1/3/97

DATA EVALUATION REPORT

AZOXYSTROBIN

STUDY TYPE: SUBCHRONIC NEUROTOXICITY FEEDING - RAT (82-7)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

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MRID 1/31/96

DATA EVALUATION RECORD

STUDY TYPE: Subchronic Neurotoxicity Feeding - Rat
OPPTS 870.6200 [§82-7]

DP BARCODE: D218319 SUBMISSION CODE: S489692
P.C. CODE: 128810 TOX. CHEM. NO.: not assigned (new chemical)

TEST MATERIAL (PURITY): ICIA5504 (Azoxystrobin) (96.2% w/w)

SYNONYMS: None

CITATION: Rattray, N.J. (1994) ICIA5504: Subchronic Neurotoxicity Study in Rats. Zeneca Central Toxicology Laboratory, Cheshire, UK. Report No. CTL/p/4322 (study no. PRO964), July 8, 1994. MRID 43678138. Unpublished study.

SPONSOR: Zeneca, Inc., Agricultural Products, Wilmington, DE 19897

EXECUTIVE SUMMARY: In a subchronic neurotoxicity study (MRID 43678138), ICIA5504 (96.2% a.i.) was administered to 12 Alpk:APfSD rats/sex/dose in the diet at 0, 100, 500 or 2000 ppm for 13 weeks (average daily consumption of 0, 8.0, 38.5 or 161 mg/kg/day, males and 0, 9.1, 47.9 or 201.5 mg/kg/day, females). All animals were used for functional observational battery (FOB) and motor activity (MA) testing and 6 control and high dose animals/sex were perfused in situ and evaluated for microscopic neuropathology.

At 2000 ppm, mean body weights of males were statistically significantly decreased throughout the study (at week 13, 12.6% less than controls). Mean body weights of females were slightly decreased (at week 13, 5.1% less than controls; significant only at week 2). Cumulative body weight gains were 18% lower (males) and 10% lower (females). Food consumption was statistically significantly lower in males (5.4% to 15.4%) but not females. Food utilization in males at 2000 ppm was statistically significantly decreased during Weeks 1-4 (9.7%) and 1-13 (11.7%) and was non-significantly less in females during the same periods (11.8% and 14.4%, respectively). There were no consistent indications of treatment-related neurotoxicity (clinical signs, qualitative or quantitative neurobehavioral effects, brain weight/ dimensions, or gross/microscopic pathology). [Statistically significant decreases in landing foot splay in males (week 5, 19%, 16.4% and 24.1%, low to high dose; week 9, 18% at high dose), forelimb grip strength

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(males week 5, 14.3%, 14.3% and 19%, low to high dose and females week 14, 12.9%, high dose), hindlimb grip strength in males (week 5, 13.3%, 15.3% and 12.9%, low to high dose) and motor activity in females (21%, week 9) are noted but not considered treatment-related due to lack of dose-response, inconsistency of observations at different time points, variability of pretreatment values and/or small magnitude of response; see review for details]. **The systemic toxicity LOAEL is 2000 ppm (161 mg/kg/day), based on decreased body weight/weight gain and food utilization in both sexes (marginal in females). The NOAEL is 500 ppm (38.5 mg/kg/day).** A NOEL was not established due to the occurrence of gastric disturbances at all levels.

This study is classified as **Supplementary (upgradable)** and does not satisfy the guideline requirement for a subchronic oral neurotoxicity study (82-7) in rats. The study may be upgraded to Acceptable pending submission of (1) validation (positive control) studies demonstrating proficiency of the testing laboratory in performing neurobehavioral testing and (2) submission of a complete list of FOB parameters evaluated.

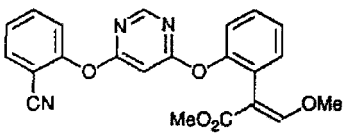
COMPLIANCE: Signed and dated GLP (July 6, 1994), Quality Assurance (July 5, 1994), Data Confidentiality (April 20, 1995), and Flagging (July 6, 1994) statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: ICIA5504

   Description: light brown solid
   Lot/Batch #: P49/D7534/46
   Purity: 96.2% w/w
   Stability of compound: stable for the duration of the study
   CAS #: 131860-33-8
   Structure:



2. Vehicle and/or positive control: none

3. Test animals

   Species: Rat
   Strain: Alpk:APfSD
   Age and weight at week 1: approximately 42 days; males, 168 to 228 g; females, 121 to 181 g.

