

US EPA ARCHIVE DOCUMENT

**DATA EVALUATION REPORT**

**LINDANE**

**STUDY TYPE: DEVELOPMENTAL NEUROTOXICITY – RAT [870.6300 (§83-6)]  
MRID 45073501**

Prepared for

Health Effects Division  
Office of Pesticide Programs  
U.S. Environmental Protection Agency  
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Prepared by

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<b>DATA EVALUATION RECORD</b>
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STUDY TYPE: Developmental Neurotoxicity - Rat [OPPTS 870.6300 (§83-6)]

DP BARCODE: D260975, D264799

SUBMISSION CODE: S570995

P.C. CODE: 009001

TOX. CHEM. NO.: none

TEST MATERIAL (PURITY): Lindane (99.78% a.i.)

SYNONYMS: 1,2,4,5/3,6-gamma stereo isomer of 1,2,3,4,5,6-hexachlorocyclohexane

CITATION: Myers, D.P. (1999) Lindane: Developmental neurotoxicity study in the Han Wistar rat by dietary administration. Huntingdon Life Sciences Ltd. Eye, Suffolk, IP23 7PX, England. Laboratory Project No. CIL/022, September 21, 1999. MRID 45073501. Unpublished.

SPONSOR: CIEL, 56, rue des Colonies (Box 14), B-1000 Brussels, Belgium

EXECUTIVE SUMMARY: In a developmental neurotoxicity study (MRID 45073501), lindane (Batch No. HLS 96/1; 99.78% a.i.) was administered to presumed pregnant Hsd Brl Han:Wist (Han Wistar) rats in the diet at concentrations of 0, 10, 50, or 120 ppm from gestation day (GD) 6 through lactation day 10. These concentrations resulted in F<sub>0</sub> maternal doses of 0.8-0.9, 4.2-4.6, and 8.0-10.5 mg/kg/day, respectively, during gestation and 1.2-1.7, 5.6-8.3, and 13.7-19.1 mg/kg/day, respectively, during lactation. The developmental neurotoxicity of lindane was evaluated in the F<sub>1</sub> offspring. F<sub>1</sub> animals (10/sex) were evaluated for FOB, motor activity, auditory startle response, and learning and memory as well as developmental landmarks such as vaginal perforation and balanopreputial separation, and brain weights and histopathology on days 11 and 65, including morphometrics.

Small differences in absolute maternal body weights (7-8%) were observed between the high dose and control groups during gestation and early lactation (through day 11). Body weight gains by the high-dose dams from GD 6 through GD 20 were 64-79% ( $p \leq 0.01$ ) of the control level. Body weight changes during lactation were similar between the treated and control groups. During gestation, food consumption by the high-dose group was significantly ( $p \leq 0.01$ ; 74-92% of controls) less than the control group for the intervals of GD 10-13, 14-17, and 18-19. Food consumption by the low- and mid-dose groups during gestation and by all treated groups during lactation was similar to the controls.

Absolute body weights of the treated male and female pups in mid and high dose groups during lactation were 12-18% and 16-20% less than controls, respectively on days 4-11 of lactation with recovery to less than 10% by day 21. Body weight gains ( $p \leq 0.05$  or  $0.01$ ) on lactation days 1-4

and 1-11 were 76% and 84%, respectively, of the control levels for mid-dose males, 79% and 79%, respectively, for mid-dose females, 60% and 73%, respectively for high-dose males, and 63 and 75%, respectively, for high-dose females. Body weight gains by all treated groups were similar to the controls during lactation days 11-21. Except for mid and high dose females, postweaning, body weight gains were similar between the treated and control groups. Body weight differences for high dose dams were 10% less at the beginning of lactation and recovered to 6% less by the end of the study.

The high-dose group had a greater number of stillborn pups as indicated by a live birth index of 77% compared with 99% for the control group. In addition, nine high-dose litters either died or were sacrificed moribund on lactation days 1-4. This resulted in a viability index for the high-dose group of 71% compared with 89% for the controls. Pup mortality in the mid and high-dose groups in litters surviving to weaning was greater before day 4 than in controls [3 pups in 2/20 controls; 18 pups in 8/22 litters, mid dose; 14 pups in 4/15 litters, high dose]. Survival was not affected at any time in the low dose group as compared with the control group. No dose- or treatment-related differences were observed between treated and control groups for duration of gestation, number of pups/litter on day 1, or per cent male offspring.

At necropsy, no treatment-related gross abnormalities were observed in the dams or offspring. Absolute and relative liver and kidney weights of the offspring were not affected by treatment.

A few clinical signs were observed in high dose dams and pups; increased reactivity to handling in dams on weeks 2 and 3 of dosing, and slower surface righting in pups on day 4. There were no effects on measures of physical or sexual development.

There was an increase in motor activity at the mid and high dose during lactation in both sexes. Some decrease in habituation of motor activity in females on day 22 was also seen. While there was no effect on auditory startle reflex amplitudes, there was a clear reduction in auditory startle response habituation in both sexes at the high dose on day 28 and on day 60. Slight decreases in absolute, but not relative, brain weights in mid and high dose female pups were observed on postnatal day 11 (9-10%) but narrowed to 3-5% less by day 65. Brain lengths and widths were similar between the treated and control pups. Morphometric brain measurements did not show any significant differences in the sizes of the neocortex, hippocampus, corpus callosum, or cerebellum on days 11 or 65. There were no effects on histopathology of the nervous system.

**The maternal toxicity LOAEL is 120 ppm (13.7 mg/kg/day) based on decreased body weight gains, decreased food consumption, and increased reactivity to handling.**

**The maternal toxicity NOAEL is 50 ppm (5.6 mg/kg/day).**

**The offspring toxicity LOAEL is 50 ppm (5.6 mg/kg/day) based on reduced pup survival, decreased body weights and body weight gains during lactation, increased motor activity, and decreased motor activity habituation.**

**The offspring toxicity NOAEL is 10 ppm (1.2 mg/kg/day).**

This study is classified as **Unacceptable/Guideline** [870.6300 (§83-6)] since laboratory validation studies of the neurobehavioral tests were not included, but it may be upgraded and found acceptable if this information is obtained. The number of animals tested at the highest dose is only 6 compared to the required number of 10 animals per dose.

COMPLIANCE: Signed and dated GLP and Data Confidentiality statements were provided. A Quality Assurance statement was included but not signed. A Flagging statement was not included.

