sperm-positive female Wistar rats on gestation day 6 through lactation day 21; dietary concentrations were adjusted during lactation to provide for a constant dosage throughout the treatment period. These concentrations provided an average daily intake of 0, 3.8, 37, and 354 mg/kg bw/day. The homogeneity, stability and concentration of the test substance in the feed were confirmed. The rats were at least 12 weeks of age at the beginning of co-housing with untreated males, and weighed 172.2-198.5 g. During gestation and lactation, the rats were housed individually with corn-cob bedding in plastic cages. Food and water were provided *ad libitum* except during neurobehavioral testing. Dams were observed for clinical signs at least once daily. FOB (functional observational battery) tests were conducted during gestation (GD 13, 20) and lactation (LD 11, 21). Body weight and food consumption were measured on a weekly basis, on gestation days 6, 13, and 20, and lactation days 0, 7, 14, and 21. Maternal body weight was also measured on lactation day 4 and litters were culled on this day to eight pups, with four male and four female pups wherever possible. Dams were sacrificed on lactation day 21 following weaning of their litters, and a gross necropsy examination was conducted.

As soon as possible after pup birth, anogenital distance was measured and pups were tattooed. Surviving pups were counted, sexed, and weighed individually on lactation days 0, 4, 11, 17, and 21. Offspring were monitored daily throughout lactation for clinical signs or morbidity. After weaning on day 21, the pups were monitored twice daily for morbidity and mortality, and were weighed on a weekly basis as well as on the day that vaginal patency or balanopreputial separation were achieved. Food consumption was not measured. Pups were examined daily starting from postnatal day 29 (females) or postnatal day 38 (males) for developmental landmarks, and pupil constriction was tested in all pups on postnatal day 21. The following table summarizes examinations that were conducted on offspring from postnatal day 4 onwards. All tests used at least 10 offspring per sex per dose, and with the exception of learning and memory, no animal was tested more than once in the same test. However, different tests of learning and memory were conducted in weanling and adult animals.

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Timing of neurobehavioral examinations in offspring of females administered AE 0317309 by dietary incorporation during gestation and lactation.

Parameter	Postnatal day											
	4	11	13	17	21	22	29	35†	45†	60†	67†	75‡
Detailed clinical observations / FOB	X	X			X			X	X	X		
Motor activity			X	X	X					X		
Auditory startle habituation						X				X		
Learning and memory						X	X			X	X	
Brain weight					X							X
Neuropathology					X							X

† Date given is ± 2 days.; ‡ Date given is ± 5 days.

Ten to thirteen male and 10-13 female offspring per dose group were selected for ophthalmoscopic examination at approximately 50-60 days of age. On postnatal day 21, 10 male and 10 female offspring were sacrificed and the brains were collected whole for micropathological examination and morphometric analysis and weighed. The animals were anesthetized and perfused via the left ventricle with sodium nitrite in phosphate buffer followed by in situ fixation with universal fixative in phosphate buffer. On postnatal day 75, a further 10 male and 10 female offspring were sacrificed and perfused, and brain, spinal cord, both eyes with optic nerves, bilateral sciatic, tibial, and sural nerves, gasserian ganglion, gastrocnemius muscle, and both forelimbs were collected and fixed. Brains were weighed. On both occasions, prior to sectioning, the anterior-posterior length of the cerebrum and of the cerebellum were measured with Vernier calipers. Other measurements, made after histologic sectioning, were the thickness of the frontal cortex, parietal cortex, and hippocampal gyrus, horizontal width of the caudate putamen, and height of the cerebellum. The offspring not selected for neuropathological examination were sacrificed without examination.

Findings for parental animals

Relevant tables from the study report are attached as an appendix at the end of this review.

Mortalities: There were no mortalities in parental females during either gestation or lactation.

Clinical signs: There were no treatment-related clinical signs observed during gestation. During lactation, ocular opacities were observed in up to 5/21 females from LD 9 at 450 ppm and in up to 14/20 females from LD 10 at 4500 ppm. No staining of the fur was observed (other than red nasal staining in one animal in the high dose group during gestation).

FOB: Ocular opacities, evaluated as related to treatment, were observed during the FOB in 3/10 females at 450 ppm and 7/10 females at 4500 ppm on LD 11 and in 2/10 (450 ppm) and 7/10 (4500 ppm) females on LD 21. This increase at 4500 ppm was statistically significant compared to controls. Red nasal stain was also observed in one high-dose dam on GD 13.

Body weight and body weight gain: Body weight and body weight gain were not

affected during gestation or lactation at any dose.

Food consumption: Food consumption was statistically significantly increased at 4500 ppm during gestation, although this was considered by the study authors to be due to wastage from palatability issues. Installation of grates to reduce wastage in week 3 of gestational treatment markedly reduced food consumption at 4500 ppm, relative to the preceding 2 weeks. During lactation, food consumption was statistically significantly reduced, relative to controls, at both 450 ppm and 4500 ppm during lactation days 0-7 and 7-14.

Mean food consumption (g/animal/day) during gestation and lactation

Days	Dose in ppm[1]			
	0	45	450	4500
Gestation days 6-13	19.7	19.5	21.4	47.6**
Gestation days 13-20	19.6	19.8	19.9	23.0**
Lactation days 0-7	41.7	36.3	33.6*	33.5*
Lactation days 7-14	56.0	54.9	49.5**	50.8*
Lactation days 14-21	66.7	64.3	61.4	55.9

[1] Gestational concentrations in ppm ("doses") are utilized in all tables throughout this review, even though concentrations were increased during lactation to achieve somewhat equivalent doses throughout both gestation and lactation

* $p < 0.05$.** $p < 0.01$.

Reproductive performance: The fertility index was decreased (without reaching statistical significance) at 450 ppm (by 3.3%) and at 4500 ppm (by 13.3%); however, this was not related to dietary administration of AE 0317309, since dosing of dams began on GD 6. Some aspects of the data in the report are unclear (for example, the significance of the parameter "No. of Dams with One Implantation Site"), but it does not appear that there were any other noteworthy observations on reproductive parameters.

Selected reproductive parameters in female rats

Parameter	AE 0317309, dietary concentration in ppm[1]			
	0	45	450	4500
Number of females co-housed	30	30	30	30
Number of females mated	30	30	30	30
Dams not pregnant	0	0	1	4
Mating index	100	100	100	100
Fertility index	100	100	96.7	86.7
Gestation length, days	22.0	22.0	22.1	22.1

[1] Gestational concentrations only

Findings for offspring

Viability: There were no effects of treatment on litter size, viability, or other litter parameters.

Clinical signs: There were no treatment-related signs during lactation. In the post-weaning phase, treatment-related findings were restricted to ocular opacities in 6/58 males on or after PND 29 and 1/60 females at 4500 ppm, and 2/63 females at 450

ppm.

Mortalities and moribundity: There was no effect of dietary administration of AE 0317309 on the incidence of moribund or found-dead pups.

Body weight: Body weight at birth was similar at all doses. However postnatal pup weights and body weight gains were frequently decreased to a statistically significant extent, particularly in males, at and above 450 ppm.