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Source: Barriered Animal Breeding Unit at Zeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, UK.
Housing: 4 rats/suspended stainless steel cage with stainless steel mesh floor
Diet: CT1 diet supplied ad libitum (Special Diets Services Limited, Essex, UK)
Water: tap water supplied ad libitum
Environmental conditions:
Temperature: 19-23°C
Humidity: 40-70%
Air changes: 25-30 per hour
Photoperiod: 12 hrs light/12 hrs dark
Acclimation period: approximately 2 weeks

B. STUDY DESIGN

1. In-life dates

Start: between September 14 and 16, 1993; End: December 1993

2. Animal assignment

Animals were assigned randomly to the test groups in Table 1, below. A total of 6 single-sex replicate groups, each consisting of 1 cage per dose group, were randomly selected.

TABLE 1. Study design

Test Group	Conc. in Diet (ppm)	Mean Dose to Animals* (mg/kg/day)		Number of Animals	
		Male	Female	Male	Female
Control	0	N/A	N/A	12	12
Low	100	8.0	9.1	12	12
Mid	500	38.5	47.9	12	12
High	2000	161.0	201.5	12	12

Data taken from Table 1, page 15, MRID 43678138.
*Data taken from Appendix I, page 78-79, MRID 43678138.

3. Validation of test methods

Validation studies for FOB and motor activity were not provided.

4. Dose selection rationale

Dose levels were selected on the basis of a previous study conducted in this laboratory. Details were not provided.

5. Diet preparation and analysis

Diet was prepared by initially mixing with 3.1, 15.6, or 62.4 g in 1 kg of milled CT1 diet for concentrations of 100, 500, or 2000 ppm, respectively. This mixture was then mixed with 29 kg of CT1 diet in a TK Fielder Pharma Matrix Blender (model PMA100s). The diet was stored at ambient temperature.

Homogeneity was tested at the bottom, middle, and top of the low and high dose mixtures on September 8, 1993. The concentration of 0, 100, 500, and 2000 ppm diets were tested on September 8, 1993 and November 5, 1993. Also, data from a previous study were presented demonstrating that the ICIA5504 was stable in the diet mixtures.

Results - Homogeneity Analysis: The 100 ppm diet samples ranged from 89.8 to 104.5 ppm and 2000 ppm samples ranged from 1894 to 2191 ppm. The mean concentration and deviation of the 100 ppm samples at top, middle and bottom ranged from 92.4 to 101.5 ppm and -5.3 to 4.0%, respectively. The mean concentration and deviation of the 2000 ppm samples at top, middle and bottom ranged from 1952 to 2091 ppm and -2.4 to 4.6%, respectively.

Stability Analysis: 100 ppm ranged from 101.3 to 101.8 ppm, 500 ppm ranged from 490 to 495 ppm, and 2000 ppm ranged from 1845 to 1876 ppm. These data were generated in a previous study (PM0893) at ambient temperature for 56 days.

Concentration Analysis: In the Sept. 8 analysis, the 100 ppm treatment diet ranged from 89.8 to 104.5 ppm with a mean concentration of 98.1 ppm (98.1% of target); 500 ppm treatment diet ranged from 471 to 507 ppm with a mean concentration of 484 ppm (96.8% of target); and 2000 ppm treatment diet ranged from 1802 to 2191 ppm with a mean concentration of 1954 ppm (97.7% of target). The Nov. 5 analysis of 100, 500 and 2000 ppm diets gave concentrations that were 101.6%, 98.6% and 92.6% of target concentration.

6. Statistics

Body weights were analyzed by covariance. Weekly food consumption, food utilization, motor activity measurements, time to tail flick, landing foot splay,

and grip strength were analyzed by analysis of variance. Brain weight, brain length, brain width, and final body weight were analyzed by the analysis of covariance. Pairwise comparisons of treated groups to controls were made. The reviewer has no objection to the statistics employed.

C. METHODS

1. Observations

For signs of toxicity and mortality, animals were inspected daily by cageside checks, and weekly by physical examination outside the cage.

2. Body weight

Animals were weighed weekly, beginning at 1 week pretreatment.