## I. MATERIALS AND METHODS

### A. MATERIALS

#### 1. Test material: Lindane

Description: white, crystalline powder

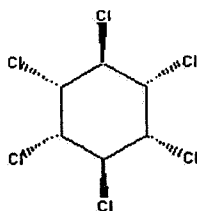
Batch No.: HLS 96/1

Purity: 99.78%, a.i.

Stability of compound: minimum 2 years

CAS No.: 58-89-9

Structure:



#### 2. Vehicle and/or positive control

Laboratory Animal Diet No. 2 SQC (Special Diet Services Ltd., Witham, Essex, England), was used as vehicle and negative control. No positive control was used in this study.

#### 3. Test animals

Species: rat

Strain: Hsd Brl Han:Wist (Han Wistar)

Age and weight at start of study: approximately 10-11 weeks; 200-251 g

Source: Harlan UK Limited, Bicester, Oxon, England

Housing: After mating, females were individually housed in stainless steel grid cages until GD 17. From GD 17 to lactation day 18, females and their litters were housed in solid polypropylene cages with bedding material (wood shavings).

Diet: Laboratory Animal Diet No. 2 SQC was available *ad libitum*.

Water: Tap water was available *ad libitum*.

Environmental conditions:

Temperature: 19-23°C  
Humidity: 40-70%  
Air Changes: not stated  
Photoperiod: 12 hour light/dark  
Acclimation period: minimum of 8 days

## B. STUDY DESIGN

This study was designed to assess the developmental neurotoxicity potential of Lindane when administered in the feed to rats from GD 6 to lactation day 10, inclusive.

### 1. In life dates

Start: January 14, 1999; end: April 21, 1999

### 2. Mating procedure and schedule

Females were paired 1:1 with stock males of the same strain. The day on which a sperm positive vaginal smear or at least three copulation plugs were found in the trays beneath the cages was designated as GD 0.

### 3. Animal assignment

Females showing unequivocal evidence of mating were allocated to group and cage position in sequence, thus ensuring that animals mated on any one day were evenly distributed among the groups as far as possible. The allocation of females was adjusted to avoid a given male having mated with more than one female in each group. No indication was given as to whether the groups were standardized with respect to body weight. Animal assignment is given in Table 1. An untreated group of 10 females and 10 males was added to allow checking of the calibration of the automated auditory startle response system for testing of 60 day old F<sub>1</sub> animals. Following completion of calibration of the equipment, the animals were discarded.

TABLE 1. F <sub>0</sub> Female assignment		
Dose Group	Conc. in Diet <sup>a</sup> (ppm)	No. of Females
2 (Control)	0	24
1 (Low)	10	24
4 (Mid)	50	24
3 (High)	120	24

Data taken from pp. 18, MRID 45073501.

<sup>a</sup>Diets were administered to the F<sub>0</sub> females from GD 6 through lactation day 10.

5

#### 4. Validation of testing procedures

Laboratory validation of the testing procedures for developmental neurotoxicity testing were not included in the study.

#### 5. Dose selection rationale

Doses were selected by the sponsor on the basis of a dose range-finding study (CIL020). Treatment with 180 and 250 ppm resulted in increased post implantation loss, a marked increase in post natal pup mortality, and lower body weights and weight gains of the offspring. At 120 ppm, no adverse effects on pup survival or weight gain were observed, although mean body weights on lactation day 1 were lower than controls. No other details of the range-finding study were included in the main report.

#### 6. Diet preparation and analysis

Fresh diets were prepared once every two weeks. A premix was prepared by grinding an appropriate amount of test article with a mortar and pestle. A similar amount of 355  $\mu$ m sieved diet was then added and ground. Further sieved diet was added to the mixture to make it up to half the final premix weight. This mixture was then ground with a coffee grinder. Coarse diet was then added to complete the mix. The premix was then mixed in a Turbular mixer for 100 resolutions. For each required dietary concentration, appropriate amounts of premix and plain diet were mixed together in a Turbular mixer to achieve the required concentration. Prior to study initiation, sample diets containing 5 and 250 ppm were analyzed for homogeneity and stability. Samples from each diet prepared for the start of treatment and during the first week of lactation were collected and analyzed for concentration.

#### Results –

**Homogeneity analysis:** The concentration of test article in samples taken from the top, middle, and bottom of the 5 and 250 ppm sample diets ranged from 84.2-96.4% and 92.0-96.4%, respectively, of nominal.

**Stability analysis:** Following 22 days of storage at room temperature, the 5 and 250 ppm diets were 105% and 103% of their initial measured concentrations.

**Concentration analysis:** Absence of test article was confirmed in the control diet. Mean concentrations of test article in the low-, mid-, and high-dose diets were 90.7-94.9%, 90-91.6%, and 96.7-98.3% of nominal, respectively.

Results of the dietary analyses indicate that mixing was adequate and that the actual dosages to the animals were acceptable.

#### 7. Statistical analyses

Body weight, food intake, litter data, and pup development data were analyzed by either the analysis of variance followed by Williams' test (parametric tests) or by the

6

Kruskal-Wallis test followed by Shirley's test (nonparametric tests) as appropriate depending on the heterogeneity of variances. Also dependent on the heterogeneity of variance between treatment groups, statistical analyses of motor activity, arena activity and rearing data, Morris water maze, and auditory startle response data were performed using parametric tests followed by pairwise t tests or, nonparametric tests followed by pairwise Wilcoxon tests. When 75% or more of the values for a given variable were the same, a Fisher's exact test was used. Surface righting reflex on days 4 and 11 of age, maximum pivoting angle data on day 4 of age, and maximum distance traveled on day 4 of age were analyzed by a linear-by-linear association test.

### C. METHODS

#### 1. Maternal clinical observations and mortality

All animals were observed twice daily for clinical signs of toxicity. Ten animals per group were subjected to more detailed clinical examinations outside the home cage on days 4, 12, 19, 26, and 31 after mating. These examinations included reactivity to removal from cage and handling, grooming, salivation, lacrimation, exophthalmos, piloerection, pupil closure reflex, gait and posture abnormalities, counts of urination and defecation, degree of any palpebral closure, convulsions, tremors, activity and rearing counts, stereotypies, emaciation, dehydration, hypotonia/hypertonia, altered appearance of fur, and red or crusty deposits around the eyes, nose, or mouth.

