1-3-97

ICIA5504 Developmental Study OPPTS 870.3700 (§83-3(b))

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DATA EVALUATION RECORD

STUDY TYPE: Prenatal Developmental Study - Rabbit; OPPTS 870.3700 [§83-3b

DP BARCODE: D218319 SUBMISSION CODE: S489692
P.C. CODE: 128810 TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): ICIA5504

SYNONYMS: Azoxystrobin

CITATION: Moxon, M.E. 1995. ICIA5504: Assessment of Teratogenicity in the Rabbit. Zeneca Central Toxicology Laboratory. Report No. CTL/P/4757 Oct. 26, 1995. MRID 44058701. Unpublished.

SPONSOR: Zeneca Inc., Wilmington, DE

EXECUTIVE SUMMARY:

In a developmental toxicity study (MRID 44058701) ICIA5504, 96.2% a.i. was administered to 21 New Zealand White rabbits/dose by gavage at dose levels of 0, 50, 150 or 500 mg/kg/day (in 1 ml corn oil/kg body weight) from days eight through 20 of gestation.

At 150 mg/kg/d and 500 mg/kg/d significant ($p<0.01$) but transient reductions (-33%, -51%, resp.) in food consumption were observed during the first three days of dosing. At 500 mg/kg/d, decreased body weight gain (-45%) was observed during the dosing period. **The maternal LOEL is 500 mg/kg/day, based on decreased body weight gain. The maternal NOEL is 150 mg/kg/day.**

In the conceptus, no treatment-related adverse effects were observed. **The developmental LOEL is >500 mg/kg/day. The developmental NOEL is 500 mg/kg/d.**

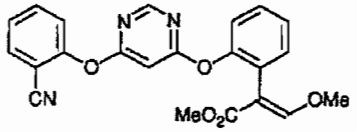
The developmental toxicity study in the rabbit is classified acceptable and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; §83-3 b) in the rabbit.

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

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: ICIA5504
   Description: light brown solid
   Lot/Batch #: YO6654/014
   Purity: 96.2 % a.i.
   CAS #: None



2. Vehicle: corn oil
   Description: None provided
   Lot/Batch #: Y00790/004
   Purity: 100% a.i.

3. Test animals: Species: rabbit
   Strain: New Zealand white
   Age at mating: not specified
   Weight at mating: not specified
   Source: Interfauna UK Ltd., Huntingdon, Cambridgeshire, UK
   Housing: individually in mobile rabbit units
   Diet: SDS Standard Rabbit Diet ad libitum
   Water: filter-sterilized tap ad libitum (initial supply in bowl in cage until satisfactory food intake observed)
   Environmental conditions:
   - Temperature: 59 - 66°F
   - Humidity: 40 - 70%
   - Air changes: 25 - 30/hr
   - Photoperiod: 12 hrs dark/12 hrs light

   Acclimation period none specified. Animals arrived at the test sight after mating, and dosing began on gd 8.

B. PROCEDURES AND STUDY DESIGN

1. In life dates - not specified

2. Mating: method not specified. Animals were mated at the supplier, and arrived at testing laboratory thereafter.

3. Animal Assignment: Animals were assigned to dose groups as indicated in Table 1. Assignment was random.

TABLE 1 Animal Assignment

Test Group	Dose (mg/kg/day)	Number of Females
Control	0	21
Low (LDT)	50	21
Mid (MDT)	150	21
High (HDT)	500	21

4. Dose selection rationale: Dose selection was based upon preliminary range-finding studies (MRIDs 44058702, 44058703, 44028705, 44028706, 44058707, 44073202)

5. Dosage preparation and analysis ICIA5504 was administered in corn oil and the concentrations was adjusted to give a constant volume of 1 ml/kg bodyweight at each dose level. Fresh aliquots were prepared each day, and stored at room temperature.

   Test substance formulations were prepared daily by mixing appropriate amounts of test substance with corn oil and were stored at room temperature. The results of concentration and homogeneity analyses are as follows:

   Results - Homogeneity Analysis: Within 5% of means.

   Stability Analysis: confirmed at room temperature for 29 days

   Concentration Analysis: within 3% of nominal.

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

6. Dosage administration: All doses were administered once daily by gavage, on gestation days eight through 20, in a volume of 1 ml/kg of body weight/day. Dosing was adjusted daily according to body weight.

