DATE: August 31, 2000

MEMORANDUM

SUBJECT: ***AZOXYSTROBIN*** - Report of the Hazard Identification Assessment Review Committee.

FROM: Ghazi A. Dannan, Pharmacologist
Registration Action Branch 3
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair
and
Elizabeth Doyle, Co-Chair
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Kelly O'Rourke, Risk Assessor
Registration Action Branch 3
Health Effects Division (7509C)

PC Code: 128810

On August 15, 2000, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for **Azoxystrobin** with regard to certain endpoints that were not covered in the previous Toxicology Endpoint Selection (TES) peer review (HED document no. 013102, dated 12/10/96). In the TES document (attached to this report as Appendix I), no appropriate endpoints were identified and no risk assessments were required for the acute dietary or short term, intermediate term. and chronic term dermal and inhalation occupational or residential exposures. **The HIARC evaluated the appropriate toxicity studies and recommended endpoints for the following exposure scenarios: acute dietary, short- and intermediate-term incidental oral, in addition to an acute-, intermediate-, and long-term inhalation.** The conclusions drawn at this meeting are presented in this report.

Committee Members in Attendance

Members present were: Ayaad Assaad, William Burnam, Jonathan Chen (from AD), Pamela Hurley, Tina Levine (from RD), Elizabeth Mendez, David Nixon, Jess Rowland (Co-Chairman).

Member(s) in absentia were: Elizabeth Doyle, Brenda Tarplee (Executive Secretary) and Yung Yang

Data evaluation prepared by: Ghazi Dannan of the Registration Action Branch 3

Also in attendance were: Kelly O'Rourke, Stephen Dapson, and Clark Swentzel

Data Evaluation / Report Presentation

Ghazi A. Dannan, Ph.D.
Pharmacologist

1. INTRODUCTION

On August 15, 2000, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for **Azoxystrobin** with regard to the acute Reference Dose (RfD) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The Toxicology Endpoint Selection (TES) Committee has previously evaluated the existing toxicology database for azoxystrobin and assessed appropriate toxicology endpoints and dose levels of concern for earlier risk assessment purposes. A copy of the TES document, dated 12/10/96, is attached to this proposal as Appendix 1.

As required by the Food Quality Protection Act (FQPA) of 1996, the potential for increased susceptibility of infants and children from exposure to azoxystrobin, was also previously evaluated. The HED FQPA Safety Factor Committee recommended that the 10-fold safety factor for increased susceptibility of infants and children should be removed for azoxystrobin (August 24, 1998).

The HED RfD/Peer Review Committee determined that azoxystrobin should be classified as "Not Likely" to be a human carcinogen according to the proposed revised Cancer Guidelines, based on lack of evidence of carcinogenicity in the long-term rat and mouse feeding studies (November 7, 1996).

2. HAZARD IDENTIFICATION

2.1 Acute Reference Dose (RfD)

Study Selected: Acute Oral Neurotoxicity in Rats §798.6050 (81-8)

MRID No.: 43678134

Executive Summary:

In an acute neurotoxicity study (MRID 43678134), ICIA5504 (Azoxystrobin, 96.2% a.i.) was administered once in corn oil (10 ml/kg body wt) by gavage to 3 groups of 10 Alpk:ApfSD rats/sex/dose at doses of 0, 200, 600 or 2000 mg/kg. All animals were evaluated in functional observational battery (FOB) and motor activity (MA) testing on Days -7, 1 (2 hr post-dosing), 8 and 15. Five control and high dose animals/sex perfused in situ were evaluated for microscopic neuropathology.

At 200 mg/kg and higher, diarrhea/signs of diarrhea were observed at 2 hr post-dosing in both sexes (males, 1, 4, 5 and 10; females, 0, 9, 9 and 6). Tip-toe gait and upwardly curved spine at 2 hr were also observed in treated but not control animals (no dose-response observed). No treatment-related effects on survival, food consumption, motor activity, brain weight/dimensions, or gross/ microscopic pathology were observed. Body weights of males at 2000 mg/kg were slightly decreased (2.9% and 2.6% at day 8 and 15). Statistically significant increases in landing foot splay on Day 8 in females at 600 and 2000 mg/kg are noted (23.7% and 20.5% higher than controls, respectively; on Day 1 females at 600 and 2000 mg/kg had nonstatistically significantly

increased values of 11.8 and 12.5%, respectively). These were not considered indicative of neurotoxicity due to lack of effect on day of dosing (only marginal non-significant increase seen) and to lack of a clear dose-response and indications of other effects. These effects are also exacerbated by the observed gastric distress, a non-neurotoxic response. **The systemic toxicity LOEL is 200 mg/kg, based on occurrence of transient diarrhea in both sexes. The systemic toxicity NOEL is < 200 mg/kg. There was no indication of neurotoxicity at the doses tested.**