Body weight (g) of male and female pups

Postnatal Day	Dose in ppm[1]							
	Males				Females			
	0	45	450	4500	0	45	450	4500
0	6.0	6.1	6.1	5.9	5.7	5.8	5.7	5.6
4 (before culling)	10.0	10.0	9.6	9.2	9.6	9.6	9.1	8.9
4 (after culling	10.0	10.1	9.6	9.1* (9)	9.6	9.6	9.1	8.9
11	25.2	25.6	23.5* (7)	22.5* (11)	24.6	24.8	22.7* (8)	22.1** (10)
17	38.2	39.4	35.9* (6)	35.2** (8)	37.4	37.8	34.8* (7)	34.5* (8)
21	48.5	48.8	45.3* (7)	43.3** (11)	47.0	47.2	43.5** (7)	42.1** (10)
28	76.8	75.4	70.1* (9)	67.0* (13)	75.1	74.3	69.3* (8)	66.9* (11)
35	123.8	121.2	113.8* (8)	109.5* (12)	111.7	110.6	104.1* (7)	102.9* (8)
42	170.4	165.7	159.9* (6)	155.6* (9)	134.2	134.7	128.7* (4)	129.5
49	213.1	206.4	199.8* (6)	196.8* (8)	150.5	151.0	145.1	147.5
56	255.8	247.8	240.3* (6)	237.2* (7)	163.9	164.8	159.6	163.5
63	288.0	279.0	271.7* (6)	268.3* (7)	176.9	176.8	171.2	175.8
70	317.6	308.2	299.6* (6)	295.9* (7)	186.6	186.8	181.9	188.4

[1] Maternal gestational concentrations only

* $p < 0.05$.** $p < 0.01$.

Developmental landmarks: Preputial separation was statistically significantly delayed at 4500 ppm (46.7 days, $p \leq 0.01$) and statistically non-significantly delayed at 450 ppm (46.0 days), compared to controls (44.1 days). This increase in time to preputial separation was considered by the study authors to be related to treatment as a secondary effect of reduced body weight. Preputial separation was also delayed in F1 pups at similar doses in the rat 2-generation reproduction toxicity study (Study report KIIA 5.6.1). There was no effect on time to vaginal patency. Pupillary constriction on day 21 in both males and females was not affected by treatment.

FOB: The only treatment-related changes observed at FOB assessment were ocular opacities in 1/15 females at 450 ppm and 1/15 females at 4500 ppm. These changes were first noted on postnatal days 45 and 35, respectively, and persisted in both cases

through postnatal day 60.

Motor and locomotor activity: There were no treatment-related effects observed on motor or locomotor activity in either males or females at any dose level during either lactation or post-weaning phases. Loco/motor activity habituation was observed in control and all treated groups, except in females on PND 60. The expected developmental pattern for motor activity was not observed for control or treated animals.

Auditory startle habituation: There were no treatment-related effects on auditory startle at any time during the study or at any dose level. Peak amplitude at 4500 ppm was decreased by 26% in PND 22 females and by 40% in PND 60 females, however without attaining statistical significance. Peak amplitude at 450 and 4500 ppm was decreased by 36% and 31% in PND 60 males, however without dose response or attaining statistical significance.

Passive avoidance: As the following table (Study Report 5.7.5/01-5) indicates, there is a tendency for reduced performance among males on PND 22 at the mid and high dose in these tests, which sometimes reached statistical significance. This included more "trials to criterion" and reduced latency at trials 1 and 2 during the learning session; and more "trials to criterion" and reduced latency at trial 1 (high dose only) during the retention session.

Passive avoidance performance, as measured on postnatal day 22, in male and female offspring

Session	Parameter	AE 0317309, dietary conc. in ppm[1]			
		0	45	450	4500
Males					
1 (Learning)	Number of animals tested	16	16	16	16
	Number of animals included in analysis	16	16	16	16
	Trials to criterion	2.9±0.3	3.0±0.0	3.5±0.9*	3.4±0.6*
	Latency, trial 1 (sec)	49.0	39.6	31.2	27.5
	Latency, trial 2 (sec)	180±0.0	180±0.0	162.5±42.2	151.0±56.9*
	Failed to meet criterion	0	0	0	0
	Failed to cross during learning phase	2	0	0	0
2 (Retention)	Number of animals tested	14	16	16	16
	Number of animals included in analysis	14	16	16	16
	Trials to criterion	2.2±0.6	2.0±0.0	2.4±0.8	2.8±0.7*
	Latency, trial 1 (sec)	169.4±39.6	180.0±0.0	175.4±18.5	137.7±53.4*
	Latency, trial 2 (sec)	177.0±11.3	180.0±0.0	174.2±18.9	169.7±28.5
Females					
1 (Learning)	Number of animals tested	16	16	16	16
	Number of animals included in analysis	16	16	16	16
	Trials to criterion	3.2	3.5	3.3	3.1
	Latency, trial 1 (sec)	24.8	20.8	45.0	41.8
	Latency, trial 2 (sec)	179.2	171.8	177.8	180.0
	Failed to meet criterion	0	0	0	0
	Failed to cross during learning phase	0	0	1	1

2 (Retention)	Number of animals tested	16	16	15	15
	Number of animals included in analysis	16	16	14	15
	Trials to criterion	2.4	2.7	2.6	2.9
	Latency, trial 1 (sec)	153.2	162.3	139.5	125.1
	Latency, trial 2 (sec)	177.9	166.9	170.2	169.4

[1] Maternal gestational concentrations only
* $p < 0.05$.** $p < 0.01$.

Water maze: There were no treatment-related effects on acquisition and retention in either males or females during the water maze testing. Increases in the mean times required to complete trial 1 were observed in the learning ($P<0.05$) and retention (NSS) phases in males at 450 ppm; however, the results were not considered treatment-related in the absence of dose response and treatment-related effects on the number of trials to reach criterion.

Ophthalmoscopic findings: Retinal degeneration was statistically significantly increased at 4500 ppm, with four males and four females affected at this dose. There was also a dose-response relationship in females, with 0/13, 1/13, 3/11 and 4/10 animals showing retinal degeneration at 0, 45, 450 and 4500 ppm, respectively. The four cases in the 4500 ppm dose group and the three cases in the 450 ppm dose group are considered to be treatment-related, whereas the single instance in the female 45 ppm dose group (NSS) may simply be a sporadic effect of the kind observed in the controls in Study Report no. KIIA 5.7.4/01 (subchronic neurotoxicity study). In addition, retinal degeneration was not observed at a similar dose in F1 or F2 offspring in the 2-generation reproduction study.

Ocular findings in offspring

Observation	Dose (ppm[1])			
	0	**45**	**450**	**4500**
Males				
N	13	13	11	10
Corneal opacity	2	2	3	2
Retinal degeneration	0	1	0	4*
Females				
N	13	13	11	10
Corneal opacity	2	0	0	1
Retinal degeneration	0	1	3	4*

[1] Maternal gestational concentrations only
* $p < 0.05$.

Necropsy: An increased incidence of opacity was observed in the eyes of 3/10 PND 75 males (perfused) at 4500 ppm.

Brain weight: Absolute fixed brain weight was statistically significantly decreased for males (8%) and females (11%) at 4500 ppm and females at 450 ppm (6%) on day 21, and for females at 4500 ppm (5%) on day 75. Relative brain weight in these groups was no different from controls, which the study authors suggested indicated that the decreased absolute brain weight was related to the reduced body weight at these doses. However, brain mass is often considered to be conserved under conditions that lead to reduced body weight.

Gross brain measurements: At day 21, cerebellum length was statistically significantly decreased in perfused males (6%) and females (7%) at 4500 ppm. Cerebrum length was also statistically significantly decreased in females at 450 (4%) and 4500 (5%) ppm. At day 75, cerebellum length was statistically significantly decreased in males at 4500 ppm (5%), and statistically non-significantly decreased (4%) in females at 4500 ppm. There was no effect on cerebrum length in either males or females at day 75. These decreases observed on day 21 and 75 were considered to be related to treatment.