3. Food consumption and compound intake

Animals were housed 4/cage. Food consumption for each animal was calculated weekly as g food/rat/day. Food utilization (body weight gain per 100 g food consumed) was determined by the study author (Table 4). Compound intake (mg/kg/day) values were calculated as time-weighted averages from the consumption and body weight gain data (Table 1).

4. Functional observational battery

Detailed clinical observations conducted outside of the cage and quantitative assessments of landing foot splay, sensory perception (tail flick test), and muscle weakness (forelimb and hindlimb grip strengths) were measured on Weeks -1, 5, 9, and 14. Clinical observations included, but were not limited to, the following: assessment of autonomic function (lacrimation, salivation, piloerection, exophthalmus, urination, defecation, pupillary function, ptosis); description, incidence and severity of any convulsions, tremors, abnormal motor function, abnormal behavior; reactivity to stimuli; changes in level of arousal; sensorimotor responses; and alterations in respiration. Some parameters usually included in FOB examinations, such as handling observations, were not specifically reported to have been evaluated, and the types of reactivity to stimuli that were evaluated were not indicated.

5. Motor activity

Locomotor activity was monitored by an automated activity recording apparatus (type and number of beams not specified). All animals were tested at Weeks -1, 5, 9, and 14. Each observation period was divided into ten scans of five-minute duration. Treatment groups were counter balanced across test times and across devices, and when the trials were repeated each animal was returned to the same activity monitor at approximately the same time of day. Motor activity was assessed in a separate room to minimize disturbances but the study report did not indicate whether animals were tested under dimmed light with white noise.

6. Sacrifice/necropsy/and neurohistopathology

At termination of the study 6 designated rats/sex/group were deeply anaesthetized with an intraperitoneal injection of barbiturate and killed by perfusion-fixation with modified Karnovsky's fixative. The tissues listed below were collected. Tissues from rats in the control and 2000 ppm groups and the brains from rats in the 100 and 500 ppm groups were processed and examined microscopically. The remaining 6 rats/sex/group were exsanguinated under terminal anesthesia with halothane. The same tissues as were removed from the perfused rats were collected and stored.

X	Brain	X	Spinal Cord	X	Peripheral nerves
X	Whole	X	Cervical	X	Sciatic nerve
	(sectioned	X	Lumbar	X	Sural nerve
	at 7 levels	X	Dorsal root ganglion	X	Tibial nerve
	for	X	Spinal roots		
	microscopic	X	cervical		Other
	examination)	X	lumbar	X	Gastrocnemius
				X	Abnormal tissues
				X	Gasserian ganglion

II. **RESULTS**

A. OBSERVATIONS

1. Toxicity

No clinical signs were considered related to the feeding of the ICIA5504.

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2. Mortality

No deaths occurred prior to the scheduled sacrifice.

B. BODY WEIGHT

Male rats in the 2000 ppm group had statistically significantly decreased body weights for Weeks 2-14, ranging from 7 to 12.6% (Table 2). On Week 2 the male rats in the 500 ppm group had statistically significantly decreased body weights of 3.0%, and nonstatistically significantly decreased body weights for Weeks 3-14 ranging from 2.3 to 4.1%. The females in the 2000 ppm group had decreased body weights ranging from 2.6 to 5.1% for Weeks 2-14. Cumulative body weight gains were also lower in both sexes (males 18% less than controls and females 10% less than controls; calculated by reviewer).

C. FOOD CONSUMPTION AND COMPOUND INTAKE

1. Food consumption

The males in the 500 and 2000 ppm groups had statistically significantly decreased food consumption (7-12% less than controls, Table 3). Since the 500 ppm males did not show decreased body weight gain or food utilization (see Table 4, below), the effect at that dose was not considered treatment-related. The males in the 100 ppm group and the females in the 100 and 500 ppm groups did not have an alteration in food consumption. The females in the 2000 ppm group for Weeks 1-8 had slightly decreased food consumption ranging from 1.5 to 5.7% lower. From Weeks 9-13, food consumption was higher than controls, ranging from 12.3 to 27.8%.

2. Compound consumption

The mean doses received by the animals are listed in Table 1.

