1/3/97

DATA EVALUATION REPORT

AZOXYSTROBIN

STUDY TYPE: CARCINOGENICITY [FEEDING] - MOUSE (83-2(b))

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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Toxicology Branch I (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Carcinogenicity [feeding] - Mouse
OPPTS 870.3200 [§83-2(b)]

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

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

SYNONYMS: methyl (E)-2-{2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate

CITATION: Moxon, M. (1995) ICIA5504: Two year feeding study in mice. Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Laboratory report number CTL/P/ 4483, Study number PM0893, April 19, 1995. MRID 43678141. Unpublished.

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

EXECUTIVE SUMMARY: In a carcinogenicity toxicity study (MRID 43678141), ICIA5504 (azoxystrobin, 96.2% a.i., Lot# P49/D7534/46) was administered in the feed to 55 C57BL/10JfAP/Alpk mice/sex/dose at concentrations of 0, 50, 300, or 2000 ppm (males: 0, 6.2, 37.5, or 272.4 mg/kg/day; females: 0, 8.5, 51.3, or 363.3 mg/kg/day) for 104 weeks.

No effects were observed on mortality, clinical signs, hematology, or gross or microscopic pathology. Mean body weights of the 2000 ppm-group males were significantly ($p \leq 0.01$) lower (5-12%) than the weights of controls beginning at study week 2 and continuing until the end of the study. Females receiving 2000 ppm had significantly ($p \leq 0.01$; week 8 only $p \leq 0.05$) lower mean body weights (2-7%) as compared to controls beginning at study week 3 and continuing until the end of the study. Although food consumption was similar between treated and control groups, overall food utilization was significantly ($p \leq 0.01$) less in the high-dose males and females for weeks 1-12 (the only interval for which food utilization was calculated). **The systemic toxicity LOEL is 2000 ppm, based on reduced body weights of males and females (272.4 and 363.3 mg/kg/day, respectively). The systemic toxicity NOEL is 300 ppm (37.5 and 51.3 mg/kg/day).**

March 1996

There was no evidence of carcinogenicity at the dose levels tested. Dosing was considered adequate based on reduced body weights at the high dose in both males and females.

This study is acceptable and satisfies the guideline requirement for a carcinogenicity study (83-2(b)) in mice.

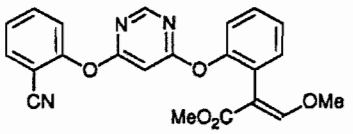
COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

## I. MATERIALS AND METHODS

### A. MATERIALS

1. Test material: ICIA5504

   Description: light brown solid
   Lot/Batch #: P49/D7534/46
   Purity: 96.2% a.i.
   Stability of compound: stable for duration of study
   CAS #: none




2. Vehicle and/or positive control

   CT1 diet was used as carrier and negative control. No positive control was used in this study.

3. Test animals

   Species: mouse
   Strain: C57BL/10JfAP/Alpk
   Age and weight at study initiation: 5-6 weeks; males: 21.6 g; females: 17.8 g
   Source: Barriered Animal Breeding Unit (BABU), Alderley Park, Macclesfield, Cheshire, UK
   Housing: Animals were housed 5/cage/sex in wire-mesh stainless steel cages.
   Diet: CT1 diet supplied by Special Diets Services Limited, Stepfield, Witham, Essex, UK was available ad libitum.
   Water: Filtered tap water was available ad libitum from an automatic watering system.
   Environmental conditions:
      Temperature: 16-29°C
      Humidity: 26-77%
      Air changes: 15/hour
      Photoperiod: 12-hour light/dark
   Acclimation period: 1 week

B. STUDY DESIGN

1. In life dates

Start: May 1992; end: May 1994

2. Animal assignment

The study was divided into 22 replicates (randomized blocks) of four cages each. Each cage in the replicate was given a group number by a shuffle card system. Animals were assigned to groups randomly. Numbered cards, indicating a study group, were picked out of a "hat" and simultaneously a mouse was picked out of the cage at random. The mouse was then allocated to the appropriate group number after it had been ear punched with its experimental number. This was repeated until every cage contained 5 mice. Males and females were allocated separately and any animals at the extremes of weight range or that appeared unhealthy were excluded. Ten males and ten females not selected for the study were used as microbiological sentinels and subjected to the same environment as the study animals; they were fed either control diet or diet containing 2000 ppm ICIA5504. Animal assignment is given in Table 1.