Micropathology brain measurements: On day 21, males at 450 (7%) and 4500 (8%) ppm and females at 4500 ppm (10%) showed a statistically significant decrease in cerebellum height. There were indications of a dose-related decrease for this measurement in both sexes at this time, but this was not the case at postnatal day 75. Cerebellar height on PND 75 was statistically significantly changed at 450 and 4500 ppm in males (↑14% and ↓6%, respectively) and females (↑13% and ↓6%). The hippocampal gyrus was significantly decreased ($P<0.05$) by 11% and 9% in males and females, respectively, at 4500 ppm on PND 21. In general, concurrent control data were either at the extreme end of the historical range or exceeded the historical range.

Brain measurements, from offspring sacrificed on postnatal day 21 or postnatal day 75.

	Dose in ppm[1]							
	Males				Females			
Parameter	**0**	**45**	**450**	**4500**	**0**	**45**	**450**	**4500**
Postnatal day 21								
Ant/post cerebrum length, mm	13.52	13.67	13.31	13.24	13.63	13.38	13.07*	13.00*
Ant/post cerebellum length, mm	7.20	7.03	7.12	6.80*	7.13	7.06	6.83	6.65*
Frontal cortex, mm	1.728	---[a]	1.769	1.805	1.823	---	1.763	1.749
Parietal cortex, mm	2.008	1.918	1.901*	1.922	1.999	1.939	1.846*	1.850*
Caudate putamen, mm	2.982	---	3.097	3.052	3.029	---	2.974	2.915
Hippocampal gyrus, mm	1.723	---	1.673	1.541*	1.737	---	1.696	1.575*
Cerebellum height, mm	4.367	4.165	4.057*	4.005*	4.292	4.164	4.086	3.869*
Postnatal day 75								
Ant/post cerebrum length, mm	14.56	14.69	14.45	14.64	14.12	14.11	14.24	13.92
Ant/post cerebellum length, mm	7.56	7.69	7.41	7.21*	7.57	7.52	7.47	7.25
Frontal cortex, mm	1.760	---	1.656*	1.713	1.76	---	1.66*	1.79
Parietal cortex, mm	1.863	---	1.808	1.880	1.855	---	1.827	1.833
Caudate putamen, mm	3.345	---	3.302	3.424	3.386	---	3.172*	3.330
Hippocampal gyrus, mm	1.758	---	1.790	1.684	1.631	---	1.731	1.543
Cerebellum height, mm	3.831	---	4.380*	3.618*	3.978	---	4.488*	3.756*

[1] Maternal gestational concentrations only

a measurement not taken

* $p < 0.05$.

Microscopic findings: On histopathological examination of the brains and other nervous tissues, the only treatment-related finding was retinal degeneration in 1/10 males at 4500 ppm.

Conclusions and Critique

The study authors proposed a NOAEL for the dams and offspring of 45 ppm (3.8 mg/kg bw/day). This is basically confirmed in the current assessment, as indicated below.

Based on decreased food consumption during lactation and ocular opacities in dams at 450 and 4500 ppm, the maternal systemic NOAEL (NOEL for Australia) was 45 ppm (3.8 mg/kg bw/day). There were no maternal neurotoxic effects.

Neonatal toxicity included decreased postnatal weights, delayed preputial separation and retinal degeneration in the offspring at 450 and 4500 ppm. The NOAEL (NOEL for Australia) for neonatal systemic toxicity was therefore 45 ppm (3.8 mg/kg bw/day).

There were decreased absolute brain weights, decreased cerebrum length and decreased cerebellum height in male and/or female offspring on postnatal day 21 at 450 and 4500 ppm. There was also diminished performance in males in the passive avoidance test at these doses. Therefore the NOAEL (NOEL for Australia) for neonatal developmental neurotoxic effects was 45 ppm (3.8 mg/kg bw/day). These developmental neurotoxic effects occurred at maternotoxic dose levels.

Appendix

The following tables were extracted from pages 37-60 in the study report (KIIA 5.7.5):

TEXT TABLE 2. Mortality and Maternal Clinical Observations [a]

Observation	Dose (ppm in diet)			
	Control	45 PPM	450 PPM	4500 PPM
Gestation (Days 6-21)				
No. of females examined on Gestation Day 6	30	30	30	30
Nasal stain	0	0	0	1
Hair loss	0	2	0	0
No. of females found dead	0	0	0	0
Lactation (Days 0-21)				
No. of females examined on Lactation Day 0 [b]	30	30	29	26
General Opacity	0	0	5	14
Exophthalmos	0	0	1	0
Hair Loss	0	2	0	2
No. of females found dead	0	0	0	0

[a] Data obtained from pages 72 and 78 in the study report. Observations during gestation (days 6-24). Values are the number of rats with the finding.

[b] The numbers of dams with no pups by Gestation Day 24 were 0, 0, 1, and 4 for the controls, low-, mid-, and high-dose groups, respectively.

TEXT TABLE 3. Maternal Functional Observations [a]

Observation	Dose (ppm in diet)			
	Control	45 PPM	450 PPM	4500 PPM
Gestation Day 13				
Number of Animals Examined:	30	30	30	30
Handling - Stains Not Observed Red Nasal Stain	30(100) 0(0)	30(100) 0(0)	30(100) 0(0)	29(97) 1(3)
Handling-Other Not Observed Alopecia	30(100) 0(0)	29(97) 1(3)	30(100) 0(0)	30(100) 0(0)
Gestation Day 20				
Number of Animals Examined:	30	30	30	30
Handling-Other Not Observed Alopecia	30(100) 0(0)	28(93) 2(7)	30(100) 0(0)	30(100) 0(0)
Lactation Day 11				
Number of Animals Examined:	10	10	10	10
Handling-Other Not Observed Alopecia	10(100) 0(0)	9(90) 1(10)	10(100) 0(0)	9(90) 1(10)
Handling-Other Not Observed Opacity	10(100) 0(0)	10(100) 0(0)	7(70) 3(30)	* 5(50) 5(50)
Lactation Day 21				
Number of Animals Examined:	10	10	10	10
Handling-Other Not Observed Alopecia	10(100) 0(0)	9(90) 1(10)	10(100) 0(0)	9(90) 1(10)
Handling-Other Not Observed Opacity	10(100) 0(0)	10(100) 0(0)	8(80) 2(20)	* 3(30) 7(70)

[a] *Data obtained from pages 109-132 in the study report.*
* *Statistically different ($p \leq 0.05$) from the control.*

TEXT TABLE 4. Mean (±SD) Maternal Body Weight and Food Consumption [a]