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TABLE 2. Body weights of male and female rats fed ICIA5504 for 14 weeks

Study Week	Control	100 ppm	500 ppm	2000 ppm
Males				
Week 1	196.0 ± 14.2	192.8 ± 13.1	192.8 ± 13.2	192.0 ± 14.1
Week 2	248.8 ± 17.1	245.7 ± 16.3	241.4* ± 14.4[a] (3.0%)	231.3** ± 15.0 (-7.0%)
Week 3	298.1 ± 18.3	292.5 ± 20.1	290.7 ± 17.6 (2.5%)	274.4** ± 13.6 (-8.0%)
Week 4	333.8 ± 19.3	330.7 ± 22.0	326.2 ± 18.2 (2.3%)	304.7** ± 18.2 (-8.7%)
Week 5	365.2 ± 22.2	361.5 ± 24.5	352.8 ± 21.4 (3.4%)	330.9** ± 18.5 (-9.4%)
Week 6	393.0 ± 23.9	389.4 ± 30.0	380.4 ± 25.9 (3.2%)	356.7** ± 21.6 (-9.2%)
Week 7	420.1 ± 26.6	413.3 ± 31.2	405.2 ± 29.3 (3.6%)	376.8** ± 22.8 (-10.3%)
Week 8	443.4 ± 31.8	436.3 ± 34.3	425.9 ± 34.2 (4.0%)	395.1** ± 24.6 (-10.9%)
Week 9	462.6 ± 32.5	454.2 ± 35.7	444.3 ± 39.3 (4.0%)	410.2** ± 30.3 (-11.3%)
Week 10	478.8 ± 34.4	474.4 ± 37.4	461.8 ± 36.1 (3.6%)	421.9** ± 34.7 (-11.9%)
Week 11	494.8 ± 34.4	486.7 ± 38.1	475.9 ± 39.0 (3.8%)	434.3** ± 36.5 (-12.2%)
Week 12	507.8 ± 38.0	498.2 ± 41.2	488.7 ± 40.5 (3.8%)	446.1** ± 40.2 (-12.2%)
Week 13	517.0 ± 38.1	507.7 ± 42.2	496.0 ± 43.1 (4.1%)	451.8** ± 43.3 (-12.6%)
Week 14	526.0 ± 39.2	517.3 ± 42.9	505.7 ± 43.7 (3.9%)	460.8** ± 45.7 (-12.4%)
Females				
Week 1	159.0 ± 8.8	157.3 ± 13.2	159.8 ± 5.5	156.6 ± 10.6
Week 2	180.8 ± 11.6	177.1 ± 16.2	179.6 ± 5.5	172.3** ± 10.1 (-4.7%)
Week 3	195.3 ± 15.1	194.3 ± 18.3	196.3 ± 8.4	189.2 ± 12.6 (-3.1%)

TABLE 2. Continued

Study Week	Control	100 ppm	500 ppm	2000 ppm
Week 4	204.3 ± 14.3	207.6 ± 17.3	208.7 ± 11.1	198.8 ± 11.7 (-2.7%)
Week 5	218.6 ± 14.8	217.8 ± 17.3	220.9 ± 7.1	208.6 ± 15.4 (-4.6%)
Week 6	229.4 ± 15.5	224.9 ± 14.9	232.8 ± 11.3	219.6 ± 16.1 (-4.3%)
Week 7	234.0 ± 16.9	237.3 ± 16.3	237.7 ± 7.9	226.6 ± 18.0 (-3.2%)
Week 8	239.8 ± 16.7	242.8 ± 15.2	241.8 ± 8.2	231.8 ± 17.2 (-3.3%)
Week 9	246.8 ± 15.6	248.9 ± 15.2	250.9 ± 11.1	236.9 ± 19.3 (-4.0%)
Week 10	251.8 ± 15.1	251.3 ± 15.6	255.7 ± 12.0	242.8 ± 18.9 (-3.6%)
Week 11	252.3 ± 18.5	259.5 ± 17.5	258.0 ± 12.0	245.8 ± 17.6 (-2.6%)
Week 12	258.8 ± 14.8	263.6 ± 17.5	262.2 ± 12.6	250.0 ± 20.7 (-3.4%)
Week 13	260.5 ± 16.3	265.8 ± 15.8	265.9 ± 9.9	253.1 ± 20.3 (-2.8%)
Week 14	266.5 ± 15.9	265.2 ± 16.3	267.2 ± 11.9	252.9 ± 21.6 (-5.1%)