Females were weighed on days 0, 6, 10, 14, 18, and 20 of gestation, then daily until parturition. Females were also weighed on days 1, 4, 11, 17, and 21 of lactation. Food consumption was recorded on GD 0-5, 6-9, 10-13, 14-17, and 18-19 and on lactation days 1-3, 4-10, 11-16, and 17-20. Compound consumption was calculated from the body weight and food consumption data and the nominal concentration of test article in the diet for each group.

#### 2. Litter clinical observations and mortality

All females were allowed to litter and the number of live and dead pups was recorded during parturition. Offspring were individually identified by toe markings on lactation day 1. Litters were observed daily for mortality and clinical signs of toxicity. On lactation day 4 litters were culled to 5 males and 5 females where possible. The sex of the offspring was determined on days 1, 4, and 21. Individual body weights of live pups were recorded on lactation days 1, 4, 11, 17, and 21. Physical development of the offspring was assessed by monitoring hair growth from day 1 and tooth eruption from day 5.

F<sub>1</sub> animals were weighed weekly from post natal day 21 until termination at approximately post natal day 65. Males were examined daily from day 38 for balanopreputial separation and females were examined daily from day 28 for vaginal opening.



### 3. Neurobehavioral evaluations

F<sub>1</sub> offspring allocated for further investigations were observed twice daily for clinical signs of toxicity. In addition to the neurobehavioral evaluations described below, on lactation day 4, one male or one female pup was allocated to either assessment of motor activity, auditory startle response habituation, or auditory startle pre-pulse inhibition, or to sacrifice and brain examination on day 11. It should be noted that with a since the sample size is small, evaluations are more variable and less sensitive.

#### a. Functional observational battery (FOB)

On post natal days 4, 11, 21, 35, 45, and 60, ten male and ten female offspring per group were subjected to more detailed examinations outside the home cage. The FOB included assessment of surface righting reflex, movement on the FOB activity sheet (open field), physical condition, grooming, urination, rearing, feces, and abnormal behaviors. On days 35, 45, and 60 more detailed in-hand and standard arena observations were made. Pupil closure reflex was assessed on day 35 only.

#### b. Motor activity

Motor activity measurements were made on postnatal days 13, 17, 22, and 59. On day 13, it was recorded whether the eyes were open or closed. One pup per litter of >5 pups was assigned resulting in 8-12 animals/sex in the control, low-, and mid-dose groups and a minimum of 6 animals/sex in the high-dose group. The motor activity of each animal was monitored over a 1-hour period with data collected over each successive 6-minute interval. The frequency with which the light beams were interrupted produced the activity score.

#### c. Auditory startle response

At approximately post natal days 28 and 60, animals were tested in an automated system for auditory startle response habituation and pre-pulse inhibition of startle. One pup per litter of >5 pups was assigned resulting in 8-12 animals/sex in the control, low-, and mid-dose groups and a minimum of 6 animals/sex in the high-dose group.

#### d. Morris water maze (learning and memory)

At approximately post natal days  $28 \pm 2$  and 65, animals were tested in a water maze paradigm. The Morris maze consisted of a circular pool constructed of white plastic with a fixed platform located in the center 1.5 cm under the water surface. One pup per litter of >5 pups was assigned resulting in 8-12 animals/sex in the control, low-, and mid-dose groups and a minimum of 6 animals/sex in the high-dose group. The same animals were tested at each interval. A series of 3 trials were conducted on each of 4 consecutive days. The animal was placed into the water at the perimeter of the pool and allowed 90 seconds to find the escape

platform. A different starting point was used for each trial. The time (latency) to reach the platform was recorded together with the number of quadrants (sectors) of the pool crossed. If the animal failed to find the platform within 90 seconds, it was placed on the platform for 30 seconds and the latency was recorded as 90 seconds.

#### 4. Postmortem Studies

##### a. Sacrifice

F<sub>0</sub> females and unallocated F<sub>1</sub> animals killed after day 21 were euthanized by carbon dioxide inhalation. Pups killed before day 21 were euthanized by intraperitoneal injection of sodium pentobarbitone or inhaled carbon dioxide, as appropriate.

##### b. Necropsy

- 1) Parental animals - F<sub>0</sub> females were killed on lactation day 21 and subjected to gross necropsy. The number of implantation sites was recorded and abnormal tissues were retained in appropriate fixative.
- 2) Offspring - Offspring dying during early lactation and culled on day 4 were discarded without further examination. Offspring killed during early lactation for animal welfare were necropsied. Weanlings not allocated for further investigations were subjected to gross necropsy on lactation day 21.
- 3) Neuropathological evaluations - At postnatal day 11, one pup per litter was killed and subjected to detailed gross examination and the brain was weighed. Of these pups, 6/sex/group were allocated to detailed neuropathological examination including brain length and width measurements and histological examination. In addition, morphometric measurements were made for thicknesses of the neocortex, hippocampus, and corpus callosum, and width of the pyramis folia in the cerebellum.

On postnatal day 65, necropsy and brain measurements were as described on day 11 except that animals killed for neuropathological examination were perfused with glutaraldehyde and paraformaldehyde prior to necropsy. From perfused animals, the following central and peripheral nervous tissues (X) were dissected, - embedded in paraffin (CNS tissues) or resin (PNS tissues), sectioned, and stained with hematoxylin and eosin or toluidine blue. Histopathological evaluation was performed on tissues from the control and high-dose groups. Detailed morphometrics of various brain regions were conducted as described for day 11.

X	brain	X	eyes
X	pituitary	X	optic nerve
X	spinal cord (C <sub>3</sub> -C <sub>6</sub> , L <sub>1</sub> -L <sub>4</sub> )	X	sciatic nerves
X	dorsal root ganglia	X	tibial nerves
X	dorsal root fibers		
X	ventral root fibers	X	skeletal muscle
	trigeminal ganglia	X	macroscopic lesions

## II. RESULTS

### A. CLINICAL OBSERVATIONS AND MORTALITY

One high-dose dam and her litter were killed on lactation day 2 following signs in the dam of hunched posture, pallor, thin appearance, and vocalization; a cause of death was not determined. All other animals survived to terminal sacrifice. No treatment-related clinical signs of toxicity were observed in any animal from routine observations. During detailed observations, an increased reactivity to handling was observed in high dose dams during weeks 2 and 3 of dosing. Smaller changes in this measure were also seen in mid dose dams at the same times. Arena observations, including activity and rearing counts, were similar between the treated and control groups.