Observations/study week	Dose (ppm in diet)			
	Control	45 PPM	450 PPM	4500 PPM
Gestation				
Mean body weight (g) Gestation day 0	204.3±2.04 (30)	206.3±1.65 (30)	201.5±1.63 (29)	205.9±2.15 (26)
Mean body weight (g) Gestation day 6	222.6±2.70 (30)	230.2±1.93 (30)	223.1±1.97 (29)	228.7±2.32 (26)
Mean body weight (g) Gestation day 13	245.1±3.56 (30)	252.5±2.07 (30)	242.2±2.28 (29)	246.1±2.83 (26)
Mean body weight (g) Gestation day 20	306.5±4.20 (30)	316.0±3.40 (30)	299.3±3.14 (29)	305.8±3.88 (26)
Mean weight gain (g) Gestation days 0 - 20	102.3±2.79 (30)	109.7±2.42 (30)	97.8±2.65 (29)	99.9±2.36 (26)
Mean food consumption (g/animal/day) Gestation days 6 - 13	19.3±0.59 (29)	19.1±0.49 (29)	21.4±1.29 (29)	47.6**±5.70 (26)
Mean food consumption (g/animal/day) Gestation days 13 - 20	19.6±0.55 (30)	19.8±0.43 (30)	19.9±0.41 (29)	23.0**±0.90 (26)
Lactation				
Mean body weight (g) Lactation day 0	235.6±3.21 (30)	242.0±2.83 (30)	233.8±2.07 (29)	237.1±3.31 (26)
Mean body weight (g) Lactation day 4	252.7±3.65 (27)	260.5±2.92 (26)	249.0±3.09 (21)	256.4±2.94 (20)
Mean body weight (g) Lactation day 7	260.8±3.46 (23)	270.9±2.51 (23)	258.5±2.70 (21)	264.8±3.77 (20)
Mean body weight (g) Lactation day 14	279.9±3.40 (23)	288.2±3.61 (23)	275.7±3.40 (21)	282.8±3.77 (20)
Mean body weight (g) Lactation day 21	269.0±2.84 (23)	273.6±3.11 (23)	267.7±3.88 (21)	272.1±3.48 (20)
Mean food consumption (g/animal/day) Lactation days 0 - 7	41.7±2.97 (23)	36.3±1.51 (23)	33.6*±1.17 (21)	33.5*±1.06 (20)
Mean food consumption (g/animal/day) Lactation days 7 - 14	56.0±1.66 (23)	54.9±1.06 (23)	49.5**±0.96 (21)	50.8*±1.05 (20)
Mean food consumption (g/animal/day) Lactation days 14 - 21	66.7±3.00 (23)	64.3±2.13 (23)	61.4±1.33 (20)	55.9**±1.07 (20)

[a] *Data obtained from pages 74-76, 80-82 in the study report. Values are mean ± standard error (n). Means for gestation period include only dams known to deliver pups (either alive or dead).*

* *Statistically different from control, $p \leq 0.05$.*

** *Statistically different from control, $p \leq 0.01$.*

TEXT TABLE 5. Mean Maternal Test Substance Intake (mg/kg body weight/day)[1]

Period	Dose (ppm in diet)		
	45 PPM	450 PPM	4500 PPM
Gestation			
Gestation days 6 - 13	3.7±0.09 (29)	42.9±2.38 (29)	890.9±103.7 [2] (26)
Gestation days 13 - 20	3.5±0.06 (30)	36.9±0.64 (29)	402.9±14.32 (26)
Lactation			
Lactation days 0 - 7	3.8±0.17 (23)	34.7±1.22 (21)	343.2±12.69 (20)
Lactation days 7 - 14	4.2±0.08 (23)	36.0±0.54 (21)	360.9±6.16 (20)
Lactation days 14 - 21	3.6±0.13 (23)	34.8±0.66 (20)	309.7±4.19 (20)

[1] *Data obtained from pages 84-85 in the study report. Values are mean ± standard error (n). Dietary concentrations were reduced during weeks 1-3 of lactation (by factors of 1.9, 2.3 and 2.8, respectively), based on estimated increases in feed consumption (g consumed/kg body wt./day) during lactation).*

[2] *Associated with observed food spillage and considered an unreliable measure of a.i. intake. This value was excluded from the mean average daily intake.*

TEXT TABLE 7. Litter Size and Viability [a]

Observation	Dose (ppm in diet)			
	Control	45 PPM	450 PPM	4500 PPM
No. of Litters	23	23	21	20
Total No. of Pups Born	259	271	240	228
Total No. of Pups Missing	2	0	3	3
Litters with Pups Missing	2	0	2	3
Total No. of Pups Found Dead	1	3	1	3
Litters with Pups Found Dead	1	3	1	3
Total No. of Pups Cannibalized	0	0	0	0
Litter with Pups Cannibalized	0	0	0	0
Litter Size	11.3±0.29 [11.0] (9.0-15.0)	11.8±0.38 [12.0] (8.0-14.0)	11.4±0.49 [11.0] (7.0-16.0)	11.4±0.36 [11.0] (9.0-16.0)
Stillborn pups: Number % Mean±S.E. [Median] (Range)	 0 0.0 0.0±0.00 [0.0] (0.0-0.0)	 1 0.4 0.0±0.04 [0.0] (0.0-1.0)	 0 0.0 0.0±0.00 [0.0] (0.0-0.0)	 0 0.0 0.0±0.00 [0.0] (0.0-0.0)
Mean No. of Viable Pups Birth Day 4 (Pre-cull)[b] Day 4 (Post-cull)[c] Day 21	 11 11 8 8	 12 12 8 8	 11 11 8 8	 11 11 8 8
Live birth index	100.0±0.00 [100.0] (100-100)	99.5±0.48 [100.0] (89-100)	100.0±0.00 [100.0] (100-100)	100.0±0.00 [100.0] (100-100)
Viability index	98.8±0.69 [100.0] (88.9-100)	99.2±0.55 [100.0] (90.0-100)	98.7±0.75 [100.0] (87.5-100)	98.2±0.83 [100.0] (88.9-100)
Lactation index	100.0±0.00 [100.0] (100-100)	99.5±0.54 [100.0] (88-100)	100.0±0.00 [100.0] (100-100)	98.8±0.86 [100.0] (88-100)

[a] *Data obtained from pages 87 in the study report.*
[b] *Before standardization (culling). Values are mean ± standard error*
[c] *After standardization (culling).*

TEXT TABLE 10. Mean (±SD) Age of Sexual Maturation (days) [a]

Parameter	Dose (ppm in diet)			
	Control	45 PPM	450 PPM	4500 PPM
N (M/F)	23	23	21	20
Preputial separation % Pups Reaching Criteria	44.1±0.52 (23) 100	43.6±0.31 (23) 99	46.0±0.58 (21) 100	46.7**±0.63 (20) 100
Vaginal opening % Pups Reaching Criteria	32.8±0.83 (23) 100	33.0±0.65 (23) 99	34.7±0.83 (21) 100	33.7±0.30 (20) 100

[a] *Data obtained from pages 104 in the study report.*
** *Statistically different from control, $p \leq 0.01$ Values are mean ± standard error (N)*

TECHNICAL GRADE AE 0317309
Summary Interval Motor Activity for Male Rats, Postnatal Day 13
Study Number 04-D72-YE

Group	Interval 1	Interval 2	Interval 3	Interval 4	Interval 5	Interval 6
0 PPM	11 ± 12	16 ± 23	12 ± 16	7 ± 11	14 ± 25	19 ± 31
45 PPM	26 ± 26	15 ± 18	15 ± 21	16 ± 29	7 ± 10	7 ± 11
450 PPM	21 ± 22	19 ± 16	13 ± 18	3 ± 5	7 ± 9	6 ± 10
4500 PPM	11 ± 14	13 ± 18	16 ± 32	9 ± 16	12 ± 18	12 ± 14

TECHNICAL GRADE AE 0317309
Summary Interval Motor Activity for Male Rats, Postnatal Day 17
Study Number 04-D72-YE

Group	Interval 1	Interval 2	Interval 3	Interval 4	Interval 5	Interval 6
0 PPM	64 ± 26	33 ± 33	20 ± 19	15 ± 22	7 ± 13	6 ± 10
45 PPM	86 ± 45	32 ± 26	18 ± 17	21 ± 27	23 ± 30	20 ± 27
450 PPM	58 ± 38	39 ± 31	20 ± 18	21 ± 33	24 ± 33	16 ± 21
4500 PPM	41 ± 29	28 ± 29	18 ± 18	18 ± 24	24 ± 28	34* ± 37