Data taken from Table 4, pages 38-39, MRID 43678138. For all groups, N = 12.
[a]Parenthesis: percent decrease of the treated group body weight as compared to the control body weight (calculated by the reviewer).
*P≤ 0.05
**P≤ 0.01

TABLE 3. Food consumption for male and female rats fed ICIA5504 for 14 weeks

Study Week	Control	100 ppm	500 ppm	2000 ppm
Males				
Week 1	27.9 ± 0.9	27.4 ± 0.6	26.2** ± 0.2 (-6.1%)[a]	23.6** ± 0.5 (-15.4%)
Week 2	30.2 ± 1.2	29.3 ± 1.5	28.5* ± 0.5 (-5.6%)	27.9** ± 0.2 (-7.6%)
Week 3	30.9 ± 1.3	30.3 ± 0.9	29.2* ± 0.7 (-5.5%)	28.5** ± 0.7 (-7.8%)
Week 4	30.3 ± 0.5	30.6 ± 1.1	28.4 ± 1.1 (-6.3%)	28.4 ± 1.0 (-6.3%)
Week 5	31.4 ± 1.4	31.7 ± 1.8	29.2* ± 1.0 (-7.0%)	29.2* ± 0.7 (-7.0%)
Week 6	31.3 ± 1.0	31.0 ± 1.4	29.3 ± 1.5 (-6.4%)	28.6* ± 0.7 (-8.6%)
Week 7	31.3 ± 0.7	30.7 ± 1.4	29.5 ± 2.2 (-5.8%)	28.4* ± 1.7 (-9.3%)
Week 8	30.7 ± 0.8	30.4 ± 1.1	28.5 ± 2.0 (-7.2%)	27.5* ± 1.0 (-10.4%)
Week 9	31.3 ± 1.1	31.3 ± 1.1	29.5* ± 1.2 (-5.8%)	29.6 ± 1.4 (-5.4%)
Week 10	31.1 ± 0.8	31.6 ± 0.6	29.6 ± 1.5 (-4.8%)	29.6 ± 1.1 (-4.8%)
Week 11	31.1 ± 1.4	31.2 ± 0.1	29.4* ± 1.7 (-5.5%)	29.3* ± 1.7 (-5.8%)
Week 12	30.3 ± 1.3	30.7 ± 0.3	28.4* ± 1.6 (-6.3%)	27.8* ± 0.1 (-8.3%)
Week 13	30.8 ± 1.3	30.7 ± 0.5	28.9* ± 0.8 (-6.2%)	28.9* ± 1.5 (-6.2%)

TABLE 3. Continued

Females				
Study Week	Control	100 ppm	500 ppm	2000 ppm
Week 1	20.0 ± 0.6	19.8 ± 1.2	19.9 ± 0.4	20.0 ± 3.6
Week 2	20.4 ± 0.6	20.2 ± 1.9	20.1 ± 0.2	21.2 ± 2.0 (+3.9%)
Week 3	20.2 ± 0.2	21.6 ± 3.7	20.5 ± 0.2	19.9 ± 1.3 (-1.5%)
Week 4	20.1 ± 0.9	20.1 ± 1.8	21.0 ± 0.5	19.7 ± 2.2 (-2.0%)
Week 5	21.1 ± 0.8	21.3 ± 1.0	22.0 ± 1.9	22.2 ± 2.9 (+5.2%)
Week 6	22.1 ± 0.2	21.4 ± 1.1	22.0 ± 2.1	21.2 ± 2.7 (-4.1%)
Week 7	20.9 ± 0.7	20.8 ± 0.7	21.4 ± 2.3	22.1 ± 3.3 (+5.7%)
Week 8	20.5 ± 1.2	20.4 ± 0.7	22.6 ± 3.2	20.9 ± 3.5 (+2.0%)
Week 9	21.1 ± 0.9	20.9 ± 1.7	23.8 ± 3.2	23.7 ± 6.8 (+12.3%)
Week 10	20.0 ± 1.0	21.2 ± 0.4	25.4 ± 8.1	23.7 ± 4.6 (+18.5%)
Week 11	20.3 ± 0.6	20.7 ± 0.8	22.5 ± 4.4	23.6 ± 6.1 (+16.3%)
Week 12	19.8 ± 0.8	20.0 ± 0.8	23.7 ± 2.5	25.3 ± 9.7 (+27.8%)
Week 13	20.4 ± 0.1	20.6 ± 1.1	22.3 ± 3.6	23.8 ± 7.7 (+16.7%)

