CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
HUMAN HEALTH ASSESSMENT BRANCH

SUMMARY OF TOXICOLOGY DATA

Azoxystrobin

Chemical Code # 4037**, Document Processing Number (DPN)** 52100
SB 950 # NA
7/15/15

DATA GAP STATUS

Chronic toxicity, rat:	No data gap; no adverse effect indicated
Chronic toxicity, dog:	No data gap; no adverse effect indicated
Oncogenicity, rat:	No data gap; no adverse effect indicated
Oncogenicity, mouse:	No data gap; no adverse effect indicated
Reproduction, rat:	No data gap; no adverse effect indicated
Developmental toxicity, rat:	No data gap; possible adverse effect
Developmental toxicity, rabbit:	No data gap; possible adverse effect
Gene mutation:	No data gap; possible adverse effect
Chromosome effects:	No data gap; possible adverse effect
DNA damage:	No data gap; no adverse effect indicated
Neurotoxicity:	No data gap; no adverse effect indicated

Toxicology one-liners are attached.

All record numbers for the above study types through 277405 (Document No. 52100-0345) were examined. This includes all relevant studies indexed by DPR as of 7/15/15.

In the 1-liners below:
indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.

File name: T071515
Revised by [redacted], 7/15/15

NOTE: The following symbols may be used in the Table of Contents which follows:
* = data adequately address FIFRA requirement
† = study(ies) flagged as “possible adverse effect”
N/A = study type not currently required

This record contains summaries of studies. Individual worksheets may be useful for detailed assessment.

Table of Contents

METABOLISM AND PHARMACOKINETICS

52100-026 146820 "ICIA5504: Excretion and Tissue Retention of a Single Oral Dose (1 mg/kg) in the Rat" (Lythgoe, R. and McAsey, S., 851, ZENECA Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Study# UR0402, 2/25/93). A mixture of ICIA5504 (Azoxystrobin, CTL# Y06654/009, purity of 99.0%) and radiolabeled [14C]-Pyrimidinyl-labelled ICIA5504 (CTL# Y06654/012, specific activity 2.02GBq/mmol, purity >99%) was given by oral gavage to 6 Alpk:APfSD rats/sex at 1 mg/kg. Excretion was rapid and virtually complete by day 7. Percentages of dose excreted via feces over 7 days were 83.2% (males) and 72.6% (females). For urine, the percentages were 10.2% and 17.9% for males and females, respectively. For both feces and urine, most of the label was excreted in the first 48 hours. Less than 0.6% of the radiolabel was excreted in expired air. Levels retained in kidneys were 0.027 and 0.023 ug equiv/g for males and females, respectively and in liver were 0.009 ug equiv/g for both sexes; tissues and carcass retained less than 0.4% of the administered dose. The concentration for both sexes in blood was 0.004 ug equiv/g and in plasma was 0.002 ug equiv/g. All other tissue concentrations were less than blood. **Acceptable.** [redacted], 1/23/97.

52100-026 146821 "Whole Body Autoradiography in the Rat Following a Single Oral Dose (1 mg/kg)" (Lythgoe, R. and Howard, E., 851, ZENECA Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Study# UR0393, 1/25/93). Three radiolabeled forms of ICIA5504 ([14C]-labelled at pyrimidinyl, phenylacrylate or cyanophenyl ring and designated CTL# Y06654/012 (2.02GBq/mmol), Y06654/015 (1.895Bq/mmol) and Y06654/016 (2.307GBq/mmol), respectively), all with radiochemical purities of >98%, were given by oral gavage to 2 Alpk:APfSD rats/sex/labelled form at 1 mg/kg; for each labelled form, 1 rat of each sex was killed after 24 hours and the remaining after 48 hours. Excretion of radioactivity was monitored and frozen carcasses were sectioned for whole body autoradiography. No major differences were observed in excretion or tissue distribution profiles for the three labelled forms; highest concentrations of radioactivity were in intestinal contents, with lesser amounts in the kidneys and liver. High intestinal concentration was consistent with predominant fecal route of excretion. Little radiolabel was detected in expired air. **Acceptable.** [redacted], 1/24/97.

52100-026 146822 "ICIA5504: Excretion and Tissue Retention of a Single Oral Dose (100 mg/kg) in the Rat" (Lythgoe, R. and Howard, E., 851, ZENECA Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Study# UR0403, 2/25/93). A mixture of ICIA5504 (Azoxystrobin, CTL# Y06654/009, purity of 99.0%) and radiolabeled [14C]-Pyrimidinyl-labelled ICIA5504 (CTL# Y06654/012, specific activity 2.02GBq/mmol, purity >99%) was given by oral gavage to 5 Alpk:APfSD rats/sex at 100 mg/kg. Excretion was rapid and virtually complete by day 7. Percentages of dose excreted via feces over 7 days were 89.4% (males) and 84.5% (females). For urine, the percentages were 8.5% and 11.5% for males and females, respectively. For both feces and urine, most of the label was excreted in the first 48 hours. Less than 0.4% of the administered dose was retained in tissues. Levels retained in kidneys were 1.373 and 1.118 ug equiv/g for males and females, respectively and in liver were 0.812 and 0.714 ug equiv/g, respectively. The concentrations in blood were 0.389 and 0.379 ug equiv/g

and in plasma were <0.131 and 0.146 ug equiv/g for males and females, respectively. All other tissue concentrations were less than blood. **Acceptable.** [redacted], 1/27/97.

52100-026 146823 "ICIA5504: Excretion and Tissue Retention of a [14C]-Labelled Single Oral Dose (1 mg/kg) Following Fourteen Daily Unlabeled Doses in the Rat" (Lythgoe, R. and Howard, E., 851, ZENECA Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Study# UR0418, 8/24/93). ICIA5504 (Azoxystrobin, CTL# Y06654/009, purity of 99.0%) was administered by oral gavage to 8 Alpk:APfSD rats/sex at 1 mg/kg daily for a total of 14 doses. Radiolabeled [14C]-Pyrimidinyl-labelled ICIA5504 (CTL# Y06654/018, specific activity 2.02GBq/mmol, purity >99%) was given 24 hours after the last dose to the first five rats of each sex (single dose, 1 mg/kg). The excretion of radioactivity was rapid and virtually complete by 7 days. Tissue and carcass retention of radiolabel was very low (less than 0.8% of administered dose). For both sexes, more than 96% of administered label was excreted during the first 48 hours, mainly via the feces. This indicated that the repeat dosing of male and female rats with unlabeled test compound for 14 days had little or no effect on excretion or tissue retention of the subsequent radiolabeled dose. **Acceptable.** [redacted], 1/27/97.