TECHNICAL GRADE AE 0317309
Summary Interval Motor Activity for Male Rats, Postnatal Day 21
Study Number 04-D72-YE

Group	Interval 1	Interval 2	Interval 3	Interval 4	Interval 5	Interval 6
0 PPM	107 ± 31	58 ± 28	44 ± 25	37 ± 33	29 ± 23	25 ± 26
45 PPM	111 ± 41	45 ± 30	41 ± 22	26 ± 25	19 ± 20	26 ± 33
450 PPM	100 ± 22	48 ± 24	31 ± 19	25 ± 22	20 ± 17	22 ± 23
4500 PPM	93 ± 41	57 ± 29	36 ± 24	41 ± 29	29 ± 27	35 ± 25

TECHNICAL GRADE AE 0317309
Summary Interval Motor Activity for Male Rats, Postnatal Day 60
Study Number 04-D72-YE

Group	Interval 1	Interval 2	Interval 3	Interval 4	Interval 5	Interval 6
0 PPM	110 ± 19	96 ± 28	102 ± 30	81 ± 33	91 ± 40	73 ± 31
45 PPM	107 ± 18	85 ± 30	95 ± 27	90 ± 40	73 ± 38	74 ± 28
450 PPM	116 ± 21	86 ± 37	79 ± 30	87 ± 47	72 ± 36	72 ± 39
4500 PPM	125 ± 29	94 ± 34	97 ± 35	96 ± 31	77 ± 37	82 ± 26

TECHNICAL GRADE AE 0317309
Summary Interval Motor Activity for Female Rats, Postnatal Day 13
Study Number 04-D72-YE

Group	Interval 1	Interval 2	Interval 3	Interval 4	Interval 5	Interval 6
0 PPM	22 ± 21	21 ± 30	12 ± 21	10 ± 16	8 ± 18	15 ± 28
45 PPM	19 ± 15	11 ± 13	8 ± 10	13 ± 20	8 ± 15	1 ± 2
450 PPM	13 ± 21	14 ± 18	18 ± 17	11 ± 15	7 ± 10	11 ± 21
4500 PPM	12 ± 17	7 ± 12	8 ± 11	8 ± 9	11 ± 18	4 ± 8

TECHNICAL GRADE AE 0317309
Summary Interval Motor Activity for Female Rats, Postnatal Day 17
Study Number 04-D72-YE

Group	Interval 1	Interval 2	Interval 3	Interval 4	Interval 5	Interval 6
0 PPM	55 ± 31	23 ± 21	14 ± 17	15 ± 24	5 ± 10	18 ± 34
45 PPM	75 ± 43	39 ± 31	24 ± 22	13 ± 21	11 ± 16	12 ± 18
450 PPM	62 ± 36	47 ± 24	40 ± 26	36 ± 35	24 ± 27	15 ± 18
4500 PPM	59 ± 45	37 ± 31	24 ± 19	20 ± 21	21 ± 26	19 ± 24

TECHNICAL GRADE AE 0317309
Summary Interval Motor Activity for Female Rats, Postnatal Day 21
Study Number 04-D72-YE

Group	Interval 1	Interval 2	Interval 3	Interval 4	Interval 5	Interval 6
0 PPM	116 ± 29	66 ± 35	42 ± 23	39 ± 32	30 ± 30	21 ± 25
45 PPM	114 ± 24	62 ± 25	34 ± 21	33 ± 20	23 ± 22	26 ± 26
450 PPM	99 ± 24	50 ± 24	36 ± 24	34 ± 27	28 ± 30	24 ± 19
4500 PPM	101 ± 30	49 ± 32	30 ± 23	34 ± 25	25 ± 26	24 ± 23

TECHNICAL GRADE AE 0317309
Summary Interval Motor Activity for Female Rats, Postnatal Day 60
Study Number 04-D72-YE

Group	Interval 1	Interval 2	Interval 3	Interval 4	Interval 5	Interval 6
0 PPM	135 ± 43	108 ± 34	112 ± 38	121 ± 48	122 ± 49	119 ± 31
45 PPM	125 ± 27	97 ± 32	102 ± 33	106 ± 36	108 ± 36	96 ± 33
450 PPM	122 ± 26	103 ± 27	107 ± 42	107 ± 36	91 ± 35	87 ± 40
4500 PPM	141 ± 38	121 ± 51	124 ± 50	131 ± 53	126 ± 61	106 ± 36

TECHNICAL GRADE AE 0317309
Summary Interval Locomotor Activity for Male Rats, Postnatal Day 13
Study Number 04-D72-YE

Group	Interval 1	Interval 2	Interval 3	Interval 4	Interval 5	Interval 6
0 PPM	2 ± 2	2 ± 6	1 ± 2	1 ± 1	2 ± 6	3 ± 7
45 PPM	3 ± 4	1 ± 2	2 ± 3	1 ± 3	1 ± 3	1 ± 2
450 PPM	3 ± 4	1 ± 2	0 ± 1	0 ± 1	1 ± 2	1 ± 2
4500 PPM	1 ± 2	0 ± 1	0 ± 0	1 ± 1	0 ± 1	1 ± 2

TECHNICAL GRADE AE 0317309
Summary Interval Locomotor Activity for Male Rats, Postnatal Day 17
Study Number 04-D72-YE

Group	Interval 1	Interval 2	Interval 3	Interval 4	Interval 5	Interval 6
0 PPM	17 ± 12	8 ± 7	6 ± 7	3 ± 5	2 ± 5	1 ± 3
45 PPM	20 ± 15	8 ± 7	5 ± 6	5 ± 8	6 ± 8	5 ± 9
450 PPM	18 ± 14	9 ± 8	4 ± 4	5 ± 5	6 ± 9	3 ± 5
4500 PPM	8 ± 8	6 ± 7	5 ± 5	4 ± 5	6 ± 7	8 ± 9

TECHNICAL GRADE AE 0317309
Summary Interval Locomotor Activity for Male Rats, Postnatal Day 21
Study Number 04-D72-YE

Group	Interval 1	Interval 2	Interval 3	Interval 4	Interval 5	Interval 6
0 PPM	35 ± 9	14 ± 8	12 ± 7	10 ± 10	9 ± 8	8 ± 9
45 PPM	32 ± 15	14 ± 9	11 ± 7	8 ± 8	6 ± 7	8 ± 10
450 PPM	36 ± 10	15 ± 9	10 ± 6	7 ± 7	7 ± 6	7 ± 8
4500 PPM	33 ± 16	17 ± 8	10 ± 8	11 ± 8	8 ± 7	9 ± 7

TECHNICAL GRADE AE 0317309
Summary Interval Locomotor Activity for Male Rats, Postnatal Day 60
Study Number 04-D72-YE

Group	Interval 1	Interval 2	Interval 3	Interval 4	Interval 5	Interval 6
0 PPM	77 ± 12	65 ± 18	74 ± 23	57 ± 27	58 ± 27	49 ± 23
45 PPM	74 ± 14	58 ± 26	67 ± 26	69 ± 32	52 ± 29	49 ± 23
450 PPM	81 ± 19	59 ± 31	55 ± 25	60 ± 39	46 ± 31	48 ± 31
4500 PPM	88 ± 24	68 ± 27	71 ± 33	71 ± 28	53 ± 31	44 ± 23

TECHNICAL GRADE AE 9317309
Summary Interval Locomotor Activity for Female Rats, Postnatal Day 13
Study Number 04-D72-YE