Data taken from Table 5, pages 40-41, MRID 43678138. For all groups, N = 12.
[a]Parenthesis: percent decrease (-) or increase (+) of the treated group food consumption as compared to the control food consumption (calculated by the reviewer).
*P≤ 0.05
**P≤ 0.01

3. Food utilization

Food utilization for the males in the 2000 mg/kg group was statistically significantly decreased during Weeks 1-4 and 1-13 (Table 4). During Weeks 5-8 and 9-13, nonstatistically significant decreases were also present with percentages of 11.3 and 14.9%, respectively. The females in the 2000 ppm group had nonstatistically significantly decreases of 11.8, 0, 28.5, and 14.4% for the Weeks 1-4, 5-8, 9-13, and 1-13, respectively.

TABLE 4. Food utilization (g of growth/100 g food) for male and female rats fed ICIA5504 for 14 weeks

Study Week	Control	100 ppm	500 ppm	2000 ppm
Males				
Weeks 1-4	20.27 ± 0.3	20.49 ± 0.59	20.34 ± 1.66	18.31* ± 0.58 (-9.7%)
Weeks 5-8	11.19 ± 0.68	10.70 ± 0.96	11.13 ± 1.92	9.93 ± 1.35 (-11.3%)
Weeks 9-13	5.85 ± 0.27	5.81 ± 0.79	6.02 ± 0.14	4.98 ± 0.85 (-14.9%)
Weeks 1-13	11.84 ± 0.32	11.68 ± 0.69	11.91 ± 0.98	10.45** ± 0.86 (-11.7%)
Females				
Weeks 1-4	10.55 ± 0.34	10.57 0.99	10.72 ± 0.34	9.31 ± 1.77 (-11.8%)
Weeks 5-8	4.78 ± 0.47	5.33 ± 1.13	4.87 ± 0.14	4.78 ± 1.01 (0%)
Weeks 9-13	2.77 ± 0.38	2.26 ± 0.56	1.96 ± 0.07	1.98 ± 0.61 (-28.5%)
Weeks 1-13	5.76 ± 0.14	5.74 ± 0.38	5.35 ± 0.12	4.93 ± 1.12 (-14.4%)

Data taken from Table 6, pages 42-43, MRID 43678138. For all groups N = 12.
[a]Parenthesis: percent decrease of the treated group food utilization as compared to the control food utilization (calculated by the reviewer).
*P≤ 0.05
**P≤ 0.01

D. FUNCTIONAL OBSERVATIONAL BATTERY

The qualitative clinical observations are discussed above under "Clinical Signs".

Landing foot splay values for males are shown below in Table 5. Males in the 2000 ppm group had statistically significantly decreased landing foot splay at Weeks 5 and 9. Males in the 100 and 500 ppm groups had decreased landing foot splay at Weeks 5 (statistically significant) and 9 (nonstatistically significant). Due to the lack of clear dose response (eg. at week 5, decreases of 19% at 100 ppm, 16% at 500 ppm and 24% at 2000 ppm) and lack of sustained effect throughout the study, the decreased foot splay in males is not considered to be treatment-related. The females had no significant changes in the landing foot splay measurements.

TABLE 5. Landing foot splay (mm) for male rats fed ICIA5504 for 14 weeks

Study Week	Control	100 ppm	500 ppm	2000 ppm
Week -1	50.8 ± 8.9	48.8 ± 6.4 (-3.9%)[a]	45.6 ± 7.7 (-10.2%)	48.3 ± 5.6 (-4.9%)
Week 5	80.0 ± 15.5	64.8* ± 17.5 (-19.0%)	66.9* ± 12.8 (-16.4%)	60.7** ± 13.5 (-24.1%)
Week 9	74.0 ± 15.5	64.0 ± 15.1 (-13.5%)	69.9 ± 12.9 (-5.5%)	60.7* ± 10.8 (-18.0%)
Week 14	74.4 ± 18.9	67.3 ± 13.9 (-9.5%)	62.9 ± 13.8 (-15.5%)	62.3 ± 12.4 (-16.3%)

Data taken from Table 8, p. 48, MRID 43678138. For all groups, N = 12.
[a]Parenthesis: percent decrease of the treated group landing foot splay as compared to the control landing foot splay (calculated by the reviewer).
*P≤ 0.05
**P≤ 0.01

A small but statistically significant decrease in the forelimb grip strength (12.9% less than controls) was observed in the females from the 2000 ppm group on Week 14 (Table 6). For the males in all dose groups on Week 5, the forelimb (Table 6) and hindlimb grip (Table 7) strengths were statistically significantly decreased.