52100-026 146824 "ICIA5504: Biotransformation in the Rat" (Lappin, G. and Gledhill, A., 851, ZENECA Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Study# UR0397, 6/13/94). Metabolites of ICIA5504, Azoxystrobin (CTL# Y06654/009, purity of 99.0%) and radiolabeled pyrimidinyl-[14C]-ICIA5504 (CTL# Y06654/012, specific activity 2.02GBq/mmol, purity >99%) present in urine, feces and bile extracts from 6 Alpk:APdSD bile duct-cannulated rats/sex and in urine and feces obtained from previous metabolism studies (DPR# 52100-026:146820, 146822, 146823) were characterized by mass-spectroscopy, tandem mass-spectroscopy and NMR spectroscopy. At least 15 metabolites were produced after oral exposure to test compound, with females producing more types than males. Absorption appeared quantitative at 1 mg/kg and about 70% was absorbed at 100 mg/kg. Metabolic pathways were identified: hydrolysis of methoxyacid followed by glucuronic acid conjugation occurred as well as glutathione conjugation of the cyanophenyl ring leading to mercapturic acid formation. Another pathway was identified involving hydroxylation of the 8 and 10 position on the cyanophenyl ring followed by glucuronic acid conjugation; several other minor pathways were identified. **Acceptable.** [redacted], 1/28/97.

Summary: After oral administration, excretion is rapid and by 48 hours 96% of the radioactive dose is excreted. 73% to 89% of the administered radioactivity is found in the feces, whereas 9% to 18% of the radioactivity appeared in urine. Less than 0.6% of the radiolabel wa excreted in expired air. There was no evidence for accumulation after multiple oral dosing.

GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

Acute oral toxicity, rat

009; 146784; "(ICIA5504) E5504: Acute Oral Toxicity to the Rat" (Robinson, P., ICI Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Study No. AR5268, Report No. CTL/P/3555, 11/12/91). 811. E5504 (reference: P32/A1016/34, purity=95.2%), prepared in corn oil, was administered by gavage to 5 Wistar-derived (Crl:(WI)BR) rats per sex per dose level. One dose level of 5000 mg/kg was used. No animals died. Diarrhea, stains around mouth and nose, signs of urinary incontinence, ungroomed appearance, piloerection, hairloss, and upward curvature of spine were observed. Necropsy revealed no treatment-related macroscopic abnormalities. LD_{50} (M/F)> 5000 mg/kg. NOEL (M/F)< 5000 mg/kg. Toxicity Category IV. **Acceptable**. ([redacted], 12/11/96)

Acute dermal toxicity

009; 146785; "(ICIA5504) E5504: Acute Dermal Toxicity to the Rat" (Robinson, P., ICI Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Study No. CR2897, Report No. CTL/P/3556, 11/12/91). 812. E5504 (reference: P32/A1016/34, purity=95.2%), made into a paste using corn oil, was applied to the clipped skin of 5 Wistar-derived (Crl:(WI)BR) rats per sex per dose level. One dose level of 2000 mg/kg was used. Animals were exposed for 24 hours using an occlusive wrap. No animals died. No significant clinical signs were observed. Erythema, edema, and desquamation were observed at the test site. Necropsy revealed no treatment-related macroscopic abnormalities. LD_{50} (M/F)> 2000 mg/kg. Toxicity Category III. **Acceptable**. ([redacted], 12/12/96)

Acute inhalation toxicity, rat

009; 146786; "ICIA5504: 4-Hour Acute Inhalation Toxicity Study in the Rat" (Parr-Dobrzanski, R.J., ICI Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Study No. HR2172, Report No. CTL/P/3908, 12/15/92). 813. ICIA5504 (no lot number, purity=96.2%) was administered as a dust to 5 Alpk:APfSD (Wistar-derived) rats per sex per dose level. Dose levels (mean gravimetric concentration) of 0.257, 0.511, 0.767, and 1.010 (males only) mg/l were used with MMAD of 1.13, 1.17, 1.35, and 1.17 mm, respectively, and GSD of 1.82, 1.83, 1.86, and 2.26, respectively. A nose-only method was used and the animals were exposed for 4 hours. Mortalities occurred as follows- males: 0/5, 1/5, 1/5, 3/5, respectively; females: 0/5, 1/5, 3/5, respectively. Hunched posture, activity decrease, shaking, reduced stability, piloerection, stains around nose, test substance around snout, wet fur, chromodacryorrhea, increased breathing depth, reduced breathing rate, irregular breathing, abnormal respiratory noise, mucus secretion from nose, splayed gait, tip toe gait, tail erection, reduced splay reflex, signs of urinary incontinence, ungroomed appearance, and absence of pinna reflex were observed. Necropsy on the mortalities revealed mottled and/or dark lungs. LC_{50} (M)=962 ug/l, LC_{50} (F)=698 (509-2425) ug/l. Toxicity Category III. **Acceptable**. ([redacted], 12/12/96)

Primary eye irritation, rabbit

009; 146787; "(ICIA5504) E5504: Eye Irritation to the Rabbit" (Robinson, P., ICI Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Study No. FB4519, Report No. CTL/P/3558, 11/6/91). 814. 100 mg of E5504 (reference: P32/A1016/34, purity=95.2%) was placed into the conjunctival sac of one eye of each of six New Zealand White rabbits. No corneal opacity or iritis was observed. Grade 1 conjunctival irritation was observed in 3 of 6 treated eyes 1 day after treatment clearing in all 2 days after treatment. Toxicity Category IV. **Acceptable**. ([redacted], 12/16/96)

Primary dermal irritation

009; 146788; "(ICIA5504) E5504: Skin Irritation to the Rabbit" (Robinson, P., ICI Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Study No. EB4003, Report No. CTL/P/3557, 11/6/91). 815. 500 mg of E5504 (reference: P32/A1016/34, purity=95.2%), moistened with deionized water, was applied to the clipped skin of each of six New Zealand White rabbits. Animals were exposed for 4 hours using an occlusive wrap. Grade 1 erythema and grade 1 edema were observed in one animal 1 day after patch removal clearing 7 days after patch removal. Toxicity Category IV. **Acceptable**. ([redacted], 12/16/96)

Dermal sensitization

009; 146789; E5504 (ICIA5504): Skin Sensitization to the Guinea Pig; Per Worker Health & Safety memorandum of March 3, 1997, Exposure of guinea pig skin to E5504 (purity: 95.2%) in the Buehler test did not result in a sensitizing response.