Reactivity to handling	Rank (1-5)	Females (# of animals)			
		0 ppm	10 ppm	50 ppm	120 ppm
Week 1	2	5	8	5	4
	3	5	2	4	6
	4	0	0	1	0
Week 2	2	7	6	4	3
	3	3	4	6	6
	4	0	0	0	1
Week 3	2	7	8	6	3
	3	1	1	3	4
	4	0	0	1	0
Week 4	2	5	7	7	3
	3	3	2	2	4
	4	0	0	0	0

Data taken from pp. 137-144, MRID 45073501

The high-dose group had a greater number of stillborn pups as indicated by a live birth index of 77% compared with 99% for the control group. In addition, nine high-dose litters either died or were sacrificed moribund on lactation days 1-4. One mid-dose F<sub>1</sub> male was killed on day 45 of age following the finding of traumatic keratitis and panophthalmitis in the left eye. A mid-dose F<sub>1</sub> female was found dead on day 27 of age,

but the cause of death was not determined (animal was partially cannibalized). No treatment-related clinical signs of toxicity were observed in the F<sub>1</sub> animals from routine observations.

#### B. BODY WEIGHT AND FOOD CONSUMPTION

Maternal body weights and body weight gains during gestation and lactation are given in Table 2. No statistically significant differences in absolute body weights were observed between the treated ad control groups during gestation or lactation. While high dose dams weighed 7-8% less than control dams on gestation day 20, and lactation days 1 and 11, this lacked statistical significance by the author's analyses. However, body weight gains by the high-dose group during gestation were significantly ( $p \leq 0.01$ ) less than the controls after the initiation of treatment on GD 6. From GD 6 through GD 20, body weight gains by the high-dose group were 64-79% of the control level. Body weight gains during lactation were similar between the treated and control groups. Food consumption by the low- and mid-dose groups during gestation and by all treated groups during lactation was similar to the controls. During gestation, food consumption by the high-dose group was significantly ( $p \leq 0.01$ ; 74-92% of controls) less than the control group for the intervals of GD 10-13, 14-17, and 18-19.

TABLE 2. Maternal body weights and body weight gains during gestation and lactation				
Observation	Treatment Group			
	0 ppm	10 ppm	50 ppm	120 ppm
Mean body weight (g)				
Day 0 of gestation	221 ± 11	222 ± 12	220 ± 12	220 ± 10
Day 6 of gestation	243 ± 13	247 ± 14	243 ± 13	242 ± 11
Day 20 of gestation	334 ± 20	336 ± 23	330 ± 24	310 ± 17 (93)
Day 1 of lactation	251 ± 25.1	252 ± 19	241 ± 16	232 ± 14 (93)
Day 11 of lactation	285 ± 21	283 ± 26	274 ± 20	262 ± 20 (92)
Day 21 of lactation	281 ± 21	288 ± 20	276 ± 21	275 ± 20
Mean body weight gain (g)				
Day 0-6 of gestation	22 ± 5	24 ± 5	24 ± 5	23 ± 6
Day 6-20 of gestation	91 ± 10	89 ± 13	86 ± 13	68 ± 16** (75) <sup>a</sup>
Day 1-11 of lactation	34 ± 19	31 ± 18	33 ± 11	30 ± 17
Day 1-21 of lactation	30 ± 23	36 ± 18	36 ± 16	43 ± 19

Data taken from Tables 12, 13, 15, and 16, pp. 72, 73, 75, and 76 respectively, MRID 45073501.

<sup>a</sup>Number in parentheses is percent of control.

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

11

TABLE 3: F <sub>1</sub> Body weights and body weight changes during lactation (g)				
Day of Age	0 ppm	10 ppm	50 ppm	120 ppm
Males - Absolute body weights				
Day 1	5.9 ± 0.6	6.1 ± 0.6	5.6 ± 0.7 (95)	5.4 ± 0.7 (91)
Day 4 (precull)	8.6 ± 1.3	8.5 ± 1.1	7.6 ± 1.3 (88)	7.1 ± 1.6 (83)
Day 4 (postcull)	8.5 ± 1.3	8.5 ± 1.1	7.5 ± 1.3 (88)	7.1 ± 1.6 (84)
Day 11	20.1 ± 2.8	19.9 ± 2.1	17.5 ± 2.0 (87)	16.0 ± 3.4 (80)
Day 21	43.7 ± 6.0	43.1 ± 4.3	40.6 ± 5.2 (93)	39.3 ± 5.5 (90)
Males - Body weight changes				
Day 1-4	2.5 ± 1.0	2.4 ± 0.6	1.9 ± 0.9* (76) <sup>a</sup>	1.5 ± 1.2** (60)
Day 1-11	14.1 ± 2.5	13.8 ± 1.7	11.8 ± 1.7** (84)	10.3 ± 3.2** (73)
Day 11-21 <sup>b</sup>	23.6	23.2	23.1	23.3
Day 1-21	37.6 ± 5.7	37.0 ± 3.9	34.9 ± 4.9	33.7 ± 5.2
Females - Absolute body weights				
Day 1	5.7 ± 0.6	5.8 ± 0.8	5.2 ± 0.6 (91)	5.1 ± 0.7 (89)
Day 4 (precull)	8.3 ± 1.2	8.2 ± 1.1	7.0 ± 1.4 (84)	6.8 ± 1.7 (82)
Day 4 (postcull)	8.3 ± 1.2	8.2 ± 1.1	7.1 ± 1.4 (86)	6.8 ± 1.7 (82)
Day 11	19.6 ± 2.4	19.1 ± 2.1	16.1 ± 2.3 (82)	15.7 ± 3.4 (80)
Day 21	42.1 ± 5.2	41.6 ± 4.3	38.0 ± 6.0 (90)	37.7 ± 5.9 (90)
Females - Body weight changes				
Day 1-4	2.4 ± 0.8	2.4 ± 0.6	1.9 ± 1.0* (79)	1.5 ± 1.2** (63)
Day 1-11	13.8 ± 2.0	13.2 ± 1.6	10.9 ± 2.0** (79)	10.4 ± 3.0** (75)
Day 11-21 <sup>b</sup>	22.5	22.5	21.9	22.0
Day 1-21	36.2 ± 4.9	35.7 ± 3.7	32.7 ± 5.7* (90)	32.4 ± 5.5* (90)

Data taken from Tables 24-27, pp. 84-87, respectively, MRID 45073501.

Significantly different from control, \*p ≤ 0.05, \*\*p ≤ 0.01.

<sup>a</sup>Number in parentheses is percent of control.

<sup>b</sup>Calculated by reviewer from group means.