However, no dose response was evident in the males, nor was the effect present at other time points. It is also noted that in males, the 100 and 2000 ppm pretreatment values were 10-11% less than the controls, which may indicate slightly lower baseline values in the treatment groups. The reviewer agreed with the study author that the fore- and hind-limb grip strength reductions were probably not due to treatment because of the small magnitude of effect (<20%) and/or lack of dose-response and consistent observation throughout the study.

TABLE 6. Forelimb grip strength (g) for male and female rats fed ICIA5504 for 14 weeks

Study Week	Control	100 ppm	500 ppm	2000 ppm
Males				
Week -1	435 ± 97	392 ± 53 (-9.9%)[a]	421 ± 82 (-3.2%)	388 ± 84 (-10.8%)
Week 5	1308 ± 215	1121* ± 210 (-14.3%)	1121* ± 205 (-14.3%)	1060** ± 146 (-19.0%)
Week 9	1469 ± 217	1333 ± 242 (-9.3%)	1398 ± 270 (-4.8%)	1269 ± 242 (-13.6%)
Week 14	1531 ± 298	1573 ± 203	1506 ± 303	1513 ± 281
Females				
Week -1	446 ± 99	435 ± 59 (-2.5%)	417 ± 98 (-6.5%)	413 ± 53 (-7.4%)
Week 5	929 ± 163	969 ± 154	977 ± 252	942 ± 123
Week 9	1115 ± 216	1065 ± 111	1133 ± 263	1008 ± 201 (-9.6%)
Week 14	1192 ± 174	1198 ± 170	1275 ± 193	1038* ± 179 (-12.9%)

Data taken from Table 10A, p. 50, MRID 43678138. For all groups, N = 12.
[a]Parenthesis: percent decrease of the treated group forelimb grip strength as compared to the control forelimb grip strength (calculated by the reviewer).
*P≤ 0.05
**P≤ 0.01

TABLE 7. Hindlimb grip strength (g) for male and female rats fed ICIA5504 for 14 weeks

Study Week	Control	100 ppm	500 ppm	2000 ppm
Males				
Week -1	342 ± 65	300 ± 51 (-12.3%)[a]	321 ± 38 (-6.1%)	317 ± 69 (-7.3%)
Week 5	892 ± 103	773** ± 78 (-13.3%)	756** ± 76 (-15.3%)	777** ± 82 (-12.9%)
Week 9	1098 ± 211	979 ± 207 (-10.8%)	994 ± 214 (-9.5%)	935 ± 185 (-14.9%)
Week 14	1150 ± 145	1023 ± 155 (-11.0%)	1148 ± 184 (-0.2%)	1110 ± 188 (-3.5%)
Females				
Week -1	340 ± 58	379 ± 76 (+11.5%)	350 ± 74 (+2.9%)	352 ± 46 (+3.5%)
Week 5	765 ± 103	763 ± 116 (-0.3%)	692 ± 98 (-9.5%)	715 ± 109 (-6.5%)
Week 9	802 ± 165	810 ± 116	819 ± 107	785 ± 130
Week 14	783 ± 132	844 ± 217	769 ± 109	783 ± 141

Data taken from Table 10B, p. 51, MRID 43678138. For all groups, N = 12.
[a]Parenthesis: percent decrease (-) or increase (+) of the treated group hindlimb grip strength as compared to the control hindlimb grip strength (calculated by the reviewer).
**P≤ 0.01

E. MOTOR ACTIVITY

No statistically significant changes were noted for the males in any dose group. The females in the 2000 ppm group during Week 9 had a statistically significant decrease (21.4%) in motor activity for the overall session (1 to 50 minutes) (Table 8). For individual 5-minute intervals, activity tended to be slightly lower during the early portion of the study but was statistically significant only during the last two five-minute intervals. The reviewer agreed with the study author that this was probably not a treatment-related effect because it was only observed at one time point in one sex and was within the variability observed in the pretreatment group.