SUBCHRONIC STUDIES (units of mg/kg/day unless specified)

Rat Subchronic Dietary Toxicity Study:

012; 146792; "ICIA5504: 90 Day Feeding Study in Rats" (Milburn, G.M., ICI Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Study No. PR0850, Report No. CTL/P/3649, 7/21/92). 821. ICIA5504 (Batch P32, CTL reference number Y06654/004, purity=95.2%) was admixed to the feed at concentrations of 0, 200, 2000, or 6000 (reduced to 4000 during week 3) ppm and fed to 12 Alpk:APfSD (Wistar-derived) rats per sex per dose level for a period of 90 days. Distended abdomen was observed in animals at the 2000 and 4000 ppm dose levels. Statistically significant reduction in body weight gain and decrease in food consumption were observed at the 2000 and 4000 ppm dose levels. Increases in mean relative liver weights were observed at the 2000 and 4000 ppm dose levels. Gross necropsy revealed enlarged, pale liver with distended bile duct in one male at the 4000 ppm dose level. Histopathological examination revealed liver with proliferation of intrahepatic bile ducts/ductiles and oval cells in 2 males at the 4000 ppm dose level and slight hepatitis and moderate hepatocyte hyperplasia in 1 male at the 4000 ppm dose level. **No adverse effects.** NOEL=200 ppm (20.4 mg/kg/day for males, 22.4 mg/kg/day for females based on decreased mean body weight gain, decreased food consumption, and increased relative liver weights). **Acceptable**. ([redacted], 1/3/97)

Dog Subchronic Oral Toxicity Study:

013; 146793; "ICIA5504: 90 Day Oral Dosing Study in Dogs" (Allen, S.L., Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Study No. PD0899, Report No. CTL/P/3890, 5/11/93). 821. ICIA5504 (Batch P49, CTL reference number Y06654/014, purity=96.2%) was administered orally (capsule) to 4 beagle dogs per sex per dose level at levels of 0, 10, 50, or 250 mg/kg/day for a period of 90 days. Salivation and salivation at dosing were observed at the 50 and 250 mg/kg/day dose levels. Statistically significant reduction in body weight gain was observed at the 250 mg/kg/day dose level throughout the study. Necropsy revealed no treatment-related macroscopic or microscopic abnormalities. **No adverse effects.** NOEL (M/F)=10 mg/kg/day based on clinical signs (salivation and salivation at dosing). **Acceptable**. ([redacted], 1/7/97)

Rat 21-Day Repeated Dosing Dermal Toxicity Study:

011; 146791; "ICIA5504: 21-Day Dermal Toxicity Study in the Rat" (Robinson, P., Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Study No. LR0561, Report No. CTL/P/4360, 5/24/94). 822. ICIA5504 (Batch P49, CTL reference number Y06654/014, purity=96.2%) was made to a paste with deionized water and applied to the clipped back of 5 Alpk:APfSD rats per sex per dose level at concentrations of 0, 200, 500, or 1000 mg/kg/day, 6 hours per day 5 days per week for 30 days (21 individual exposures). No significant clinical signs or signs of skin irritation were observed. Necropsy revealed no compound-related macroscopic or microscopic abnormalities. **No adverse effects.** Systemic and dermal irritation NOEL (M/F)=1000 mg/kg/day. **Acceptable**. ([redacted], 1/8/97)

CHRONIC STUDIES

Chronic, rat

** 016 146796 "2 Year Feeding Study in Rats," (Milburn, G.M., Zeneca Central Toxicology Laboratory, Cheshire, UK; Report #: CTL/P/4552; Study #: PR0892; 5/23/95). Azoxystrobin technical (96.2% pure) was fed in diet to Alpk:APfSD rats (main study: 52/sex/dose; satellite group: 12/sex/dose) at 0, 60, 300 and 1500 ppm for 104 weeks. The dose for males in the main study was lowered to 750 ppm during the second year of the study. NOEL = **300 ppm** (There

was decreased survival in males at 1500 ppm from week 39. The main treatment group showed increased abdominal distension in males at 1500 ppm from week 17. There was decreased body weight and food consumption in both sexes at 1500 ppm. An increased incidence in males with hazy cataracts and total cataracts was observed at 1500 ppm. Hematology and clinical chemistry parameters were affected in both sexes at 1500 ppm. Kidney weights were decreased in both sexes at 1500 ppm. Adrenal weights were decreased in females at 1500 ppm. Macroscopically, effects were observed in the common bile duct and liver only in males dying intercurrently at 1500 ppm. Females at 1500 ppm showed increased pallor of pancreas and red mesenteric lymph nodes. Histopathologically the 13 males at 1500 ppm that died on study had distension of the common bile duct, due to cholangitis, epithelial hyperplasia, epithelial ulceration, thickening of the wall and deposits in the lumen. Marked biliary hyperplasia in the liver was observed in 10/13 of these males. Females surviving to termination showed increased pituitary cysts and blood filled sinuses within the mesenteric lymph node at 1500 ppm.) **No adverse effect**. **Acceptable**. [redacted] 12/10/96

Chronic, dog

** 015 146795 "1 Year Oral Toxicity Study in Dogs," (Allen, S.L., Zeneca Central Toxicology Laboratory, Cheshire, UK; Report #: CTL/P/4440; Study #: PD0941; 11/21/94). Azoxystrobin technical (96.2% pure) was administered in capsules to Beagle dogs (4/sex/dose) at 0, 3, 25 and 200 mg/kg for 52 weeks. NOEL = 3 mg/kg/day (Both sexes showed an increase in liquid feces and in vomiting and regurgitation at 200 mg/kg throughout the study. Females showed increased salivation and salivation at dosing at 200 mg/kg. Hemoglobin levels were decreased in males at 200 mg/kg. Both sexes had decreased monocyte count and albumin at 200 mg/kg. Increased cholesterol, alkaline phosphatase was observed at $\geq$ 25 mg/kg. In both sexes gamma-glutamyl transferase, triglycerides and phosphorous (males only) levels were increased at 200 mg/kg. There was a significant increase in liver weight in both sexes at 200 mg/kg.) **No adverse effect**. **Acceptable**. [redacted] 11/26/96.

Oncogenicity, rat

See Chronic rat above.

Oncogenicity, mouse

** 017 146797 "Two Year Feeding Study in Mice," (Moxon, M.E., Zeneca Central Toxicology Laboratory, Cheshire, UK; Report #: CTL/P/4483; Study #: PM0893; 4/19/95). Azoxystrobin technical (96.2% pure) was fed in diet to C57BL/10JfAP/Alpk mice (55/sex/dose) at 0, 50, 300 and 2000 ppm for 2 years. NOEL = **300 ppm** (There was decreased body weight (6-13%) in both sexes at 2000 ppm. At termination there was a statistically significant decrease in mean cell hemoglobin for males at 2000 ppm. There was an increase in liver weights in both sexes at 2000 ppm. Distension of the duodenum was increased in both sexes at 2000 ppm. Females showed distension of the jejunum at 2000 ppm. There was an increase in females with discharge from the eye at $\geq$ 300 ppm.) **No adverse effect**. **Acceptable**. [redacted], 12/11/96.