TABLE 1: Study design

| Test Group | Conc. in Diet (ppm) | Mean Dose Received (mg/kg/day) | | Microbiological Sentinels (N) | | Main Study 2 years (N) | |
|---|---|---|---|---|---|---|---|
| | | Male | Female | Male | Female | Male | Female |
| Control | 0 | 0 | 0 | 5 | 5 | 55 | 55 |
| Low (LDT) | 50 | 6.2 | 8.5 | 0 | 0 | 55 | 55 |
| Mid (MDT) | 300 | 37.5 | 51.3 | 0 | 0 | 55 | 55 |
| High (HDT) | 2000 | 272.4 | 363.3 | 5 | 5 | 55 | 55 |

Data taken from pp. 15, 18, 268, and 269, MRID 43678141.

3. Dose Selection

Dietary levels for this study were selected on the basis of results from a 90-day feeding study conducted in the C57BL/10JfAP/Alpk mouse by the performing laboratory. No further details were available with the main study.

4. Diet preparation and analysis

Experimental diets were prepared in 40 kg batches as needed. A premix was prepared by mixing the appropriate amount of test substance with 1 kg of CT1 milled diet with an automatic mortar and pestle for 15 minutes. The premix was added to 39 kg of CT1 diet and mixed in a Pharma Matrix Blender Model PMA 150S (T. K. Fielder) for 2 minutes. The amount of test substance added was based on 96.2% purity. Control diet was similarly prepared with the exclusion of test substance. The prepared diets were stored at room temperature. Samples from all dietary levels from each batch were analyzed for test substance concentration. Homogeneity and stability of the 50- and 2000-ppm diets were tested.

Results -
Homogeneity Analysis: Samples from the top, middle, and bottom ranged from -5.3 to 7.1% of the overall measured concentration in the 50 ppm diet and -2.0 to 1.9% in the 2000 ppm diet.

Stability Analysis: Test substance concentrations after 56 days were 104.3% and 92.8% of the initial measured concentrations in the 50- and 2000-ppm diets, respectively. This interval exceeded the period of use.

Concentration Analysis: The measured test substance concentration for each diet preparation was within 10% of nominal with the exception of one 2000 ppm diet that was 117% of nominal. The overall mean achieved concentrations were within 5% of nominal.

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dietary levels was acceptable.

5. Animals received fresh diet as required.

6. Statistics

Males and females were considered separately in all statistical analyses. Body weights were analyzed by analysis of covariance based on week 1 body weights; feed consumption, feed utilization, and hematology were analyzed by analysis of variance. Organ weights were analyzed by analysis of variance and analysis of covariance based on final body weight. Statistical

differences between treated and control groups were determined by the Student's t-test. Mortality data were analyzed by the logrank test and Kaplan-Meier survival estimates were calculated for each test group.

Tumor incidence data in control and treated groups were analyzed using Fisher's Exact Test and dose-related trends by the Cochran-Armitage Test.

C. METHODS

1. Observations

All mice were observed daily for changes in clinical condition and behavior. A detailed examination of each animal was performed at the same time it was weighed.

2. Body weight

Initial body weights were recorded immediately prior to first feeding the experimental diets (week 1). Body weights of all mice were then recorded weekly for the first twelve weeks (weeks 2-13), every two weeks thereafter, and at termination.

3. Food consumption and compound intake

Food consumption for each cage of mice was calculated each week for the first twelve weeks and every fourth week thereafter. Food utilization per cage was calculated as the g body weight gain by the mice in a cage per 100 g food eaten. The dose of test compound was based on nominal dietary levels and calculated in terms of mg ICIA5504/kg body weight/day using the formula: dose = (dietary conc. x cage food consumption)/cage mean body weight at middle of week.

4. Ophthalmoscopic examination

Ophthalmoscopic examinations are not required in Subdivision F Guidelines and were not performed.