TABLE 8. Motor activity (overall session counts) for female rats fed ICIA5504 for 14 weeks

Study Week	Control	100 ppm	500 ppm	2000 ppm
Week -1	256.3 ± 126.8	190.9 ± 68.9 (-25%)[a]	307.8 ± 169.4 (+20%)	211.8 ± 125.6 (-18%)
Week 5	536.2 ± 128	508.6 ± 113.7	589.4 ± 112.6 (-10%)	469.6 ± 125.1 (-12%)
Week 9	588.2 ± 120.4	515.3 ± 118.8 (-10%)	592.8 ± 140.0	462.5* ± 187.5 (-21.4%)
Week 14	573.9 ± 104.6	589.8 ± 115.5	635.1 ± 133.3 (+11%)	542.8 ± 189.4 (-5%)

Data taken from Table 11, p. 52-59, MRID 43678138. For all groups, N = 12.
[a]Parenthesis: percent decrease (-) or increase (+) of the treated group motor activity as compared to the control motor activity (calculated by the reviewer).
*P≤ 0.05

F. SACRIFICE/NECROPSY/NEUROHISTOPATHOLOGY

1. Brain measurement

No treatment-related effects were observed for the brain weight, length, or width.

2. Gross pathology

No treatment-related effects were observed.

3. Microscopic pathology

No treatment-related effects were observed. Findings of minimal neuronal cell necrosis in the hippocampal formation/pyriform cortex and minimal sciatic nerve fiber degeneration were observed in controls and at high dose with no treatment-related increase in incidence and were considered to represent background incidence.

III. DISCUSSION

In this study, decreased body weight and body weight gain were observed in both sexes at 2000 ppm (HDT). In females, the decrease was marginal and not statistically significant and may indicate a threshold effect on body weight. Food utilization values were lower in males (significant, weeks 1-4 and weeks 1-13) and in females, but not significantly. Although numerous statistically significant effects on several quantitative FOB parameters were noted, the reviewer

agreed with the study author that the effects were most probably incidental rather than treatment-related. As discussed in the Results section, the reported decreases in forelimb and hindlimb grip strength, landing foot splay of the males in all dose groups during Week 5 and motor activity in high dose females at week 14 either did not show a clear dose-response, were not consistently observed throughout the study, were of a small magnitude or were within variability of the pretreatment controls. These effects were not observed in the acute neurotoxicity study (MRID 43678134), in which landing foot splay for high dose females at day 8 was increased rather than decreased, but was not considered to be clearly treatment-related due to lack of a dose-response. It is also noted that no treatment-related clinical signs were reported in the rat combined chronic toxicity/carcinogenicity feeding study (MRID 43678139) at doses up to 1500 ppm (117.1 mg/kg/day in females and 108.6 mg/kg/day in males; reduced during second year in males to 750 ppm or 34 mg/kg/day).

Based on decreased body weight/body weight gain and food efficiency in both sexes, the LOEL is 2000 ppm (161 mg/kg/day) and the NOEL is 500 ppm (38.5 mg/kg/day).

STUDY DEFICIENCIES

1. Minor

On page 65, the analytical percentage of the ICIA5504 was presented to be 96.2% (w/w). This was obtained on March 30, 1992. On page 66, four dates were given on which the stability of the ICIA5504 was confirmed. However, no percentages were recorded. These percentages should have been presented.

The study protocol, protocol deviations, protocol amendments should be included.

2. Major

FOB and motor activity validation data were not provided.

The FOB data were not presented in the usual format (for each testing session and dose group, listing each parameter evaluated with indication of how many animals were affected), but rather was presented only for positive findings. Because of this presentation and because the list of observations

was apparently not complete, it could not be determined whether certain parameters usually included in an FOB were evaluated. For example, the report stated that stimuli response were evaluated but did not indicate what types were evaluated. The study report did not indicate whether righting reflex, corneal/pinna reflexes or muscle tone were evaluated. Evaluation of response to handling is usually performed but there was no indication in the report as to whether this was done.

Classification: Supplementary - upgradable; Pending on the submission of the following information: (1) FOB and motor activity validation data; (2) clarification of FOB parameters evaluated (eg. which types of stimuli responses were evaluated, whether handling parameters such as ease of/responses to handling, righting, corneal and pinna reflexes, muscle tone were evaluated).

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