C. OBSERVATIONS

1. Maternal Observations and Evaluations - The animals were checked for mortality or clinical signs at least twice daily. Body weights were recorded upon arrival on gestation days 4, 8 - 20, 23, 26, and 30. Food consumption data were obtained on gestation days 8, 11, 14, 17, 20, 23 and 26. Dams were sacrificed on day 30 of

805

gestation. Examinations at sacrifice consisted of: uterine weight, number and positions of implantations; corpora lutea in each ovary; individual fetal weights, percent preimplantation loss, percent post-implantation loss.

2. Fetal Evaluations - The fetuses were first examined externally including oral cavity. An internal examination followed which included sex determination and observation for visceral abnormalities. They were then eviscerated and fixed in 70% industrial methylated spirits. After approx. 24 hrs the brain was examined for macroscopic abnormalities and the carcasses stained with Alizarin Red S for skeletal evaluation.

D. DATA ANALYSIS

1. Statistical analyses: performed according to standard techniques.

2. Indices: The following indices were calculated from cesarean section records of animals in the study: Preimplantation loss and post-implantation loss were calculated as follows:

$$\%\ \text{preimplantation} = \frac{(\#\ \text{corpora lutea} - \#\ \text{implantations})}{(\#\ \text{corpora lutea})} * 100$$

$$\%\ \text{postimplantation} = \frac{(\#\ \text{implantations} - \#\ \text{live fetuses})}{(\#\ \text{implantations})} * 100$$

3. Historical control data: Historical control data were provided to allow comparison with concurrent controls.

II. RESULTS

A. MATERNAL TOXICITY

1. Mortality and Clinical Observations: The occurrence of intercurrent deaths was 1, 2, 1, and 2 in the control, 50, 150 and 500 mg/kg/d groups, respectively. Animals died or were sacrificed in moribund condition; the causes (including severe body weight loss, and intususception of the colon) were not related to treatment. Clinical signs included diarrhea and/or staining in genital area in 1, 7, 15, and 18 animals in the controls through high-dose group, beginning generally around gd 9. No other treatment related signs were observed.

2. Body Weight - Body weight gain data are summarized in Table 2 and Figure 1 (taken from the report), and as

follows: Maternal body weights were statistically lower than controls ($p \leq 0.01$) at 500 mg/kg/d throughout the dosing period, and at 50 and 150 mg/kg/d ($p \leq 0.05$) on gd 9, 10, and 11. However, these reductions in body weight were low (3 - 6% at 500 mg/kg/d, 1 - 2% at the lower dose levels). Body weight gains (table 2) were lower (-45%) than controls at the 500 mg/kg/d dose level during the dosing period. Body weight gains were 35 - 46% lower than controls in all dose levels compared with controls during the post-dosing period, but these reductions did not occur in a dose related manner. It should be noted that control mean body weight gains were low in the predosing period compared with the treatment groups (table 2) and that the data calculations reflected in table 2 are based on means adjusted for initial weight differences.

TABLE 2 Maternal Body Weight Gain (g)[a] (includes intercurrent deaths)

Interval	Dose in mg/kg/day (# of Dams)			
	Control (N)	50 (N)	150 (N)	500 (N)
Pretreatment: Days 4 - 8	45(18)	91(19)	84(18)	114(19)
Treatment[b]: Days 9 - 20	233(18)	282(19)	310(18)	129(19)
Posttreatment[b]: Days 23- 30	368(18)	200(19)	228(18)	241(19)

a Data extracted from report no. CTL/P/4757 and table 7 (p 37-39) and calculated by reviewer

b based on adjusted weights

3. Food Consumption - During the first three days of the dosing period, food consumption was lower than controls in all three treatment groups (-14%, -33% -51%, resp.). The decrease observed at 50 mg/kg/d was not statistically significant, while the reductions at 150 and 500 mg/kg/d were ($p \leq 0.01$). These decreases were transient.

4. Gross Pathology - No dose-related increases in lesions were observed.

5. Cesarean Section Data - As summarized in Table 3, no dose-related adverse observations were made at the time of test animal sacrifice.

TABLE 3 Cesarean Section Observations[a]