5. Blood was collected for hematology from the tail veins of 11 males and 11 females per group during weeks 53 and 79; differential white counts and examination of red cell morphology were performed on blood smears from the control and 2000 ppm groups. At scheduled sacrifice, blood was collected by cardiac puncture from all surviving mice and the CHECKED (X) parameters were examined.

a. Hematology

| | | | |
|---|---|---|---|
| X | | X | |
| X | Hematocrit (HCT) | X | Leukocyte differential |
| X | Hemoglobin (HGB) | X | count* |
| X | Leukocyte count (WBC) | X | Mean corpuscular HGB (MCH) |
| X | Erythrocyte count (RBC) | X | Mean corpusc. HGB |
| X | Platelet count | X | conc.(MCHC) |
| | Blood clotting measurements | | Mean corpusc. volume (MCV) |
| | (Thromboplastin time) | | Reticulocyte count[1] |
| | (Thromboplastin time) | | |
| | (Clotting time) | | |
| | (Prothrombin time) | | |

*Minimum required for carcinogenicity studies (only on Cont. and HDT unless effects are observed based on Subdivision F Guidelines).
[1]Performed only on animals showing anemia.

b. Clinical chemistry

Clinical chemistry is not required for carcinogenicity studies based on Subdivision F Guidelines and was not performed in this study.

6. Urinalysis

Urinalysis is not required for carcinogenicity studies based on Subdivision F Guidelines and was not performed in this study.

7. Sacrifice and pathology

Mice requiring euthanasia during the study as well as those terminated at the end of the study were anesthetized with halothane Ph. Eur. (FLUOTHANE, Zeneca Pharmaceuticals) and killed by exsanguination. All animals were subjected to gross pathological examination and the CHECKED (X) tissues were collected and examined for histological lesions. For animals killed at terminal sacrifice, a bone marrow smear was made but not examined. The (XX) organs, in addition, were weighed.



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| X | DIGESTIVE SYSTEM | X | CARDIOVASC/HEMAT | X | NEUROLOGIC |
|---|---|---|---|---|---|
| | Tongue | X | Aorta* | XX | Brain* |
| X | Salivary glands* | X | Heart* | X | Periph. nerve* |
| X | Esophagus* | X | Bone marrow* | X | Spinal cord (3 levels)* |
| X | Stomach* | X | Lymph nodes* | | |
| X | Duodenum* | X | Spleen* | X | Pituitary* |
| X | Jejunum* | X | Thymus* | X | Eyes (optic n.)* |
| X | Ileum* | | | | |
| X | Cecum* | | UROGENITAL | | GLANDULAR |
| X | Colon* | XX | Kidneys*+ | XX | Adrenal gland* |
| X | Rectum* | X | Urinary bladder* | X | Lacrimal gland (Harderian) |
| XX | Liver*+ | XX | Testes*+ | | |
| X | Gall bladder* | X | Epididymides | X | Mammary gland* |
| X | Pancreas* | X | Prostate | X | Parathyroids* |
| X | Oral cavity | X | Seminal vesicle | X | Thyroids* |
| | | X | Ovaries | X | Preputial gland |
| | RESPIRATORY | X | Uterus* | | |
| X | Trachea* | X | Cervix | | OTHER |
| X | Lung* | | | X | Bone* (femur and sternum) |
| X | Nasal passages | | | | |
| | Pharynx | | | X | Skeletal muscle* |
| | Larynx | | | X | Skin* |
| | | | | X | All gross lesions and masses* |

* Required for carcinogenicity studies based on Subdivision F Guidelines.
+ Organ weight required in carcinogenicity studies.

## II. RESULTS

### A. OBSERVATIONS

#### 1. Toxicity

No clinical signs of toxicity were associated with dietary intake of ICIA5504. Common observations in males and females generally recorded early in the study, and probably a result of group housing, included generalized hair loss, tail damage, reduced number of whiskers, and torn ears. Later in the study observations such as malocclusion, abnormal respiratory noise or irregular breathing, distended abdomen, sores, subdued/hunched posture, discharge from eye, and greying of the coat are typical of aging mice.