Group	Interval 1	Interval 2	Interval 3	Interval 4	Interval 5	Interval 6
0 PPM	3 ± 4	2 ± 5	2 ± 7	2 ± 5	2 ± 7	1 ± 3
45 PPM	2 ± 2	1 ± 2	0 ± 0	1 ± 1	1 ± 1	0 ± 0
450 PPM	2 ± 2	1 ± 2	1 ± 4	1 ± 2	1 ± 3	3 ± 8
4500 PPM	2 ± 2	0 ± 1	1 ± 1	1 ± 1	0 ± 1	0 ± 1

TECHNICAL GRADE AE 0317309
Summary Interval Locomotor Activity for Female Rats, Postnatal Day 17
Study Number 04-D72-YE

Group	Interval 1	Interval 2	Interval 3	Interval 4	Interval 5	Interval 6
0 PPM	15 ± 12	7 ± 6	4 ± 4	5 ± 9	1 ± 3	5 ± 9
45 PPM	22 ± 15	8 ± 7	6 ± 5	4 ± 6	3 ± 5	4 ± 7
450 PPM	14 ± 11	12 ± 9	9 ± 8	11 ± 11	8* ± 10	5 ± 6
4500 PPM	15 ± 13	8 ± 8	6 ± 6	5 ± 7	7 ± 9	5 ± 7

TECHNICAL GRADE AE 0317309
Summary Interval Locomotor Activity for Female Rats, Postnatal Day 21
Study Number 04-D72-YE

Group	Interval 1	Interval 2	Interval 3	Interval 4	Interval 5	Interval 6
0 PPM	39 ± 10	17 ± 9	12 ± 8	11 ± 10	7 ± 7	6 ± 7
45 PPM	39 ± 9	19 ± 9	8 ± 6	9 ± 6	5 ± 6	6 ± 8
450 PPM	36 ± 12	15 ± 9	10 ± 8	11 ± 10	8 ± 8	8 ± 6
4500 PPM	37 ± 9	13 ± 7	10 ± 8	11 ± 8	7 ± 9	8 ± 8

TECHNICAL GRADE AE 0317309
Summary Interval Locomotor Activity for Female Rats, Postnatal Day 60
Study Number 04-D72-YE

Group	Interval 1	Interval 2	Interval 3	Interval 4	Interval 5	Interval 6
0 PPM	88 ± 23	64 ± 28	73 ± 32	82 ± 40	81 ± 44	76 ± 30
45 PPM	82 ± 15	59 ± 27	65 ± 29	72 ± 37	72 ± 25	63 ± 23
450 PPM	77 ± 19	58 ± 22	62 ± 35	65 ± 33	58 ± 29	56 ± 34
4500 PPM	97 ± 35	82 ± 43	83 ± 38	89 ± 41	90 ± 48	68 ± 30

TEXT TABLE 14. Auditory Startle Reflex Peak Amplitude Data (mean ±S.D.) [a]

Block		Dose (ppm in diet)			
		Control	45 PPM	450 PPM	4500 PPM
Males					
PND 22	Block 1	32 ± 14	32 ± 17	26 ± 11	28 ± 8
	Block 2	31 ± 17	29 ± 17	27 ± 18	22 ± 8
	Block 3	29 ± 13	27 ± 13	26 ± 14	22 ± 7
	Block 4	24 ± 10	26 ± 14	20 ± 11	18 ± 7
	Block 5	25 ± 14	25 ± 13	20 ± 11	19 ± 8
	Avg. For Total Session	**28±11**	**28±14**	**24±12**	**22±7**
	No. Of Animals	16	16	16	16
	Body Weight	51	51	48	44
PND 60	Block 1	229 ± 112	182 ± 98	152 ± 136	187 ± 127
	Block 2	252 ± 147	169 ± 109	140 ± 129	165 ± 138
	Block 3	220 ± 126	156 ± 105	140 ± 115	143 ± 114
	Block 4	168 ± 107	124 ± 83	118 ± 94	111 ± 79
	Block 5	140 ± 64	130 ± 98	100 ± 80	94 ± 56
	Avg. For Total Session	**202±92**	**148±74**	**130±103**	**140±93**
	No. Of Animals	16	16	16	16
	Body Weight	274	274	267	255
Females					
PND 22	Block 1	29 ± 12	27 ± 12	23 ± 9	28 ± 13
	Block 2	30 ± 16	25 ± 14	24 ± 10	22 ± 9
	Block 3	27 ± 14	23 ± 10	24 ± 15	18 ± 8
	Block 4	26 ± 15	24 ± 12	20 ± 10	17 ± 8
	Block 5	23 ± 10	19 ± 10	19 ± 9	17 ± 8
	Avg. For Total Session	**27±11**	**24±11**	**22±9**	**20±7**
	No. Of Animals	16	16	16	16
	Body Weight	49	49	44	44
PND 60	Block 1	110 ± 64	81 ± 51	81 ± 54	74 ± 49
	Block 2	110 ± 74	82 ± 62	89 ± 76	66 ± 36
	Block 3	102 ± 69	73 ± 49	78 ± 72	61 ± 40
	Block 4	88 ± 64	54 ± 28	61 ± 57	50 ± 31
	Block 5	82 ± 72	55 ± 35	49 ± 30	43 ± 24
	Avg. For Total Session	**99±61**	**69±38**	**72±55**	**59±33**
	No. Of Animals	16	16	16	16
	Body Weight	170	171	168	169

[a] *Data obtained from pages 215-216 in the study report.*
Values are mean ± standard deviation

TEXT TABLE 15. Auditory Startle Reflex Latency to Peak Data (miliseconds) [a]

Block		Dose (ppm in diet)			
		Control	45 PPM	450 PPM	4500 PPM
Males					
PND 22	Block 1	38±4	39±6	39±5	39±4
	Block 2	39±6	36±2	38±5	38±6
	Block 3	38±5	36±3	37±3	37±4
	Block 4	39±6	36±2	37±5	39±4
	Block 5	39±6	34±2	35±4	36±7
	Avg. For Total Session	38±4	36±2	37±2	38±4
	No. Of Animals	16	16	16	16
	Body Weight	51	51	48	44
PND 60	Block 1	43±3	42±8	40±6	40±4
	Block 2	40±2	41±5	38±6	39±5
	Block 3	40±3	42±4	38±3	39±5
	Block 4	40±3	41±4	40±3	39±4
	Block 5	39±3	41±5	38±4	37±3
	Avg. For Total Session	41±2	41±4	39±3	39±3
	No. Of Animals	16	16	16	16
	Body Weight	274	274	267	255
Females					
PND 22	Block 1	40±7	38±5	37±3	39±7
	Block 2	39±5	38±6	37±4	38±6
	Block 3	37±6	37±6	37±4	38±4
	Block 4	37±4	36±2	37±4	38±5
	Block 5	36±9	38±6	35±5	36±5
	Avg. For Total Session	38±4	37±3	37±2	38±4
	No. Of Animals	16	16	16	16
	Body Weight	49	49	44	44
PND 60	Block 1	42±3	44±6	42±5	43±6
	Block 2	43±5	41±8	38±7	38±4
	Block 3	43±6	39±6	37±4	36±3
	Block 4	43±6	41±7	39±3	37±5
	Block 5	42±6	42±7	39±4	38±5
	Avg. For Total Session	43±4	41±6	39±4	38±3
	No. Of Animals	16	16	16	16
	Body Weight	170	171	168	169

a Data obtained from pages 218-221 in the study report.
Values are mean ± standard deviation