Observation	Dose (mg/kg/day)			
	0	50	150	500
# Animals Assigned (Mated)	20	20	19	20
# Animals Pregnant Pregnancy Rate (%)	18 (90)	19 (95)	18 (95)	19 (95)
# Nonpregnant	2	1	1	1
Maternal Wastage # Died # Aborted # Premature Delivery	 2 0 0	 1 0 0	 2 0 0	 1 0 0
Corpora Lutea/Dam	11.3	11.2	11.6	12.5
Implantations/Dam	10.11	9.32	10.56	10.47
Total # Litters	18	19	18	19
Live Fetuses/Dam	9.06	8.37	9.83	9.47
Resorptions/Dam Early % Late % Litters Affected Early Late	 5.0 5.1 5 8	 5.2 3.9 6 6	 2.3 4.6 3 7	 3.9 6.1 5 7
Mean Fetal Weight (g) Mean Litter Weight (g)	43.4 388	44.5 364	42.2 411	42.0 387
Sex Ratio (% Male)	45.4	47.5	47.4	46.2
Mean Preimplantation Loss (%) Implants affected Litters affected	 10.2 61.1	 16.8 63.2	 8.7 61.1	 15.3 68.1
Mean Postimplantation Loss (%) Implants affected Litters affected	 10.1 66.7	 9.1 52.6	 6.9 50.0	 10.1 52.6

a Data extracted from Report No. CTL/P/4757 and Table No. 10
* $p \leq 0.05$
** $p \leq 0.01$

B. DEVELOPMENTAL TOXICITY

1. External/Visceral - No dose-related or statistically significant increases in external anomalies were observed. Similarly, there was an absence of dose-related or statistically significant increases in visceral anomalies.

2. Skeletal Examination - Although skeletal anomalies, mainly variations were common in all groups, including concurrent controls, there were no statistically significant increases, nor were there any dose-response trends observed. The test substance had no adverse effect on skeletal development. There were no significant differences in the Manus and Pes scores.

TABLE 4a. External/Visceral Examinations[a]

Observations+	Dose (mg/kg/day)			
	0	LDT	MDT	HDT
#Fetuses(litters) examined	163(18)	159(19)	177(18)	180(19)
#Fetuses(litters) affected	2(2)[b]	3(3)	0(0)	1(1)
Aorta enlarged, pulmonary artery reduced	1(1)	2(2)	0(0)	0(0)
Meningocoele, integration of interparietal and occipital		1(1)		
Spina Bifida mengocoele				1(1)

\+ Some observations may be grouped together
a Data extracted from Report No. CTL/P/4757, Table No. 11.
b Fetal (litter) incidence

TABLE 4b Skeletal Examinations[a]

Observations+	Dose (mg/kg/day)			
	0	50	150	500
#Fetuses(litters) examined	154(17)	159(19)	154(16)	167(17)
Major Skeletal Defects #Fetuses(litters) affected	3(3)[b]	2(2)	1(1)	0(0)
Minor Skeletal Defects #Fetuses(litters) affected	64(17)	79(18)	71(15)	67(17)
Skeletal Variants #Fetuses(litters) affected	131(17)	135(19)	136(16)	148(17)
11th-12th left thoracic arches fused				1(1)
11th thoracic to 3 3rd lumbar arches misaligned, etc.			1(1)	

\+ Some observations may be grouped together
a Data extracted from Report No. CTL/P/4757, Table No. 11.
b Fetal (litter) incidence

III. DISCUSSION

A. INVESTIGATORS' CONCLUSIONS

Administration of ICIA5504 resulted in maternal effects that were dose-related. At 500 mg/kg/d reduced body weight and food intake were observed during the dosing period, along with signs of diarrhea and/or staining of the genital area. Similar effects were seen at 150 mg/kg/d, although less severe for a shorter duration. At 50 mg/kg/d, there was also a transient decrease in body weight, although no change in food consumption. Clinical signs were minimal at this level, and not considered to represent an adverse effect of treatment. The maternal LOEL was therefore 150 mg/kg/d. The NOEL was 50 mg/kg/d.

There was no evidence of adverse effects on the conceptus at any dose level. Therefore, **the developmental LOEL was >500 mg/kg/d. The NOEL was 500 mg/kg/d.**

B. REVIEWER'S DISCUSSION

1. MATERNAL TOXICITY: While there was a dose-related and statistically significant decrease in body weight during treatment, the actual decrease was small, 6% or less. Also, body weight gain was greater than control in all treatment groups, at all stages of the study, with the exception of the 500 mg/kg/d group, which showed a 45% decrease vs. controls. Food consumption was statistically significantly less than controls in the mid and high dose groups during the initial three days of dosing only. No significnat gross pathological changes were seen, and Cesarean section data showed no adverse effects on related parameters. Thus we conclude that maternal toxicity is not significant at 150 mg/kg/d and that **the LOEL for this study is 500 mg/kg/d, making the NOEL 150 mg/kg/d.**
2. DEVELOPMENTAL TOXICITY: in this study ICIA5504 was innocuous regarding the conceptus at all dose levels. Therefore we concur with the investigator's conclusions.

C. STUDY DEFICIENCIES No major deficiencies were noted.

ATTACHMENTS

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Azoxystrobin

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