Body weights and body weight gains of the F<sub>1</sub> pups during lactation are given in Table 3. Body weights of treated pups in the high dose group on day 1 were 9-11% less than controls. Body weights of treated pups in the high dose group were 16-20% less between day 4 and day 11, with recovery to 10% less by day 21.

Body weights of treated pups in the mid dose group on day 1 were 5-9% less than controls. Body weights of treated pups in the mid dose group were 12-18 % less between day 4 and day 11, with recovery to 7-10 % less by day 21. None of these changes achieved statistical

significance by the author's analyses.

However, body weight gains of mid- and high-dose pups were significantly less than the controls with the most pronounced effect during lactation days 1-11 when the dams were receiving the treated diets. Weight gains by the mid-dose male pups were 76% ( $p \leq 0.05$ ) and 84% ( $p \leq 0.01$ ) of the control levels on days 1-4 and 1-11, respectively. Mid-dose females had body weight gains of 79% ( $p \leq 0.01$ ) of the controls through lactation day 11. Body weight gains by the high-dose males were 60-73% of controls ( $p \leq 0.01$ ) and by the high-dose females were 63-75% of controls ( $p \leq 0.01$ ) through lactation day 11. Body weight gains by all treated groups were similar to the control levels for lactations days 11-21.

TABLE 4: F <sub>1</sub> Body weights and body weight changes after weaning (g)				
Day of Age	0 ppm	10 ppm	50 ppm	120 ppm
Males - Absolute body weights				
Day 28	74.4 ± 9.0	76.1 ± 7.1	71.0 ± 8.6	71.8 ± 9.4
Day 35	118 ± 10	119 ± 7	113 ± 12	115 ± 12
Day 49	205 ± 16	210 ± 9	199 ± 16	201 ± 16
Day 63	281 ± 19	290 ± 14	278 ± 18	281 ± 18
Males - Body weight changes				
Day 1-35	112 ± 10	113 ± 6	107 ± 11	109 ± 12
Day 1-49	199 ± 16	204 ± 9	194 ± 15	195 ± 16
Day 1-63	275 ± 19	284 ± 14	272 ± 18	276 ± 18
Day 21-63	238 ± 16	247 ± 14	237 ± 15	241 ± 15
Females - Absolute body weights				
Day 28	71.2 ± 8.4	70.7 ± 7.8	67.2 ± 7.1	64.3 ± 8.8 (90)
Day 35	108 ± 10	107 ± 7	102 ± 8	98 ± 11
Day 49	160 ± 10	160 ± 10	153 ± 11	149 ± 10
Day 63	196 ± 11	197 ± 11	189 ± 14	184 ± 12 (94)
Females - Body weight changes				
Day 1-35	102 ± 9	101 ± 7	96 ± 8* (94) <sup>a</sup>	92 ± 11** (90)
Day 1-49	154 ± 10	155 ± 9	148 ± 11* (96)	144 ± 10** (94)
Day 21-63	154 ± 9	155 ± 10	150 ± 13	147 ± 8
Day 1-63	191 ± 11	191 ± 11	183 ± 14	179 ± 12* (94)

Data taken from Tables 54-57, pp. 115-118, respectively, MRID 45073501.

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

<sup>a</sup>Number in parentheses is percent of control.

## LINDANE

## Developmental Neurotoxicity - Rat [OPPTS 870.6300 (§83-6)]

Body weights and body weight gains of the F<sub>1</sub> animals after weaning are given in Table 4. Absolute body weights and body weight gains of the males were similar between the treated and control groups during the postweaning period. Body weights for high dose females were 10% less than controls on day 28, and recovered to 6% less than controls by day 63. Cumulative body weight gains of the mid-dose females were significantly ( $p \leq 0.05$ ; 94-96% of controls) less than the controls for days 1-35 and 1-49. High-dose females had significantly ( $p \leq 0.05$  or  $0.01$ ; 90-94% of controls) lower body weight gains than the controls for the cumulative intervals throughout days 1-63. When body weight gains were considered for just the postweaning period (days 21-63), there was only a 6% difference between high dose and control females.

### C. MATERNAL TEST SUBSTANCE INTAKE

Based on food consumption and nominal Lindane concentrations in the diet, the doses expressed as mg of test substance/kg body weight/day during the treatment period are presented in Table 5. Because treatment ended on lactation day 10, it is unlikely that the pups directly consumed the test article. Therefore, exposure to the pups would only have been *in utero* and through the milk.

TABLE 5: Maternal Lindane intake during gestation and lactation (mg/kg/day)			
Study Interval	Concentration in Diet		
	10 ppm	50 ppm	120 ppm
Gestation			
day 6-9	0.9	4.6	10.5
day 10-13	0.9	4.4	9.6
day 14-17	0.8	4.2	9.7
day 18-19	0.8	4.2	8.0
Lactation			
day 1-3	1.2	5.6	13.7
day 4-10	1.7	8.3	19.1

Data taken from Tables 18 and 19, pp. 78 and 79, respectively, MRID 45073501.

### D. DELIVERY AND LITTER DATA

Delivery and litter data are summarized in Table 6. No dose- or treatment-related differences were observed between treated and control groups for duration of gestation, number of pups/litter on day 1, or per cent male offspring. Mean gestation length was not calculated by the study authors, however 100% of the dams in the control, low-, and mid-dose groups and 96% of the high-dose dams had delivered by GD 23; one high-dose dam delivered on GD 23.5. The high-dose group had a greater number of stillborn pups as indicated by a live birth index of 77% compared with 99% for the control group. In addition, nine high-dose litters either died or were sacrificed moribund on lactation days 1-4. This resulted in a viability index for the high-dose group of 71% compared with 89% for the controls. Pup survival in the high-dose group after lactation day 4 was similar to the control level. Survival was not affected at any time in the low dose group

**LINDANE****Developmental Neurotoxicity - Rat [OPPTS 870.6300 (§83-6)]**

as compared with the control group. There was no increase in litter mortality at 50 ppm. However, pup mortality during early lactation was increased among those litters which survived to weaning; 18 pups (8/22 litters) died between birth and Day 4 of age compared with the 3 Controls (2/20 litters).

No differences were observed between treated and control groups in the rate of physical development of the pups. Onset and completion of hair growth and tooth eruption were similar between the treated and control groups. Mean day of balanopreputial separation or vaginal opening attainment was 45.5-46.8 and 34.7-36.0, respectively, for all groups including controls.