TEXT TABLE 16. Passive Avoidance Performance at PND 22 Offspring (mean ± S.D.) [a]

Session/Parameter		Dose (ppm in diet)			
		Control	45 PPM	450 PPM	4500 PPM
Males					
Session 1 (Learning Phase)	Number of Animals Tested	16	16	16	16
	Number of Animals Included in Analysis	16	16	16	16
	Trials to criterion	2.9±0.3	3.0±0.0	*3.5±0.9	*3.4±0.6
	Latency trial 1 (sec)	49.0±58.7	39.6±35.8	31.2±22.6	27.5±22.9
	Latency trial 2 (sec)	180.0±0.0	180.0±0.0	162.5±42.2	*151.0±56.9
	Failed to Meet Criterion	0 (0%)	0 (0)%	0 (0)%	0 (0%)
	Failed to Cross During Learning Phase	2 (13%)	0 (0)%	0 (0)%	0 (0%)
Session 2 (Retention Phase)	Number of Animals Tested	14	16	16	16
	Number of Animals Included in Analysis	14	16	16	16
	Trials to criterion	2.2±0.6	2.0±0.0	2.4±0.8	*2.8±0.7
	Latency trial 1 (sec)	169.4±39.6	180.0±0.0	175.4±18.5	*137.7±53.4
	Latency trial 2 (sec)	177.0±11.3	180.0±0.0	174.2±18.9	169.7±28.5
Females					
Session 1 (Learning Phase)	Number of Animals Tested	16	16	16	16
	Number of Animals Included in Analysis	16	16	16	16
	Trials to criterion	3.2±0.5	3.5±0.9	3.3±0.8	3.1±0.6
	Latency trial 1 (sec)	24.8±25.2	20.8±11.9	36.0±42.6	41.8±47.8
	Latency trial 2 (sec)	179.2±3.1	171.8±18.4	179.5±2.1	180.0±0.0
	Failed to Meet Criterion	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Failed to Cross During Learning Phase	0 (0%)	0 (0%)	1 (6%)	1 (6%)
Session 2 (Retention Phase)	Number of Animals Tested	16	16	15	15
	Number of Animals Included in Analysis	16	16	14	15
	Trials to criterion	2.4±0.6	2.7±1.0	2.6±0.8	2.9±0.9
	Latency trial 1 (sec)	153.2±48.4	162.3±44.5	139.5±66.9	125.1±57.9
	Latency trial 2 (sec)	177.9±8.2	166.9±39.7	170.2±24.8	169.4±31.4

[a] *Data extracted from pages 223-224 of the study report.*
Trials to Criterion = Mean # Trials per Group ± S.D.
Latency to Trial 1 = Mean Session 1 duration (seconds) per Group ± S.D.
Latency to Trial 2 = Mean Session 2 duration (seconds) per Group ± S.D.
Failed to Meet Criterion = Number of Animals that received the shock but did not demonstrate acquisition.
Failed to Cross = Number of Animals that never received the shock.
* *Statistically different from control, $p \leq 0.05$*

TEXT TABLE 17. Water Maze Performance in PND 60 (+2 days) Offspring (mean ± S.D.) [a]

Session/Parameter		Dose (ppm in diet)			
		Control	45 PPM	450 PPM	4500 PPM
Males					
Session 1 (Learning Phase)	Number of Animals	16	16	16	15
	Trials to Criterion (Mean±S.D.)	7.8±3.1	6.8±3.2	7.7±2.8	8.5±3.2
	Trial 1 - Errors (Mean±S.D.)	0.8±1.0	0.3±0.4	0.6±0.7	1.0±1.1
	Trial 1 - Duration (sec) (Mean±S.D.)	18.9±15.0	10.9±4.4	*12.9±7.3	19.7±15.8
	Trial 2 - Errors (Mean±S.D.)	0.3±0.8	0.1±0.3	0.4±0.5	0.3±0.5
	Trial 2 - Duration (sec) (Mean±S.D.)	13.4±9.0	11.8±11.9	13.4±7.4	10.6±6.1
	Failed to Meet Criterion	1 (6%)	0 (0%)	0 (0%)	1 (7%)
Session 2 (Retention Phase)	Number of Animals	15	16	16	14
	Trials to Criterion (Mean±S.D.)	5.6±0.8	5.3±0.8	5.4±0.6	5.5±0.9
	Trial 1 - Errors (Mean±S.D.)	0.4±0.9	0.1±0.3	0.8±1.1	0.3±0.5
	Trial 1 - Duration (sec) (Mean±S.D.)	8.9±5.2	7.3±4.0	17.9±13.9	9.6±5.2
	Trial 2 - Errors (Mean±S.D.)	0.3±0.8	0.0±0.0	0.1±0.3	0.0±0.0
	Trial 2 - Duration (sec) (Mean±S.D.)	6.3±5.6	3.4±1.1	4.8±2.5	3.4±0.7
Females					
Session 1 (Learning Phase)	Number of Animals	16	16	16	16
	Trials to Criterion (Mean±S.D.)	7.4 ± 3.0	7.2 ± 3.0	8.8 ± 3.1	8.7 ± 2.6
	Trial 1 - Errors (Mean±S.D.)	1.3 ± 1.8	0.6 ± 0.7	0.9 ± 1.5	1.5 ± 1.3
	Trial 1 - Duration (sec) (Mean±S.D.)	19.9 ± 17.9	14.5 ± 8.2	17.8 ± 13.7	21.9 ± 12.1
	Trial 2 - Errors (Mean±S.D.)	0.3 ± 0.4	0.8 ± 1.4	0.6 ± 0.9	0.5 ± 0.6
	Trial 2 - Duration (sec) (Mean±S.D.)	13.9 ± 7.1	14.2 ± 14.2	13.1 ± 8.2	10.6 ± 5.0
	Failed to Meet Criterion	0 (0%)	1 (6%)	1 (6%)	0 (0%)
Session 2 (Retention Phase)	Number of Animals	16	15	15	16
	Trials to Criterion (Mean±S.D.)	6.6 ± 2.3	6.1 ± 1.9	6.4 ± 2.1	5.5 ± 0.8
	Trial 1 - Errors (Mean±S.D.)	0.4±0.7	0.3±0.5	0.6±0.8	0.5±0.9
	Trial 1 - Duration (sec) (Mean±S.D.)	9.3 ± 6.9	9.7 ± 4.7	12.0 ± 8.2	8.8 ± 6.2
	Trial 2 - Errors (Mean±S.D.)	0.1±0.5	0.1±0.5	0.3±0.6	0.1±0.3
	Trial 2 - Duration (sec) (Mean±S.D.)	5.0 ± 2.2	5.1 ± 2.8	6.1 ± 3.9	4.2 ± 1.8

[a] Data obtained from pages 226-227 in the study report.
Values for rats who failed to learn during session 1 were not included in means for session 2.
*Values are mean ± standard deviation * Statistically different from control, $p \leq 0.05$*

TEXT TABLE 18. Mean (±SD) Brain Weight Data [a]