2. Mortality

Dietary intake of ICIA5504 did not affect mortality of either male or female mice. At the end of the study (week 104) survival rates in the control, 50, 300, and 2000 ppm groups were 58, 61, 60, and 63%, respectively for males and 47, 38, 45, and 56%, respectively for females.

B. BODY WEIGHT

Body weights of males and females at selected times throughout the study are given in Table 2. Mean body weights of the 2000 ppm-group males were significantly ($p \leq 0.01$) lower (5-12%) than the controls beginning at study week 2 and continuing until the end of the study at week 105. Final body weights of the high-dose male group were 94% of controls. The 300 ppm-group males also had significantly ($p \leq 0.05$) lower mean body weights than the controls at study weeks 2, 3, 35, and 61-83. However, recovery was evident in the mid-dose males with final body weights 101% of the control group. No differences in body weights were observed for males given 50 ppm as compared with controls.

Females receiving 2000 ppm had significantly ($p \leq 0.01$; week 8 only $p \leq 0.05$) lower (2-7%) mean body weights as compared with controls beginning at study week 3 and continuing until the end of the study at week 105. Final body weights of the high-dose females were 93% of the control value. Body weights were occasionally greater ($p \leq 0.05$) than the controls for females in the 300 ppm (weeks 95, 97, 101, and 103) and 50 ppm (weeks 29, 33, 93, and 95) groups.

TABLE 2: Body weights of mice given ICIA5504 in the diet for 2 years (g)

| Week of Study | 0 ppm | 50 ppm | 300 ppm | 2000 ppm |
|---|---|---|---|---|
| | Males | | | |
| 1 | 21.6 ± 1.6[a] | 21.6 ± 1.5 | 21.5 ± 1.4 | 21.5 ± 1.5 |
| 2 | 23.1 ± 1.7 | 23.0 ± 1.8 | 22.7 ± 1.7* | 22.0 ± 1.7** |
| 4 | 25.2 ± 1.9 | 25.3 ± 1.7 | 24.9 ± 1.7 | 23.7 ± 2.0** |
| 8 | 28.1 ± 2.1 | 28.3 ± 2.0 | 27.8 ± 1.7 | 26.7 ± 2.2** |
| 12 | 29.9 ± 2.5 | 30.1 ± 2.4 | 29.4 ± 1.8 | 28.1 ± 2.3** |
| 25 | 32.9 ± 3.1 | 33.3 ± 2.9 | 32.3 ± 2.1 | 30.5 ± 2.1** |
| 51 | 37.9 ± 4.2 | 38.3 ± 4.0 | 37.0 ± 3.3 | 33.6 ± 2.6** |
| 75 | 38.3 ± 3.9 | 39.0 ± 4.2 | 37.1 ± 3.2* | 33.6 ± 2.4** |
| 105 | 34.2 ± 2.7 | 34.4 ± 2.6 | 34.6 ± 3.3 | 32.1 ± 2.4** |
| Wt gain: wks 0 - 12[b] | 8.3 | 8.5 | 7.9 | 6.6 |
| Overall weight gain | 12.6 | 12.8 | 13.1 | 10.6 |
| | Females | | | |
| 1 | 17.8 ± 1.1 | 18.0 ± 1.1 | 17.6 ± 1.3 | 17.8 ± 1.1 |
| 2 | 18.7 ± 1.1 | 19.0 ± 1.2 | 18.7 ± 1.3 | 18.4 ± 1.1 |
| 4 | 21.2 ± 2.2 | 21.5 ± 1.3 | 21.0 ± 1.3 | 20.3 ± 1.3** |
| 8 | 23.3 ± 1.0 | 23.7 ± 1.5 | 23.4 ± 1.3 | 22.8 ± 1.2* |
| 12 | 24.9 ± 1.2 | 25.1 ± 1.5 | 24.8 ± 1.2 | 24.1 ± 1.4** |
| 25 | 26.3 ± 1.5 | 26.7 ± 1.9 | 26.1 ± 1.6 | 25.3 ± 1.4** |
| 51 | 28.9 ± 1.9 | 29.3 ± 2.2 | 28.8 ± 1.8 | 26.8 ± 1.7** |
| 75 | 30.1 ± 2.2 | 31.0 ± 2.6 | 29.9 ± 2.2 | 27.9 ± 1.7** |
| 105 | 29.8 ± 2.2 | 30.6 ± 2.6 | 30.4 ± 2.2 | 27.8 ± 2.0** |
| Wt gain: wks 0 - 12[b] | 7.1 | 7.1 | 7.2 | 6.3 |
| Overall weight gain | 12.0 | 12.6 | 12.8 | 10.0 |

Data taken from Table 8, pp. 69-78, MRID 43678141.
[a] Mean ± S.D.
[b] calculated by reviewer
Significantly different from control; *p<0.05, **p<0.01.