TABLE 6: Delivery and litter data				
Observation/study time	0 ppm	10 ppm	50 ppm	120 ppm
Females mated (no. pregnant)	24 (23)	24 (24)	24 (24)	24 (24)
Number of litters	22	23	24	24
Gestation Index (%)	96	96	100	100
Gestation length (days)	22-23	22-23	22-23	22-23.5
Pups/litter at day 1	11.0	11.0	11.5	10.7
Pups/litter at day 4 (after cull)	9.5	9.5	9.7	8.6
Pups/litter at day 11 (after cull)	9.4	9.5	9.5	8.4
Pups/litter at day 17 (after cull)	8.4	8.5	8.4	7.5
Pups/litter at day 21 (after cull)	8.4	8.5	8.4	7.5
Sex ratio (% male)	49	49	49	51
Total litter loss	2	1	2	9
Survival indices (%)				
Live birth index	99	98	100	77
Viability index (precull; d 0-4)	89	94	90	71
Lactation index (postcull; d 4-21)	89	90	88	90

Data taken from Tables 20-23 and Appendix 17, pp. 80-83 and 182-183, respectively, MRID 45073501.

**E. NEUROBEHAVIORAL EVALUATIONS****1. Functional observational battery (FOB)**

The mean rank for surface righting reflex was significantly ( $p \leq 0.05$ ) greater (slower righting) in high dose males as compared to controls on lactation day 4 (2.4 vs 1.9, respectively). However, no differences in surface righting reflex were observed on day 11 for males or for females. Other in the hand observations and observations and



activities in the open field were similar between the treated and control groups throughout the study.

## 2. Motor activity

Total activity counts are given in Table 7 and complete data for all subsessions are shown in the Appendix. Data appears variable which raises questions regarding the sensitivity of the method. There appears to be some increase in activity detected in the mid dose group and the high dose group during the lactation period. By day 59, there does not seem to be an effect.

TABLE 7: Total motor activity				
Activity	0 ppm	10 ppm	50 ppm	120 ppm
<b>Males</b>				
Day 13 High beam Low beam	0.7 ± 2.0 101.0 ± 58.3	0.0 ± 0.0 63.7 ± 62.1	0.2 ± 0.4 158.3 ± 86.8	0.3 ± 0.5 176.3 ± 131.1
Day 17 High beam Low beam	12.4 ± 23.5 409.9 ± 364.1	7.9 ± 11.9 412.1 ± 341.8	12.5 ± 14.8 527.5 ± 390.4	4.6 ± 4.5 278.0 ± 157.8
Day 22 High beam Low beam	9.4 ± 13.2 113.5 ± 82.4	8.4 ± 8.2 93.1 ± 51.8	12.3 ± 14.7 218.1 ± 139.7*	16.7 ± 12.6 184.7 ± 98.8
Day 59 High beam Low beam	180.8 ± 91.6 783.0 ± 261.3	154.3 ± 53.8 612.2 ± 155.4	187.9 ± 70.0 813.9 ± 334.1	192.0 ± 33.8 783.4 ± 82.8
<b>Females</b>				
Day 13 High beam Low beam	0.0 ± 0.0 130.0 ± 114.3	1.3 ± 4.0 144.1 ± 129.5	2.5 ± 8.1 77.2 ± 54.4	0.0 ± 0.0 194.3 ± 135.8
Day 17 High beam Low beam	5.6 ± 6.6 182.4 ± 203.6	10.1 ± 9.5 258.3 ± 148.3	9.1 ± 7.3 481.8 ± 293.9**	2.8 ± 4.5 241.0 ± 172.3
Day 22 High beam Low beam	11.3 ± 7.8 137.5 ± 107.6	4.3 ± 3.7* 92.5 ± 50.0	13.9 ± 10.2 213.3 ± 145.2	3.2 ± 1.8* 343.3 ± 209.1*
Day 59 High beam Low beam	203.9 ± 77.3 791.8 ± 223.4	209.8 ± 96.9 816.9 ± 230.1	258.8 ± 96.7 944.2 ± 211.8	221.0 ± 95.1 758.0 ± 134.8

Data taken from Tables 38-41, pp. 99-102, MRID 45073501.

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

TABLE 8. Motor Activity Subsession Counts (Means) for minutes 6, 30, and 60 (Low Beam) as an index of habituation				
Dose		First	Middle	Last
M A L E S	control	55.3	6.2	4.1
	10 ppm	46.8	0.6	4.0
	50 ppm	66.5	15.5	8.5
	120 ppm	67.1	16.6	4.0
F E M A L E S	Controls	55.6	6.3	0
	10 ppm	50.1	4.1	0
	50 ppm	66.3	19.6	5.3
	120 ppm	67.8	36*	20.5

\* Counts at interval before and after 30 mins was significantly different from controls.

Some decrease was seen in habituation of motor activity (Table 8) in female rats at the mid and high dose on day 22. There was no apparent effect on this measure on day 60.

### 3. Auditory startle response

No statistical differences occurred between the treated and control groups for any trial block during auditory startle response habituation testing. The auditory startle pre-pulse inhibition was also similar between the treated and control groups on each testing day. There was a clear reduction in auditory startle response habituation in both sexes at the high dose on day 28 and on day 60. No data on latency was reported.

TABLE 9. Auditory Startle Reflex Habituation (Mean of first block - mean of last block)				
	Controls	Low	Mid-Dose	High Dose
Day 28				
Males	26	28	16	12
Females	21	21	17	11
Day 60				
Males	231	282	261	114
Females	105	118	183	62

LINDANE

Developmental Neurotoxicity - Rat [OPPTS 870.6300 (§83-6)]

On Day 28, there was an approximately 50% decrease in this rough measure of habituation at the high dose (Table 9). A similar decrease was also seen at day 60 in both sexes.