Parameter	Dose (ppm in diet)			
	Control	45 PPM	450 PPM	4500 PPM
Males				
Day 21(Perfused)				
Terminal Body Weight (g)	47.7±2.4 (10)	50.8±3.3 (10)	45.6±3.8 (10)	43.9*±3.4 (10)
Brain, Fixed (g)	1.432±0.102 (10)	1.441±0.061 (10)	1.368±0.050 (10)	1.313*±0.070 (10)
Brain, Fixed/Body Weight (%)	2.999±0.147 (10)	2.843±0.190 (10)	3.016±0.307 (10)	3.002±0.203 (10)
PND 75 (±5) (Termination - Perfused)				
Terminal Body Weight (g)	327.0±20.3 (10)	310.5±24.5 (10)	299.2*±15.7 (10)	304.7±18.5 (10)
Brain, Fixed (g)	1.829±0.080 (10)	1.868±0.070 (10)	1.789±0.037 (10)	1.827±0.083 (10)
Brain, Fixed/Body Weight (%)	0.561±0.031 (10)	0.604±0.036 (10)	0.602±0.051 (10)	0.601±0.039 (10)
PND 75 (±5) (Termination - Non-Perfused)				
Terminal Body Weight (g)	321.4±15.9 (10)	313.9±33.3 (10)	320.3±15.3 (10)	302.1±27.0 (10)
Brain, Fixed (g)	1.909±0.090 (10)	1.957±0.128 (10)	1.876±0.169 (9)	1.866±0.089 (10)
Brain, Fixed/Body Weight (%)	0.596±0.046 (10)	0.627±0.048 (10)	0.585±0.061 (9)	0.624±0.080 (10)
Females				
Day 21(Perfused)				
Terminal Body Weight (g)	47.2±3.7 (10)	47.3±4.6 (10)	42.3±2.9 (10)	40.0*±7.1 (10)
Brain, Fixed (g)	1.409±0.092 (10)	1.373±0.058 (10)	1.318*±0.049 (10)	1.256*±0.060 (10)
Brain, Fixed/Body Weight (%)	2.992±0.228 (10)	2.920±0.254 (10)	3.129±0.232 (10)	3.241±0.634 (10)
PND 75 (±5) (Termination - Perfused)				
Terminal Body Weight (g)	195.4±11.4 (10)	190.0±11.3 (10)	182.9±8.1 (10)	190.7±18.8 (10)
Brain, Fixed (g)	1.723±0.046 (10)	1.717±0.051 (10)	1.707±0.039 (10)	1.644*±0.084 (10)
Brain, Fixed/Body Weight (%)	0.884±0.056 (10)	0.905±0.043 (10)	0.935±0.043 (10)	0.868±0.072 (10)
PND 75 (±5) (Termination - Non-Perfused)				
Terminal Body Weight (g)	188.4±11.6 (10)	188.0±17.2 (10)	187.2±14.7 (10)	188.9±18.0 (10)
Brain, Fixed (g)	1.793±0.072 (10)	1.811±0.059 (10)	1.751±0.089 (10)	1.702*±0.101 (10)
Brain, Fixed/Body Weight (%)	0.954±0.064 (10)	0.969±0.072 (10)	0.939±0.068 (10)	0.905±0.066 (10)

[a] Data obtained from pages 839-840, 842-843, 845-846 in the study report.
* Statistically different from control, $p \leq 0.05$

TEXT TABLE 19. Histopathology Findings [a]

Parameter	Dose (ppm in diet)			
	Control	45 PPM	450 PPM	4500 PPM
Males				
Gross Measurements				
Day 21				
Ant/Post Cerebrum Length (mm)	13.52±0.37 (10)	13.67±0.25 (10)	13.31±0.22 (10)	13.24±0.23 (10)
Ant/Post Cerebellum (mm)	7.20±0.32 (10)	7.03±0.34 (10)	7.12±0.30 (10)	6.80*±0.19 (10)
PND 75 (±5) (Termination - Perfused)				
Ant/Post Cerebrum Length (mm)	14.56±0.47 (10)	14.69±0.45 (10)	14.45±0.38 (10)	14.86±0.35 (10)
Ant/Post Cerebellum (mm)	7.56±0.38 (10)	7.69±0.17 (10)	7.41±0.31 (10)	7.21*±0.25 (10)
Microscopic Measurements				
PND 21				
Frontal Cortex (mm)	1.728±0.027 (10)	--	1.769±0.006 (10)	1.805±0.012 (10)
Parietal Cortex (mm)	2.008±0.018 (10)	1.918±0.004 (9)	1.901±0.005 (10)	1.922±0.013 (10)
Caudate Putamen (mm)	2.982±0.064 (10)	--	3.097±0.021 (10)	3.052±0.020 (10)
Hippocampal Gyrus (mm)	1.723±0.007 (10)	--	1.673±0.003 (10)	1.541±0.025 (10)
Cerebellum (mm)	4.367±0.077 (10)	4.165±0.046 (10)	4.057±0.019 (10)	4.005±0.033 (10)
PND 75 (±5) (Termination - Perfused)				
Frontal Cortex (mm)	1.760±0.009 (10)	--	1.656±0.010 (10)	1.713±0.004 (10)
Parietal Cortex (mm)	1.863±0.003 (10)	--	1.808±0.005 (10)	1.880±0.004 (10)
Caudate Putamen (mm)	3.345±0.023 (10)	--	3.302±0.012 (10)	3.434±0.012 (10)
Hippocampal Gyrus (mm)	1.758±0.023 (10)	--	1.790±0.064 (10)	1.684±0.021 (10)
Cerebellum (mm)	3.831±0.047 (10)	--	4.380±0.052 (10)	3.618±0.052 (10)

Parameter	Dose (ppm in diet)			
	Control	45 PPM	450 PPM	4500 PPM
Females				
Gross Measurements				
Day 21				
Ant/Post Cerebrum Length (mm)	13.63±0.34 (10)	13.58±032 (10)	13.07*±0.19 (10)	13.00*±0.34 (10)
Ant/Post Cerebellum (mm)	7.13±0.56 (10)	7.06±0.20 (10)	6.83±0.30 (10)	6.65*±0.31 (10)
PND 75 (±5) (Termination - Perfused)				
Ant/Post Cerebrum Length (mm)	14.12±0.39 (10)	14.11±0.31 (10)	14.24±0.26 (10)	13.92±0.29 (10)
Ant/Post Cerebellum (mm)	7.57±0.31 (10)	7.52±0.33 (10)	7.47±0.41 (10)	7.35±0.38 (10)
Microscopic Measurements				
PND 21				
Frontal Cortex (mm)	1.823±0.019 (10)	--	1.763±0.008 (10)	1.749±0.011 (10)
Parietal Cortex (mm)	1.999±0.006 (10)	1.939±0.003 (10)	1.846±0.003 (10)	1.850±0.0131 (10)
Caudate Putamen (mm)	3.029±0.034 (10)	--	2.974±0.0178 (10)	2.915±0.013 (10)
Hippocampal Gyrus (mm)	1.737±0.008 (10)	--	1.696±0.003 (10)	1.575±0.005 (10)
Cerebellum (mm)	4.292±0.048 (10)	4.164±0.072 (10)	4.086±0.063 (10)	3.869±0.022 (10)
PND 75 (±5) (Termination - Perfused)				
Frontal Cortex (mm)	1.761±0.004 (10)	--	1.662±0.003 (10)	1.792±0.005 (10)
Parietal Cortex (mm)	1.855±0.001 (10)	--	1.827±0.003 (10)	1.833±0.002 (10)
Caudate Putamen (mm)	3.386±0.021 (10)	--	3.172±0.020 (10)	3.330±0.008 (10)
Hippocampal Gyrus (mm)	1.631±0.025 (10)	--	1.731±0.039 (10)	1.543±0.024 (10)
Cerebellum (mm)	3.978±0.033 (10)	--	4.488±0.093 (10)	3.756±0.057 (10)

** Data obtained from pages 848-864 in the study report.*
*Values are mean ± standard deviation * Statistically different from control, p ≤ 0.05*
-- = not evaluated