C. FOOD CONSUMPTION AND COMPOUND INTAKE

1. Food consumption

Food consumption for male and female mice is given in Table 3. There were no dose- or compound-related differences apparent for either sex at any time throughout the study. Males receiving 2000 ppm had significantly greater food intake at weeks 8 and 92 ($p \leq 0.05$) and significantly lower food intake at week 2 ($p \leq 0.01$) as compared to controls. Female mice receiving 2000 ppm had significantly greater food consumption at weeks 28 ($p \leq 0.01$) and 56 ($p \leq 0.05$) and significantly lower food consumption at week 40 ($p \leq 0.05$). Females given 300 ppm had significantly lower food consumption at week 80 ($p \leq 0.05$). No other differences were seen at any dietary concentration for either sex during the study.

TABLE 3: Food consumption and food efficiency by mice given ICIA5504 in the diet for 2 years (g)

| Week of Study | 0 ppm | 50 ppm | 300 ppm | 2000 ppm |
|---|---|---|---|---|
| | Males | | | |
| 1 | 4.4 ± 0.2[a] | 4.3 ± 0.2 | 4.3 ± 0.2 | 4.3 ± 0.2 |
| 4 | 3.8 ± 0.2 | 3.8 ± 0.2 | 3.8 ± 0.3 | 3.7 ± 0.2 |
| 8 | 3.6 ± 0.1 | 3.7 ± 0.2 | 3.7 ± 0.2 | 3.8 ± 0.3* |
| 12 | 3.9 ± 0.2 | 3.9 ± 0.5 | 4.1 ± 0.5 | 4.0 ± 0.5 |
| Food Utilization[b] (weeks 1-12) | 2.70 ± 0.23 | 2.74 ± 0.26 | 2.51 ± 0.24 | 2.19 ± 0.20** |
| 24 | 4.0 ± 0.3 | 4.0 ± 0.2 | 4.0 ± 0.2 | 4.1 ± 0.3 |
| 52 | 3.9 ± 0.3 | 4.0 ± 0.2 | 3.9 ± 0.3 | 3.9 ± 0.4 |
| 76 | 4.1 ± 0.3 | 4.1 ± 0.3 | 3.9 ± 0.2 | 4.0 ± 0.4 |
| 104 | 4.0 ± 0.4 | 4.1 ± 0.6 | 4.0 ± 0.5 | 4.2 ± 1.0 |
| | Females | | | |
| 1 | 4.2 ± 0.3 | 4.2 ± 0.3 | 4.1 ± 0.2 | 4.1 ± 0.2 |
| 4 | 4.6 ± 0.2 | 4.6 ± 0.4 | 4.7 ± 0.4 | 4.6 ± 0.5 |
| 8 | 4.6 ± 0.2 | 4.5 ± 0.2 | 4.6 ± 0.3 | 4.7 ± 0.4 |
| 12 | 4.8 ± 0.4 | 4.8 ± 0.4 | 4.9 ± 0.3 | 5.0 ± 0.4 |
| Food Utilization[b] (weeks 1-12) | 1.87 ± 0.15 | 1.89 ± 0.13 | 1.91 ± 0.16 | 1.69 ± 0.14** |
| 24 | 4.5 ± 0.2 | 4.5 ± 0.3 | 4.6 ± 0.3 | 4.7 ± 0.6 |
| 52 | 4.2 ± 0.3 | 4.1 ± 0.4 | 4.0 ± 0.2 | 4.1 ± 0.2 |
| 76 | 4.5 ± 0.6 | 4.3 ± 0.2 | 4.3 ± 0.3 | 4.2 ± 0.4 |
| 104 | 4.7 ± 0.5 | 5.3 ± 1.4 | 5.0 ± 0.7 | 4.5 ± 1.0 |

Data taken from Tables 9 and 10, pp. 79-84 and p. 85, respectively, MRID 43678141.
[a]Mean ± S.D.
[b]Calculated as g growth/100 g food.
Significantly different from control; *p<0.05, **p<0.01.