TABLE 10: Morris water maze performance of male pups				
Day of testing	0 ppm	10 ppm	50 ppm	120 ppm
Postnatal day 28				
Test day 1				
Trial time (sec)	58.2 ± 18.4	75.7 ± 16.8	76.6 ± 16.3	71.5 ± 17.3
No. failed trials	1.5 ± 1.1	2.0 ± 1.0	2.2 ± 0.9	1.7 ± 0.8
No. sector entries	16.2 ± 4.1	19.1 ± 5.3	20.2 ± 5.2	19.8 ± 7.3
Test day 2				
Trial time (sec)	52.4 ± 24.8	59.1 ± 19.8	43.8 ± 15.1	49.2 ± 24.8
No. failed trials	0.9 ± 1.1	1.3 ± 1.0	0.5 ± 0.7	1.0 ± 1.2
No. sector entries	12.8 ± 5.2	13.0 ± 3.5	11.3 ± 2.4	14.6 ± 7.2
Test day 3				
Trial time (sec)	32.3 ± 20.5	39.8 ± 23.9	38.7 ± 26.0	36.7 ± 16.3
No. failed trials	0.5 ± 0.9	0.8 ± 1.1	0.4 ± 0.7	0.4 ± 0.8
No. sector entries	8.2 ± 3.8	10.2 ± 5.5	10.5 ± 5.4	10.5 ± 3.8
Test day 4				
Trial time (sec)	29.4 ± 23.3	28.6 ± 24.3	32.8 ± 32.0	31.1 ± 15.1
No. failed trials	0.3 ± 0.5	0.3 ± 0.9	0.6 ± 1.1	0.3 ± 0.5
No. sector entries	8.7 ± 6.4	8.2 ± 4.8	9.9 ± 7.7	9.9 ± 4.4
Postnatal day 65				
Test day 1				
Trial time (sec)	29.5 ± 15.5	35.2 ± 19.1	23.6 ± 9.5	48.0 ± 22.6*
No. failed trials	0.3 ± 0.5	0.3 ± 0.7	0.1 ± 0.3	1.0 ± 0.8
No. sector entries	6.3 ± 2.6	6.4 ± 2.9	5.4 ± 1.5	9.0 ± 3.1*
Test day 2				
Trial time (sec)	18.0 ± 15.2	17.6 ± 14.7	16.3 ± 18.2	19.3 ± 12.9
No. failed trials	0.1 ± 0.4	0.0 ± 0.0	0.2 ± 0.6	0.3 ± 0.5
No. sector entries	4.9 ± 3.0	4.8 ± 3.2	4.3 ± 3.0	5.6 ± 3.1
Test day 3				
Trial time (sec)	13.8 ± 9.2	14.5 ± 13.2	9.8 ± 6.0	15.3 ± 18.4
No. failed trials	0.0 ± 0.0	0.1 ± 0.3	0.0 ± 0.0	0.1 ± 0.4
No. sector entries	4.4 ± 2.7	4.3 ± 3.4	3.2 ± 1.5	5.0 ± 4.4
Test day 4				
Trial time (sec)	9.7 ± 3.4	7.7 ± 3.6	11.0 ± 7.8	7.3 ± 5.3
No. failed trials	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
No. sector entries	3.3 ± 0.7	2.8 ± 0.9	3.4 ± 1.8	2.5 ± 1.0

Data taken from Tables 42 and 44, pp. 103 and 105, respectively, MRID 45073501.

Significantly different from control: \*p ≤ 0.05.

#### 4. Learning and memory

Data from the Morris water maze trials for male pups are presented in Table 10. Data for females and additional data for males is given in the appendix. On day 28, all treated male groups had slight increases in swimming times, number of failed trials, and number of sector entries on day 1 of testing. Females in all dose groups also had slightly higher swimming times at 28 days of age. However, statistical significance was not reached for any parameter. On day 65, high-dose males had significantly ( $p \leq 0.05$ ) greater swimming times and number of sector entries and a slightly (n.s.) greater number of failed trials on the first testing day. These differences resolved on subsequent testing days.

### F. NECROPSY RESULTS

#### 1. Gross necropsy

No dose- or treatment-related abnormalities were observed in the F<sub>0</sub> females. No treatment-related gross abnormalities were observed in selected F<sub>1</sub> animals at postnatal days 11 or 65 or in offspring not selected for further testing.

#### 2. Organ weights and brain measurements

Maternal organ weights were not obtained at necropsy.

Offspring brain weights and measurements from days 11 and 65 are given in Table 11. No statistically significant differences between absolute or relative brain weights from treated male and female pups as compared to controls were observed on postnatal days 11 or 65. Brain weight in the mid and high dose females however were 9-10% less than controls at day 11 and by day 65 the gap narrows to 3.4-4.8% less than controls. Brain lengths and widths were similar between the treated and control pups on these days. Expanded morphometry on brains from the control and high-dose pups did not show any consistent differences in the sizes of the neocortex, hippocampus, or cerebellum on days 11 or 65. On day 65, absolute and relative liver and kidney weights of the treated males and females were similar to their respective controls.

TABLE 11: Whole brain weights, lengths, and widths from F <sub>1</sub> rats <sup>a</sup>				
Measurement	Concentration in the diet			
	0 ppm	10 ppm	50 ppm	120 ppm
Males				
Brain wt day 11 absolute (g) relative (%)	0.904 ± 0.169 5.070	1.034 ± 0.084 5.254	0.930 ± 0.080 5.256	0.911 ± 0.075 5.972
Brain wt day 65 absolute (g) relative (%)	1.828 ± 0.091 0.649	1.872 ± 0.116 0.643	1.832 ± 0.146 0.655	1.824 ± 0.087 0.639
Brain length (mm) day 11 day 65	15.1 ± 1.3 20.1 ± 0.3	16.2 ± 0.7 19.8 ± 0.7	15.3 ± 0.7 19.6 ± 0.2	15.4 ± 0.6 20.0 ± 0.5
Brain width (mm) day 11 day 65	12.6 ± 0.9 15.1 ± 0.5	13.2 ± 0.3 15.2 ± 0.1	12.7 ± 0.5 14.8 ± 0.3	12.6 ± 0.5 15.1 ± 0.3
Females				
Brain wt day 11 absolute (g) relative (%)	0.977 ± 0.047 5.067	0.969 ± 0.056 5.072	0.876 ± 0.089 5.503	0.890 ± 0.100 5.364
Brain wt at day 65 absolute (g) relative (%)	1.738 ± 0.128 0.887	1.714 ± 0.110 0.870	1.655 ± 0.122 0.897	1.679 ± 0.110 0.888
Brain length (mm) day 11 day 65	15.5 ± 0.4 19.2 ± 0.4	15.8 ± 0.8 19.0 ± 0.4	14.9 ± 0.7 19.5 ± 0.5	15.3 ± 0.3 19.2 ± 0.9
Brain width (mm) day 11 day 65	13.0 ± 0.4 14.6 ± 0.4	12.9 ± 0.4 14.6 ± 0.4	12.5 ± 0.6 14.8 ± 0.3	12.5 ± 0.6 14.6 ± 0.8

Data taken from Tables 60-63 and 65-68, pp. 121-124 and 126-129, respectively, MRID 45073501.