GENOTOXICITY

Gene mutation

** 025 146815 "An Evaluation of Mutagenic Potential Using S.Typhimurium and E.Coli," (Callander, R.D., ICI Central Toxicology Laboratory, Cheshire, UK; Report #: CTL/P/3790; Study #: YV3143; 10/19/92). Azoxystrobin technical (97.2% pure) was used in a reverse mutation assay with Salmonella typhimurium (TA1535, TA1537, TA98 and TA100) and in a forward mutation assay with Escherichia coli (WP2P and WP2P uvrA) at 0 (DMSO), 100, 200, 500, 1000, 2500 and 5000 ug/plate (+/- S9, 3 replicates; 2 separate tests). Appropriate positive

controls were used. Azoxystrobin did not induce gene mutations at any dose. Positive controls functioned as expected. **Acceptable.** [redacted], 1/30/97.

**** 025 146816** "Assessment of Mutagenic Potential Using L5178Y Mouse Lymphoma Cells," (Callander, R.D. and Clay, P., Zeneca CTL, Cheshire, UK; Report #: CTL/P/3963; Study #: VV0095; 5/20/93). Azoxystrobin technical (96.2% pure) was used in a forward mutation assay with L5178Y Mouse lymphoma (TK+/-) cells at Experiment 1: 0 (DMSO), 8, 15, 30 and 60 ug/ml (+/- S9, duplicate); Experiment 2: 0 (DMSO), 34, 45, 60 or 80 ug/ml (+/- S9, duplicate); Experiment 3: 0 (DMSO), 26, 33, 41, 51, 64 and 80 ug/ml (+/- S9, duplicate). In experiment 1, there was increased mutation frequency at ≥ 8 ug/ml both with and without S9. In experiment 2, cultures without S9 were invalid due to spontaneous mutant frequency outside acceptable range and data were not presented. Cultures with S9 showed increased mutant frequency at ≥ 45 ug/ml. In experiment 3, there was increased mutant frequency at ≥ 41 ug/ml, both with and without S9. **Possible adverse effect. Acceptable**. [redacted], 1/30/97.

Chromosome damage

**** 025 146817** "An evaluation in the in vitro cytogenetic assay in human lymphocytes," (Fox, D.A. and Makay, J.M., ICI CTL, Cheshire, UK; January 27, 1992; Report #: CTL/P/3607; Study #: SV0568). Azoxystrobin technical (95.2% pure) was used in an in vitro cytogenetic assay with human lymphocytes at 0 (DMSO), 25, 100 and 200 ug/ml (+S9; 2 donors) and 0, 1, 10 and 20 ug/ml and 5, 20 and 50 ug/ml (-S9; 2 donors) at 72 hours. At 96 hours, cultures from the female donor were treated at 0 and 20 ug/ml (-S9) and 200 ug/ml (+S9). Duplicate cultures/donor/dose (4 slides/culture) were evaluated for clastogenicity. Results showed that at 72 hours: Donor #1 had increased mean % aberrant cells (excluding gaps) at 20 ug/ml and Donor #2 at ≥ 5 ug/ml (no S9). Donor #1 showed an increase in mean % aberrant cells (excluding gaps) at > 100 ug/ml and Donor #2 at 200 ug/ml (+S9). **Possible adverse effect. Acceptable**. [redacted], 1/31/97.

** 025 146818 "An evaluation in the mouse micronucleus test," (Jones, K. and Mackay, J.M., ICI CTL, Cheshire, UK; March 6, 1992; Report #: CTL/P/3647; Study #: SM0618). Azoxystrobin technical (97.2% pure) was used in a mouse miconucleus assay at 0 (corn oil) and 5000 mg/kg at 24 and 48 hours (5 mice/sex/dose/time point; bone marrow smears were prepared in duplicate). There was no increase in mean incidence of MPE/1000 PE in either sex at either time point. Males showed increased mean % polychromatic erythrocytes at 48 hours (5000 mg/kg). **Acceptable**. [redacted], 1/31/97.

DNA damage or miscellaneous effects

** 025 146819 "Assessment for the induction of unscheduled DNA synthesis in rat hepatocytes in vivo," (Kennelly, J.C., ICI CTL, Cheshire, UK, 5/28/92; Report #: CTL/P/3682; Study #: SR0615). Azoxystrobin technical (97.2% pure) was used to assess DNA repair with primary male rat hepatocytes at 0 (corn oil), 1250 and 2000 mg/kg at 2 and 16 hours (2 rats/dose/time point for controls and 5/dose/time point for treated). Three cultures per rat were assessed. There was no increase in unscheduled DNA synthesis at any dose or time point. **No adverse effect. Acceptable.** [redacted], 1/31/97.

REPRODUCTIVE TOXICITY, RAT

** 018 146798 "ICIA5504: Multigeneration study in the rat," (M.E. Moxon, Zeneca CTL, Cheshire, UK; Report #: CTL/P/4213, 11/15/94). Azoxystrobin technical (96.2% pure) was fed in diet to Alpk:APfSD (Wistar-derived; 26/sex/dose) at 0, 60, 300 and 1500 ppm for 2 generations. Systemic NOEL = 300 ppm (Relative liver weights were significantly increased at 1500 ppm in F0 & F1 parents and in F1a & F2a pups. Relative testes weights were increased at 1500 ppm in the F1a litter. Males (3/26-F0; 11/26-F1) showed bile duct distended at 1500 ppm. In the F1 parents, males showed increased proliferative cholangitis (2/25) at 1500 ppm. There was an increase in common bile duct distension, proliferative cholangitis and ulceration of the common bile duct with moderate epithelial hyperplasia (intraduodenal portion) observed in males of both generations at 1500 ppm. Livers of both generations of males showed increased proliferative cholangitis at 1500 ppm.) Reproduction NOEL > 1500 ppm (There were no effects observed at any dose.) **No adverse effect. Acceptable.** M. Silva, 12/24/96.

DEVELOPMENTAL TOXICITY

Rat

**** 019 146800** "Teratology Study in the Rat," (Moxon, M.E.; Zeneca Central Toxicology Laboratory, Cheshire, UK; Report #: CTL/P/3633; Study #: RR0560; 11/11/94). Azoxystrobin technical (95.2% pure) was administered by gavage to mated Alpk:APfSD (Wistar derived) rats (24/dose) at 0 (corn oil), 25, 100 and 300 mg/kg/day during days 7-16 of gestation (during organogenesis). Maternal NOEL = 25 mg/kg (Three of 12 rats at 300 mg/kg died after 2 doses and 1 was killed in extremis. At ≥ 100 mg/kg, urinary incontinence and diarrhea occurred during dosing. At 25 and 100 mg/kg, salivation occurred during dosing. At 100 mg/kg, there was a statistically significant reduction in maternal bodyweight during the dosing period, which was sustained throughout the study. Food consumption was statistically significantly reduced during the dosing period at 100 mg/kg (23%). Post-dosing, the food consumption was increased.) Fetal NOEL = 25 mg/kg (There was an increase in minor skeletal defects at 100 mg/kg (reduction in ossification). There was an increase in fetuses with kinked ureters at 100 mg/kg.) **Possible adverse effect:** There was an increase in skeletal defects and fetuses with kinked ureters at 100 mg/kg. **Acceptable.** [redacted], 12/30/96.