2. Compound consumption (time-weighted average)

The overall mean doses were 6.2, 37.5, and 272.4 mg/kg/day for males and 8.5, 51.3, and 363.3 mg/kg/day for females in the 50, 300, and 2000 ppm groups, respectively.

3. Food utilization

Food utilization was calculated by the study author as 4-week averages only for the first 12 weeks of the study. Males ($p \leq 0.01$) and females ($p \leq 0.05$) receiving 2000 ppm had significantly lower food utilization as compared to controls for weeks 1-4. Overall food utilization for high-dose males and females for weeks 1-12 was significantly ($p \leq 0.01$) reduced as compared to controls (Table 3). No differences were seen for 2000 ppm males or females for weeks 5-8 or 9-12, or for the 300 and 50 ppm groups of either sex at any time as compared to controls.

D. BLOOD WORK

1. Hematology

No statistically significant differences in white cell counts were observed for either sex between control and 2000 ppm groups during study weeks 53, 79, or 105. At terminal sacrifice, males in the 300 ppm group had significantly ($p \leq 0.05$) reduced hemoglobin, hematocrit, and platelet count as compared with control; while 2000 ppm males had only reduced ($p \leq 0.05$) mean cell hemoglobin as compared with controls. All significant differences were within 9% of the control values. No statistically significant differences in hematological parameters were observed in females of any group as compared with control at terminal sacrifice.

2. Clinical chemistry

Clinical chemistry is not required by Subdivision F guidelines and was not performed in this study.

E. SACRIFICE AND PATHOLOGY

1. Organ weight

Absolute and relative kidney and liver weights are given in Table 5. Absolute kidney weights of the 2000 ppm males were significantly ($p \leq 0.05$) less than controls. Kidney weights of females were not affected. No significant differences in absolute liver weights were observed for treated groups of either sex as compared to controls. However, when organ weights were adjusted for



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final body weights, high-dose males and females had significantly ($p \leq 0.05$) greater liver weights than their respective controls (113% and 118% of the control weights, respectively). Adrenal, brain, and testes weights were unaffected by treatment of mice with ICIA5504.

Table 5: Selected absolute and relative organ weights of mice fed ICIA5504 for 2 years

| Organ | 0 ppm | 50 ppm | 300 ppm | 2000 ppm |
|---|---|---|---|---|
| | males | | | |
| Kidney wt.(g)<br>% body wt.<br>adjusted wt.[a] | 0.58 ± 0.05[b]<br>1.70 ± 0.12<br>0.58 | 0.56 ± 0.06<br>1.61 ± 0.13<br>0.55 | 0.55 ± 0.06<br>1.59 ± 0.19<br>0.54 | 0.54 ± 0.09*<br>1.66 ± 0.25<br>0.55 |
| Liver wt. (g)<br>% body wt.<br>adjusted wt. | 1.75 ± 0.55<br>5.08 ± 1.46<br>1.74 | 1.79 ± 0.33<br>5.21 ± 1.13<br>1.74 | 1.78 ± 0.50<br>5.10 ± 0.98<br>1.74 | 1.89 ± 0.24<br>5.80 ± 0.49<br>1.97* |
| | females | | | |
| Kidney wt.(g)<br>% body wt.<br>adjusted wt. | 0.46 ± 0.07<br>1.55 ± 0.17<br>0.46 | 0.55 ± 0.28<br>1.80 ± 0.90<br>0.52 | 0.49 ± 0.09<br>1.62 ± 0.28<br>0.49 | 0.42 ± 0.04<br>1.53 ± 0.12<br>0.44 |
| Liver wt. (g)<br>%body wt.<br>adjusted wt. | 1.74 ± 0.72<br>5.84 ± 2.44<br>1.73 | 1.64 ± 0.24<br>5.37 ± 0.70<br>1.45 | 1.74 ± 0.41<br>5.71 ± 1.10<br>1.64 | 1.85 ± 0.72<br>6.54 ± 1.80<br>2.05* |

Data taken from Table 12, pp. 94-98, MRID 43678141.
[a]Organ weight adjusted for final body weight.
[b]Mean ± S.D.
*Significantly different from control, $p \leq 0.05$.