<sup>a</sup>N = 6-12/sex/dose on day 11; 13-22/sex/dose for weights on day 65; 6/sex/dose for lengths and widths on day 65

### 3. Histological examination

No treatment-related microscopic abnormalities were seen in the brains from control or high-dose F<sub>1</sub> animals on days 11 or 65 (Table 12). On day 11, a minimal focus of neuronal degeneration in the cerebral cortex of one high-dose male pup and an epidermal cyst in the choroid plexus of the third ventricle of a control male pup were observed. No abnormalities were found in neuronal tissues on day 65.

Table 12. Brain Morphometry				
	Males		Females	
	0 ppm	120 ppm	0 ppm	120 ppm
<b>Neo Cortex</b>				
Day 11	1.6 ± 0.2 (6)	1.6 ± 0.1 (6)	1.7 ± 0.1 (6)	1.5 ± 0.1 (6)
Day 65	1.4 ± 0.2 (5)	1.7 ± 0.2 (5)	1.7 ± 0.5 (6)	1.5 ± 0.1 (6)
<b>Hippocampus</b>				
Day 11	1.6 ± 0.3 (6)	1.5 ± 0.2 (6)	1.6 ± 0.1 (6)	1.5 ± 0.1 (6)
Day 65	1.9 ± 0.2 (6)	1.9 ± 0.2 (6)	1.9 ± 0.2 (6)	1.7 ± 0.1 (6)
<b>Corpus callosum</b>				
Day 11	0.42 ± 0.17 (6)	0.36 ± 0.06 (6)	0.28 ± 0.08 (6)	0.44 ± 0.12 (6)
Day 65	0.31 ± 0.11 (4)	0.39 ± 0.08 (4)	0.43 ± 0.13 (6)	0.45 ± 0.13 (5)
<b>Cerebellum</b>				
Day 11	0.66 ± 0.12 (4)	0.62 ± 0.06 (5)	0.57 ± 0.13 (6)	0.59 ± 0.07 (6)
Day 65	0.9 ± 0.1 (6)	0.8 ± 0.1 (5)	0.9 ± 0.1 (6)	0.9 ± 0.1 (5)

Data taken from pp. 125 and 130, MRID 45073501

Mean ± SD ; parentheses ( ) indicate # of pups examined

### III. DISCUSSION

#### A. DISCUSSION

One high dose dam was sacrificed in a moribund state. Deaths of two mid dose F<sub>1</sub> animals were considered incidental to treatment.

A few clinical signs were observed in high dose dams and pups; increased reactivity to handling in dams on weeks 2 and 3 of dosing, and slower surface righting in pups on day 4.

Reduced body weights and body weight gains by the high-dose dams after the initiation of dosing correlated with decreased food consumption and are considered treatment-related. However, the reduced food consumption may have been due to a lack of palatability of lindane to rats with the animals gradually becoming accustomed to the taste.

Pup body weight gains were also reduced in the mid- and high-dose with the most pronounced effect during lactation days 1-11 when the dams were still on the treated diets. After treatment ended, body weight gains by the treated pups began to recover. However, due to the severe effect during early lactation, cumulative body weight gains continued to be reduced postweaning in the mid- and high-dose animals. The effect on pup body weight gains in early lactation is considered a lactational effect since the pups would not have been eating the test diets yet and recovery was apparent when the dams were returned to untreated diets.

No dose- or treatment-related differences were observed between treated and control groups for duration of gestation, total number of pups delivered, or percent male offspring. Pup survival was greatly decreased in the high-dose group with a total of nine litters lost during lactation days 1-4. Despite the decrease in body weight gain and survival of pups in the mid- and/or high-dose litters, physical development and sexual maturation were not delayed.

An increase in motor activity in the mid and high dose groups and decreases in habituation of both motor activity and auditory startle habituation were seen. These are both stimulant effects which are consistent with that seen for other organochlorines. The significant decrease in performance in the water maze in the high dose males on day 65 is suggestive of a long term

## LINDANE

## Developmental Neurotoxicity - Rat [OPPTS 870.6300 (§83-6)]

memory deficit, since there were no differences on earlier or later days. The lack of effect on motor activity at day 60 suggests that these animals did not have a motor deficit.

Necropsy of both dams and pups was unremarkable. There were no significant effects on brain weights or histopathology, or morphometric measurements.

**The maternal LOAEL is 120 ppm based on reduced body weight gains, decreased food consumption, and increased reactivity to handling.**

**The maternal NOAEL is 50 ppm.**

**The developmental toxicity LOAEL is 50 ppm based on reduced survival early in lactation, reduced pup body weights and body weight gains during lactation, increased motor activity and decreased motor activity habituation.**

**The developmental toxicity NOAEL is 10 ppm.**

No clinical signs in the dams were suggestive of neurotoxicity. Pups showed increased activity and decreased habituation in motor activity and startle suggestive of stimulant effects, sometimes seen with organochlorines. In addition, the increased errors in the water maze in high dose pups on day 65 suggests a long term memory deficit.

Because of the high mortality rate in the high-dose litters, fewer than the required number of animals were available for neurobehavioral evaluations. But adequate numbers were available at the low- and mid-dose.

In conclusion, there is some evidence seen in this study for increased sensitivity of pups in relation to the effects seen at 50 ppm e.g., body weight differences, and survival, not seen in dams, and in effects seen at 50 ppm not measured in dams, increased motor activity and decreased habituation of motor activity. The apparent effect on long term memory in high dose rats is noteworthy as a potential cognitive effect, which is somewhat uncommon, although at a dose that caused considerable pup and maternal toxicity.

### B. STUDY DEFICIENCIES

Positive control data should be submitted for neurobehavioral assessment in young pups to validate the data in this study.

Reduced numbers of litters (6) were available at the high-dose for neurobehavioral evaluations.

Auditory startle latencies were not reported, although additional prepulse inhibition data were provided.

### C. CORE CLASSIFICATION

This study is classified as **Unacceptable/Guideline (870.6300 [83-6])** since laboratory validation studies of the neurobehavioral tests were not included, but it may be upgraded and found acceptable if this information is obtained.

## **APPENDIX**



**LINDANE**

SignOff Date:

DP Barcode:

HED DOC Number:

Toxicology Branch:

**Developmental Neurotoxicity - Rat [OPPTS 870.6300 (§83-6)]**

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