019 146799 "Modified Chernoff-Kavlock Assay in the Rat," (Pinto, P.J.; Zeneca Central Toxicology Laboratory, Cheshire, UK; Report #: CTL/P/4498; Study #: RR0531/F0; 12/19/94). Azoxystrobin technical (100% pure) was administered by gavage to mated Alpk:APfSD (Wistar derived) rats (10/dose) at 0 (corn oil), 100 and 500 mg/kg/day during the period of organogenesis (days 7-16 of gestation). Maternal NOEL < 100 mg/kg (All animals at 500 mg/kg and most at 100 mg/kg showed urinary incontinence and diarrhea during dosing. At 500 mg/kg, there was a statistically significant reduction in maternal bodyweight gain during the dosing period. Bodyweight loss occurred between days 8 and 10.) Developmental NOEL > 500 mg/kg (There were no effects at any dose.) This was **not a FIFRA Guideline study. No adverse effect**. [redacted], 12/26/96.

019 146801 "Maternal Toxicity Study in the Rat," (Moxon, M.E.; Zeneca Central Toxicology Laboratory, Cheshire, UK; Report #: CTL/P/4452; Study #: RR0662; 7/11/95). Azoxystrobin technical (95.2% - 97.9% pure) was administered by gavage to mated Alpk:APfSD (Wistar derived) rats (24/dose) at 0 (corn oil), 100, and 200 mg/kg/day during days 7-16 of gestation (during organogenesis). There were 3 batches of azoxystrobin used in this test: P22, P32 and P37 tested at all dose levels (1 control group + 3 groups each at 100 and 200 mg/kg--8 rats/group). Maternal NOEL < 100 mg/kg (Urinary incontinence was observed in animals at ≥ 100 mg/kg (Batch #'s: p32 & p37, milled). This effect was not observed in Batch #: p22

(unmilled). With Batch #: p22, maternal bodyweights were significantly decreased on days 8, 15, 16 and 19 at 200 mg/kg. For Batch #: p32 and p37 there was a dose-related effect on bodyweight at ≥ 100 mg/kg. The least effect was observed with unmilled material (p22). For all batches there was a dose-related decrease in food consumption. The effect was negligible at 100 mg/kg for Batch #: p22.) **No adverse effect**. Not acceptable (There were only 2 treatment groups. FIFRA Guidelines recommend there be 3 treatment groups. Fetuses were not examined.) The data are **supplemental**. [redacted], 12/31/96.

Rabbit

**** 021 146806** "Developmental Toxicity Study in the Rabbit," (Moxon, M.E.; Zeneca Central Toxicology Laboratory, Cheshire, UK; Report #: CTL/P/4012; Study #: RBO606; 11/11/94). Azoxystrobin technical (96.2% pure) was administered by gavage to mated New Zealand white rabbits (20/dose) at 0 (corn oil; 2 ml/kg), 7.5, 20 or 50 mg/kg/day during days 8-20 of gestation. Maternal NOEL = 7.5 mg/kg (The incidence of rabbits found dead or killed in extremis during the study was 2, 4, 3 and 7 at 0, 7.5, 20 or 50 mg/kg/day, respectively. There was an increased incidence of animals with diarrhea or signs of diarrhea at 50 mg/kg/day. Decreased body weight was observed at ≥ 20 mg/kg/day. Post-implantation loss as # implants, percent implants and # implants/litter was increased at ≥ 20 mg/kg/day. Stomach abnormalities (abnormal content, presence of red/black areas and detached mucosa) were observed in animals which died intercurrently at ≥ 20 mg/kg/day. Changes in the cecum and ileum were increased slightly at 50 mg/kg/day.) Fetal NOEL = 20 mg/kg/day (There was a significant increase in proportion of fetuses with major external/visceral defects (increased incidence in open eye and cleft palate at 50 mg/kg/day). There was a significant increase in fetuses with fusion of the 3rd & 4th and/or the 4th & 5th sternebrae at 50 mg/kg/day. There were other indications of skeletal developmental delay at 50 mg/kg/day.) **Possible adverse effect. Acceptable.** [redacted] 1/10/97.

020 146802 "A Review of Developmental Toxicity Studies in the Rabbit," (Lewis, R.W., Central Toxicology Laboratory, Cheshire, UK; Report #: CTL/I/380; 4/9/96). This volume contains a summary of studies: "Dose Range Finding Study in the Rabbit," (DPR volume record #: 52100-020/146803), "Embryotoxicity Study in the Rabbit," (52100-020/146804) and "Dose Range Finding Study in the Pregnant Rabbit," (52100-020/146805). The report stated that the overview explains the rationale for repeating the definitive study (020/146804) and the reasons that the second rabbit developmental toxicity study should be considered to be the definitive assessment of developmental toxicity in this species. There was no worksheet made for this review. Individual worksheets were performed for each of the individual studies. These data are **supplemental**. [redacted], 1/6/97.

020 146804 "Embryotoxicity Study in the Rabbit," (Moxon, M.E.; Zeneca Central Toxicology Laboratory, Cheshire, UK; Report #: CTL/P/4607; Study #: RBO553; 7/8/95). Azoxystrobin technical (95.2% pure) was administered by gavage to mated New Zealand white rabbits (10/dose) at 0 (corn oil), 200, 400 and 600 mg/kg/day during days 7-19 of gestation. Maternal NOEL < 200 mg/kg (The incidence of rabbits found dead or killed in extremis during the study was 3, 8, 8 and 7 at 0, 200, 400 or 600 mg/kg/day, respectively. The remaining surviving animals (6, 1, 2 and 1 at 0, 200, 400 and 600 mg/kg/day, respectively) were killed on day 22 or 23 when the study was prematurely terminated. There was an increased incidence of animals with diarrhea and/or mucous in the feces (8/group at ≥ 200 mg/kg/day), compared with control (3). All groups were affected by weight loss and decreased food consumption. The report stated that because of this, meaningful evaluation of the intergroup data were uninterpretable. Stomach abnormalities (abnormal content, hemorrhagic areas and detached mucosa) were observed, which the report stated were common in animals which have not eaten for several

days.) No fetuses were examined. Not acceptable and not upgradeable. These data are **supplemental.** [redacted] 12/31/96.