2. Gross pathology

In animals examined following intercurrent death, the most common observations were distention of the small intestines, pale kidneys, enlarged lymph nodes, enlarged spleens, and discharge from the eyes in males and females, and small testes in males. No clear dose- or treatment-related trend was apparent for any of these observations. The most common findings in animals examined at terminal sacrifice were enlarged mesenteric and hepatic lymph nodes; however, controls and treated animals were affected equally.

If the incidence rates in the animals that were killed at termination and those that died intercurrently are combined, significant, dose-related differences in several parameters are observed. A greater number of 2000 ppm animals had distention of the duodenum (males, $p \leq 0.01$; females, $p \leq 0.05$), distention of the jejunum (females, $p \leq 0.05$), and discharge from the eye



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(females, $p \leq 0.05$) as compared to respective controls. These data are listed in Table 6.

TABLE 6: Incidence rate of selected gross observations in mice fed ICIA5504 for 2 years (combined intercurrent and terminal)

| Macroscopic Observation | 0 ppm | 50 ppm | 300 ppm | 2000 ppm |
|---|---|---|---|---|
| | males | | | |
| Duodenum, distended | 1/55 | 3/55 | 1/55 | 10/55** |
| Jejunum, distended | 1/55 | 0/55 | 1/55 | 1/55 |
| Eye, discharge | 5/55 | 2/55 | 6/55 | 5/55 |
| | females | | | |
| Duodenum, distended | 4/55 | 5/55 | 8/55 | 14/55* |
| Jejunum, distended | 1/55 | 0/55 | 1/55 | 7/55* |
| Eye, discharge | 4/55 | 5/55 | 9/55 | 12/55* |

Data taken from Table 14, pp. 132-152, MRID 43678141.
Significantly different from control, *$p \leq 0.05$; **$p \leq 0.01$.

3. Microscopic pathology

a) Non-neoplastic - Pathological lesions that were significantly increased in treated animals were observed in the thyroid gland and epididymis. The incidence of mononuclear cell infiltration of the thyroid gland in females was significantly increased in the high-dose group as compared to controls: control, 3/55; 50 ppm, 4/50; 300 ppm, 8/54; 2000 ppm, 13/54 ($p \leq 0.05$). High-dose males had significantly ($p \leq 0.05$) reduced spermatozoa in the epididymis: 0/55, 0/55, 0/55, and 6/55.

Other lesions observed in a large number of animals of both sexes from all treated and control groups included brain mineralization, cortical ceroidosis of the adrenals, demyelination of the sciatic nerve, blood filled sinuses in the mesenteric lymph node, hyperplasia of the stomach, and mononuclear cell infiltration of the salivary glands and kidneys. Also observed in males was tubular degeneration and Leydig cell hyperplasia of the testes, tubular basophilia and microlithiasis of the kidneys, and inflammation of the preputial gland and, in females,

ovarian cysts and dilation of the glandular portion of the uterus.

b) Neoplastic - The incidence rate of benign adenomas of the pituitary was significantly ($p \leq 0.05$) increased in the 300 ppm females (control, 6/55; 50 ppm, 7/52; 300 ppm, 14/54; 2000 ppm, 5/52). However, the effect was not dose-related and males were not affected. The most prevalent neoplastic lesions were observed in the lymphoreticular system and included lymphosarcomas and histiocytic sarcomas but controls were affected as well as treated animals of both sexes.