022 146807 "Evaluation of the suitability of different vehicles for use in developmental toxicity studies in the rabbit," (Moxon, M.E., Zeneca Central Toxicology Laboratory, Cheshire, UK; CTL study #: XB4954; 11/10/95).

STUDY DESIGN:

Five candidate dosing vehicles were tested for use in rabbit developmental studies requiring oral, gavage admininstration. The vehicles were: 0.5% w/v hydroxypropylmethylcellulose in 0.1% w/v Tween 80 (0.5% HPMC), polyethylene glycol 300 (PEG 300), polyethylene glycol 400 (PEG 400), 0.5% w/v gum xanthan in 0.1% w/v Tween 80 (0.5% Xanthan) and corn oil. Female New Zealand White rabbits (10/dose--time-mated) were dosed by gavage with 2 or 5 ml/kg of test vehicle (5 ml/kg was not tolerated for some vehicles, so volume was decreased to 3 or 4 mg/kg). The rabbits were dosed on days 8-20 (inclusive) of gestation (period of organogenesis). On day 30 animals were killed and their uteri were examined for live fetuses and intra-uterine deaths. Fetuses were weighed, examined for external and visceral abnormalities, sexed, eviscerated and stained for skeletal examination.

RESULTS:

A slightly lower bodyweight gain was observed at 5 ml/kg with 0.5% HPMC or 0.5% Xanthan. PEG 300, PEG 400 or corn oil at dose volumes greater than 2 ml/kg was not tolerated, therefore the scheduled number of daily doses could not be given. At 2 ml/kg, dams showed diarrhea, decreased bodyweight gain and decreased food consumption and death.

CONCLUSIONS:

PEG 300, PEG 400 and corn oil, administered at $\geq$ 2 ml/kg were toxic in pregnant rabbits. Both 0.5% HPMC and 0.5% Xanthan are considered to be acceptable vehicles in rabbit. Fetal effects were not conclusive, since only a small number of litters were evaluated.

These data are supplemental. [redacted], 1/22/97.

023 146811 "Comparison of Exposure in the Non-pregnant Rabbit," (Hall, M.G., Zeneca Central Toxicology Laboratory, Cheshire, UK; CTL Ref: Y06654/014, CTL Study #: UBO480, 11/10/95). Azoxystrobin technical (96.2% pure) was administered by gavage to groups of 3 New Zealand white rabbits per group at 7.5, 20 or 50 mg/kg. Each animal received the same nominal dose in a different vehicle (carboxy methyl cellulose--CMC, 5 ml/kg; corn oil 1 or 2 ml/kg) in 3 doses. Each animal was dosed with the appropriate dose formulation on day 1 (phase 1), day 8 (phase 2) and day 15 (phase 3) of the study. Plasma samples were taken over a time course following each dose and analyzed for unchanged azoxystrobin and azoxystrobin acid. The areas under the plasma concentration versus time curve (AUC) were used along with the maximum observed plasma concentrations (Cpmax) to assess and compare the systemic exposure.

RESULTS:

Several of the analyzed concentrations of azoxystrobin were significantly higher or lower than the nominal values. This condition was considered when calculating the AUC and Cpmax for graphing. One rabbit at 7.5 mg/kg (CMC vehicle) died, cause unknown. Plasma concentrations of the acid metabolite occurred 2-6 hours post-dosing and were considerably higher than corresponding values for the parent azoxystrobin. There were no significant differences in this response among vehicles, however there was a large inter-animal variation. The acid increased with increasing dose of azoxystrobin. **These data are supplemental.** [redacted], 1/24/97.

023 146812 "Further Comparison of Exposure in the Non-pregnant Rabbit," (Hall, M.G., Zeneca Central Toxicology Laboratory, Cheshire, UK; CTL Ref: Y06654/014, CTL Study #: UBO487, 11/10/95. Azoxystrobin technical (96.2% pure) was administered by gavage to groups

of 3 New Zealand white rabbits per group at 50, 100, 200, 400 or 800 mg/kg (2 ml/kg corn oil vehicle) or 50, 200 and 400 mg/kg in either corn oil (1 ml/kg) or CMC at 5 ml/kg. Each animal was dosed with the appropriate dose formulation on day 1 (phase 1), day 8 (phase 2) and day 15 (phase 3) of the study. Plasma samples were taken following each dose over a time course and analyzed for unchanged azoxystrobin and azoxystrobin acid. The areas under the plasma concentration versus time curve (AUC) were used along with the maximum observed plasma concentrations (Cpmax) to assess and compare the systemic exposure over the broad dose range.

RESULTS:

Analyzed concentrations of azoxystrobin (100 mg/kg--phase 1) were significantly higher than the nominal values. Dosing formulations from phase 1 (50, 200 and 400 mg/kg) were not analyzed because there was insufficient sample available. This condition was considered when calculating the AUC and Cpmax for graphing. Maximum plasma concentrations of the acid metabolite occurred 2-6 hours post-dosing, except at the highest doses and were considerably higher than corresponding values for the parent azoxystrobin. The acid increased with increasing dose of azoxystrobin. The AUC began to plateau at > 400 mg/kg azoxystrobin. There were no significant differences in this response among vehicles, however there was a large inter-animal variation. **These data are supplemental.** [redacted], 1/24/97.

** 024 146814 "Assessment of Teratogenicity in the Rabbit," (Moxon, M.E., Zeneca Central Toxicology Laboratory, Cheshire, UK; Report #: CTL/P/4757; Study #: RBO696; 10/26/95.) Azoxystrobin technical (96.2% pure) was administered by gavage to mated New Zealand white rabbits (20/dose) at 0 (corn oil, 1 ml/kg), 50, 150, or 500 mg/kg/day during days 8-20 of gestation. Animals were terminated on day 30 of gestation. Maternal NOEL = 50 mg/kg/day (Mortality occurred on study: 1 at 500 mg/kg was killed day 11; 2 at 150 mg/kg were killed day 21 & 8. There was an increased incidence of animals with diarrhea or signs of diarrhea, signs of diarrhea and/or staining in the genital area (1, 7, 15 and 18 at 0, 50, 150 and 500 mg/kg/day, respectively). Decreased body weight was observed at 500 mg/kg/day. Food consumption data showed a transitional decrease, primarily at $\geq$ 150 mg/kg/day.) Fetal NOEL = 150 mg/kg/day (There was 1 fetus at 500 mg/kg/day with spina bifida meningocoele. An increase in liver cysts (per fetus & per litter) at 500 mg/kg/day. There was a significant decrease in pes scores at 500 mg/kg/day.) **No adverse effect. Acceptable.** [redacted], 1/29/97.