## III. DISCUSSION

### A. DISCUSSION

In a carcinogenicity toxicity study (MRID 43678141), ICIA5504 (azoxystrobin, 96.2% a.i.) was administered in the feed to 55 C57BL/10JfAP/Alpk mice/sex/dose at concentrations of 0, 50, 300, or 2000 ppm (males: 0, 6.2, 37.5, or 272.4 mg/kg/day; females: 0, 8.5, 51.3, 363.3 mg/kg/day) for 104 weeks. There were no treatment-related clinical signs or effects on mortality. Mean body weights of the 2000 ppm-group males and females were significantly ($p \leq 0.01$) lower than the controls beginning at study week 2 or 3 and continuing until the end of the study. Final body weights of the high-dose male group were 94% of controls and of the high-dose female group were 93% of the control value. Differences in body weights of other treated groups are not considered treatment-related because the effects were not consistent and the degree of difference as compared to controls was not biologically significant. The study author used the analysis of covariance based on week 1 body weights to determine significance between treated and control groups; this method is a comparison of weight gain throughout the study. Therefore, high-dose males and females gained significantly less weight than their controls throughout the study.

Decreased body weights in the 2000 ppm groups were not due to decreased food consumption which was similar to controls throughout the study. However, overall food utilization was significantly ($p \leq 0.01$) reduced for weeks 1-12 in both males and females. This indicates that, although the 2000 ppm males and females were eating the same amount of feed, they were unable to utilize that feed as efficiently as the control animals. The study authors calculated food utilization only for the first 12 weeks of the study which corresponds to the most rapid growth period of the animals. But the greatest differences in body weights of the 2000 ppm

groups occurred during the second year of the study. An expanded analysis of food utilization is needed to determine when the effect is most pronounced.

Although the differences in final body weights of 2000 ppm males and females were within 7% of their respective control group, significant differences occurred early in the study and continued until the end. Because food consumption was not affected but food utilization was reduced, the effect on body weight is most likely due to a generalized toxicity. Also, since absolute liver and kidney weights were within 9% of the control values, the significance reached in the adjusted liver weights is probably a consequence of the reduced body weights of these animals.

At terminal sacrifice, changes in red cell parameters in males are probably not treatment related as there was a lack of a dose response, the differences were slight and not biologically significant, and females were not similarly affected. Gross and microscopic pathologies observed in mice were not attributable to treatment with ICIA5504 but are consistent with aging mice. Distention of the small intestines was observed in 2000 ppm males and females but the effect did not appear to be dose-related and, at most, only one-fourth of the animals were affected. Intestinal distention could be due to poor nutritional status of the animals, however, inanition was not evident. No pathological lesions were identified to correlate with the changes in kidney and liver weights or with the distention of the small intestines. No effect on testicular spermatozoa accompanied the reduction described in the epididymis. The mononuclear cell infiltration of various organs, including the thyroids of 2000 ppm females, could be due to the high incidence of lymphoreticular tumors seen in all groups.

Similar results were obtained in subchronic and chronic feeding studies in rats (MRIDs 43678135 and 43678139, respectively). In both of these studies, the highest feed concentration had to be reduced after study initiation due to poor growth of the animals. In the subchronic study the high dose was reduced from 6000 ppm to 4000 ppm for males and females due to severely reduced weight gain and food consumption. The same results prompted the reduction of the high dose during the first year of the chronic study from 1500 ppm to 750 ppm in males only. Effects in rats also included signs of liver toxicity which were not apparent in the present study with mice. However, because feed consumption was reduced in the rat studies, the effects may have been due to lack of palatability of ICIA5504 to rats.

**Therefore, the systemic toxicity LOEL for this study is 2000 ppm based on reduced body weights of males and females (272.4 and 363.3 mg/kg/day, respectively). The systemic toxicity NOEL is 300 ppm (37.5 and 51.3 mg/kg/day, respectively).**

There were no treatment-related increases in the incidence of neoplastic lesions at any site. Therefore, ICIA5504 is not considered carcinogenic to mice under this protocol. Dosing was adequate as evidenced by decreases in body weights (up to 12%) in high-dose animals (2000 ppm).

B. STUDY DEFICIENCIES

No deficiencies were identified in the conduct of this study. However, more information would have been useful in the review of this study: no summary table for body weight gains was included; and food utilization was only calculated for the first 12 weeks when the greatest effect on weight gain occurred much later in the study. Details of the range-finding study were not included although doses appeared to be adequate.

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