Range-finding Teratology Studies

020 146803 "Dose Range Finding Study in the Rabbit," (Moxon, M.E.; Zeneca Central Toxicology Laboratory, Cheshire, UK; Report #: CTL/P/4608; Study #: RB0550; 5/26/95). Azoxystrobin technical (95.2% pure) was administered by gavage to New Zealand White rabbits (2 total) at 200 mg/kg (8 days), 400 mg/kg (8 days) and 800 mg/kg 3 days, sequentially for a total of 19 days. The animals were subsequently terminated without examination. Corn oil served as the vehicle control. Subsequently, 2 additional animals were treated with 800 mg/kg/day for 3 days. NOEL < 200 mg/kg/day (Animals 1 & 2 produced few or no feces during the greater part of the study and both were thin by day 19. Animals 3 & 4 had severe diarrhea after 800 mg/kg by day 3 #4 was cold, subdued and hunched. Weight loss occurred at 200 mg/kg in # 1 & 2. At 400 mg/kg, there was no change in # 1, but # 2 continued to lose weight. At 800 mg/kg all 4 animals showed severe weight loss. Food consumption was decreased (transient) in #'s 1 & 2 at 200 mg/kg. At 400 mg/kg, there was no change, however at 800 mg/kg, all animals stopped eating.) CONCLUSION: The high dose for the definitive study should be between 400 and 800 mg/kg/day. These data are supplemental. [redacted], 1/7/97.

020 146805 "Dose Range Finding Study in the Pregnant Rabbit," (Moxon, M.E.; Zeneca Central Toxicology Laboratory, Cheshire, UK; Report #: CTL/P/4538; Study #: RBO605; 2/15/95). Azoxystrobin technical (96.2% pure) was administered by gavage to mated New Zealand white rabbits (10/dose) at 0 (corn oil), 60, 90 and 120 mg/kg/day during days 7-20 of gestation. Maternal NOEL < 60 mg/kg (The incidence of rabbits found dead or killed in extremis during the study was 2, 4, 4 and 3 at 0, 60, 90 or 120 mg/kg/day, respectively. There was an increased incidence of animals with diarrhea or signs of diarrhea (4, 7, 9 and 9 at 0, 60, 90 and 120 mg/kg/day, respectively). Decreased body weight was observed at ≥ 60 mg/kg/day. Stomach abnormalities (abnormal content and detached mucosa) were observed in animals which died intercurrently.) Fetal NOEL = 90 mg/kg/day (There is a slight increase in post-implantation loss at 120 mg/kg/day (attributed to 1 litter). These data are **supplemental.** Not acceptable. [redacted], 1/8/97.

023 146809 "Second Dose Range Finding Study in the Rabbit," (Moxon, M.E.; Zeneca Central Toxicology Laboratory, Cheshire, UK; Report #: CTL/P/4791; Study #: RB0679; 10/26/95). Azoxystrobin technical (96.2% pure) was administered by gavage to New Zealand white rabbits initially at: **Group 1:** 50 mg/kg (animals 1 & 2 with 1 ml/kg corn oil) for 4 consecutive days. In the absence of effects on bodyweight, food consumption or clinical condition, animals were dosed at 100 mg/kg for 4 days, 200 mg/kg for 4 days and 400 mg/kg for 6 days. **Group 2:** Rabbits 3 & 4 were dosed according to the same regimen, except azoxystrobin was administered in 2 ml corn oil/kg. **Group 3:** Rabbits 5 & 6 were dosed at 600 mg/kg/day in 1 ml corn oil/kg for 13 days, since there was no systemic toxicity in the previous groups.

RESULTS:

No effects on bodyweight, food consumption or clinical signs were observed in animals 1 & 2 with 1 ml/kg corn oil. At 2 ml/kg corn oil, animal # 4 showed decreased bodyweight and food consumption. At 600 mg/kg (1 ml/kg corn oil) both animals showed transitional decreased food consumption.

CONCLUSION: Results indicated that the highest dose of azoxystrobin to be used in pregnant rabbits would be > 400 mg/kg, but < 600 mg/kg. **No adverse effect indicated. These data are supplemental.** [redacted], 1/22/97.

023 146810 "Second Dose Range Finding Study in the Pregnant Rabbit," (Moxon, M.E.; Zeneca Central Toxicology Laboratory, Cheshire, UK; Report #: CTL/P/4787; Study #: RB0683; 10/26/95). Azoxystrobin technical (96.2% pure) was administered by gavage to mated New Zealand white rabbits (8/dose) during days 8-20 of gestation at: 0 (corn oil = 1 ml/kg), 100, 250 or 500 mg/kg/day. Further group was dosed at 0 (corn oil = 2 ml/kg), 100 or 250 mg/kg. A third group was sham dosed (no corn oil or azoxystrobin). On day 30 of gestation, rabbits were killed and their uteri were examined for live fetuses and intra-uterine deaths. Fetuses were weighed, examined for external abnormalities, then discarded.

RESULTS:

Clinical Observations: At 1 and 2ml/kg corn oil (≥ 100 mg/kg/day azoxystrobin), there was dose-related increase in animals with diarrhea, and/or genital staining.

Bodyweight: There was a transitional decrease in bodyweight gain at ≥ 100 mg/kg when 1 ml/kg corn oil was used. With 2 ml/kg corn oil there was transitional decreased bodyweights at 100 mg/kg but the weight loss was consistent throughout treatment at 250 mg/kg. The corn oil controls at both doses were initially decreased, compared to the sham control. Overall bodyweights for both corn oil controls were lower than the sham control.

Food Consumption: The 1 ml/kg corn oil group showed decreased food consumption (transitional) at 100 and 250 mg/kg. At 500 mg/kg, food consumption was decreased throughout the study. The 2 mg/kg corn oil groups showed decreased food consumption at ≥

100 mg/kg throughout the study. Animals at both doses of corn oil controls showed overall decreased food consumption compared to the sham control.
CONCLUSION: At 250 mg/kg (2 ml/kg corn oil) exceeded the MTD. Animals were killed before scheduled termination because of severely decreased food consumption and bodyweight loss. At ≥ 100 mg/kg (1 ml/kg corn oil) the food consumption and bodyweight effects were transitional. Therefore, 2 ml/kg corn oil enhances the toxicity of azoxystrobin. These data are **supplemental.** [redacted], 1/23/97.

023 146813 "Comparison of Exposure in the Pregnant Rabbit Dose Range- Finding Study," (Hall, M.G., Zeneca Central Toxicology Laboratory, Cheshire, UK; CTL Ref. #: YO6654/014; CTL Study #: UBO488; 11/10/95). Azoxystrobin technical (96.2% pure) was administered by gavage to mated New Zealand white rabbits (3/dose) during days 8-20 of gestation at: 100, 250 or 500 mg/kg/day (corn oil = 1 ml/kg) or 100 or 250 mg/kg/day (corn oil = 2 ml/kg). Plasma samples were taken daily throughout the dosing period with more frequent sampling following the initial and final doses. Plasma was analyzed for azoxystrobin and the acid metabolite. AUC and Cpmax were calculated to assess and compare systemic exposure.
RESULTS:
At 500 mg/kg, doses were assessed as low (19% below nominal).
Clinical Observations: Two animals at 100 mg/kg (2 ml/kg corn oil) were terminated prematurely due to excessive weight loss (unlikely due to treatment).
Bodyweight: Weight loss at 1 ml/kg corn oil was transitional, where at 2 ml/kg corn oil, only 2 animals showed signs of recovery. Animals 2 & 3 (100 mg/kg, 1 ml corn oil) were not pregnant at termination, however the data from these animals were similar to the pregnant animal in their group, thus the data were included in the study.
Assessment of Exposure: Steady state plasma concentrations (SS-C) for both azoxystrobin and the acid were attained within 2-3 days. Acid mean SS-C was 15-20 fold higher than azoxystrobin. Values for AUC generally increased with dose, following treatment up to 500 mg/kg (1 ml/kg) but began to plateau at the high dose. Results were similar at 2 ml/kg corn oil up to 250 mg/kg azoxystrobin. Comparable plasma concentrations of parent and acid were obtained when the same dose levels were administered in corn oil at 1 or 2 ml/kg.
CONCLUSION: AUC and Cpmax values for parent and acid leveled at 250-500 mg/kg. The corn oil volume did not affect the systemic exposure to azoxystrobin or the acid.
These data are supplemental. [redacted] 1/28/97.

NEUROTOXICITY

Acute neurotoxicity, rat

010; 146790; "ICIA5504: Acute Neurotoxicity Study in Rats" (Horner, S.A., Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Study No. AR5648, Report No. CTL/P/4313, 6/22/94). 818. ICIA5504 (Batch number P49/D7534/46, purity=96.2%), prepared in corn oil, was administered as a single dose by gavage at concentrations of 0, 200, 600, or 2000 mg/kg to 10 Alpk:APfSD rats per sex per dose level. Transient treatment-related effects, due to general toxicity including diarrhea, signs of diarrhea, hunched posture, splayed gait, tip toe gait, and upward curvature of spine were observed. No treatment related effects on land foot splay measurements, tail flick, forelimb or hindlimb grip strength measurements, and motor activity measurements were observed. Pathology: macroscopic and microscopic examinations revealed no treatment-related abnormalities. NOEL (M/F) < 200 mg/kg (based on systemic toxicity), NOAEL (M/F)=2000 mg/kg. **No adverse effects. acceptable.** ([redacted] 1/13/97)

90-day neurotoxicity, rat

014; 146794; "ICIA5504: Subchronic Neurotoxicity Study in Rats" (Rattray, N.J., Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Study No. PR0964, Report No. CTL/P/4322, 7/8/94). 827. ICIA5504 (Batch number P49/D7534/46, purity=96.2%) was admixed to the feed at concentrations of 0, 100, 500, or 2000 ppm and fed to 12 Alpk:APfSD rats per sex per dose level for a period of 90 days. Statistically significant reduction in mean body weight gain and decrease in mean food consumption were observed in males at the 2000 ppm dose level. Clinical signs: reduced splay reflex was observed in one 100 ppm dose level male during week 14, in one 2000 ppm dose level male between week 5 and week 14, in one 500 ppm dose level female during week 14, and in one 2000 ppm dose level female between week 9 and week 14. Pathology: macroscopic and microscopic examinations revealed no treatment-related abnormalities. NOEL (M) < 8.0 mg/kg/day (based on clinical signs), NOEL (F)= 8.0 mg/kg/day (based on clinical signs), NOAEL (M/F)=161.0 mg/kg/day. **(No adverse effects). acceptable**. ([redacted] 1/15/97)

Developmental neurotoxicity, rat

Study not submitted nor required at this time.

Delayed neurotoxicity, hen

Study not submitted nor required.

IMMUNOTOXICITY

Study not submitted at this time.

ENDOCRINE DISRUPTOR STUDIES

Study not submitted nor required at this time.

SUPPLEMENTAL STUDIES

52100-0345; 277405; “Amistar 8 (A13368B)-A 28-Day Inhalation Toxicity Study in Rats”; (J. Bain; Charles River Laboratories, Preclinical Services, Tranent, Edinburgh, EH33 2NE UK; Study No. 672741; 10/22/13); Ten Han-Wistar rats/sex/group were exposed nose-only to 0, 0.049, 0.144 or 0.455 mg/l (analytical) of Amistar 8 (A13368B) (lot no. CRS-1063; a.i.: 7.79%) for 6 hours/day, 5 days/week for 4 weeks. The MMAD (GSD) values ranged from 2.59 (4.20) to 3.54 (2.60), 3.03 (2.78) to 3.96 (2.63), and 2.64 (2.42) to 3.24 (2.96) µm for the 0.049, 0.144 and 0.455 mg/l exposures, respectively. One female in the 0.049 mg/l exposure group was euthanized on study day 11 due to a wound in its tail. There was no treatment-related effect upon the mean body weights. The mean food consumption of both sexes in the 0.455 mg/l group was generally less than that of the control group over the course of the study (NS). There was no treatment-related effect noted in the hematology. Although some of the values for various parameters in the clinical chemistry evaluation were statistically different between the control and the high exposure group, there was no apparent treatment-related effect. The lung weights with body weight as a covariant were greater for both sexes in the 0.455 mg/l group and for females in the 0.049 and 0.144 mg/l groups in comparison to the controls ($p<0.05$ or 0.01). Likewise, the adrenal and thyroid weights of the females in the 0.455 mg/l group with body weight as a covariant were greater than the control group values ($p<0.05$). In the histopathological examination, squamous cell metaplasia was noted in the ventral portion of the larynx of both sexes in the 0.455 mg/l group and in the males of the 0.144 mg/l group. Squamous cell metaplasia was also evident in the arytenoid cartilage of the larynx of the males in the 0.455 mg/l group. Squamous cell metaplasia was present in the nasal cavity of both sexes in the 0.144 and 0.455 mg/l groups. The severity of these lesions was exposure-related. **Possible adverse effect:** squamous cell metaplasia in the larynx and nasal cavity. **Reported Rat 28-Day Inhalation NOEL:** (M/F): 0.049 mg/l (azoxystrobin: 3.85 µg/l) (based upon the incidence of lesions in the larynx and nasal cavity of both sexes in the 0.144 mg/l exposure

group); the analytical data which was used to calculate the exposure concentrations was not included in the report. Inclusion of this information would more definitively substantiate the value used to establish the NOEL. **Supplemental Study** (Moore, 7/14/15)