This acute neurotoxicity study in the rat is classified as **Supplementary (upgradable)** and does not satisfy the guideline requirement for an acute oral study (81-8). The study may be upgraded to Acceptable pending submission of: (1) validation studies demonstrating proficiency of the testing laboratory in conduct of neurobehavioral testing procedures, (2) provision of data supporting selection of 2 hr post-dosing as the time of peak effect and (3) clarification of parameters evaluated in the FOB (see "Discussion" for details).

Dose and Endpoint for Establishing RfD: The LOEL of 200 mg/kg/day based on occurrence of diarrhea in both sexes at two hours post-dosing.

Uncertainty Factor (UF): 300 (includes a factor of 3 for not achieving NOEL)

Comments about Study/Endpoint/Uncertainty Factor: The study is appropriate for the acute exposure via the oral route; effects in the study were seen after a single oral dose. The occurrence of diarrhea at the lowest tested dose of 200 mg/kg is supported by the similar findings at 100 mg/kg/day in the rat prenatal developmental toxicity study (MRID 43678142). There are no developmental concerns based on the two guideline acceptable prenatal developmental toxicity studies in rats and rabbits (MRID 43678142 and 44058701). This risk assessment should be valid for all population sub-groups.

2.2 Chronic Reference Dose (RfD)

Study Selected: Combined Chronic Toxicity/Carcinogenicity Rat Feeding study (as per attached TES Report, Appdx. I)

Guideline #: 870.4300

MRID No.: 43678139

Executive Summary:

In a combined chronic/oncogenicity study (MRID 43678139) ICIA5504 (azoxystrobin, 96.2% w/w a.i., Lot# P49) was administered to 52 Alpk:APfSD rats/sex/dose in the feed at dose levels

of 0, 60, 300, and 750 ppm/1500 ppm (males/females) (males: 0, 3.6, 18.2, and 34.0 mg/kg/day; females: 0, 4.5, 22.3, and 117.1 mg/kg/day) for 104 weeks. An additional 12 rats/sex/dose were designated for interim sacrifice at week 52. Due to excessive mortality the high dose was reduced to 750 ppm in males beginning at week 52 and the animals of this group designated for interim sacrifice were retained with the main study.

Distended abdomens were observed in males beginning at week 17 with 5, 0, 5, and 15 animals affected in the control, 60, 300, and 1500/750 ppm groups, respectively. Hunched posture was observed in males in a dose-related manner with 3, 11, 12, and 17 animals affected, respectively. No treatment-related clinical signs were observed in females at any dose. By week 52 survival rates of the males receiving the 0, 60, 300, and 1500 ppm diets were 97, 100, 98, and 86%, respectively prompting the dose reduction for the high-dose group. Survival rates at week 104 for the control, low-, mid-, and high-dose groups were 37, 38, 29, and 30%, respectively for males and 45, 62, 62, and 68%, respectively for females. The lower survival rate for control females did not occur until after week 100.

High-dose males had significantly lower body weights (92-95%) as compared to controls beginning at week 2 and continuing until week 101 (except for week 87 when no difference occurred; weeks 2-83, 89, 95-99: $p \leq 0.01$; weeks 85, 91, 101: $p \leq 0.05$). The differences in absolute body weights were due to reduced body weight gains (84-91%) of these animals during the first 25 weeks. High-dose females had significantly lower body weights (87-94%) than the controls beginning at week 2 and continuing until study termination (weeks 1-103: $p \leq 0.01$; week 105: $p \leq 0.05$). Lower body weights in these animals correlated with reduced weight gains of 58-93% of the control values.

Males in the high-dose group had significantly lower food consumption (95%) at weeks 1-20, 48, and 96 as compared to controls. Food consumption for high-dose females was significantly less (91-96%) than controls at weeks 1, 3-11, 13-36, 44, 56, and 68. Food utilization was significantly ($p \leq 0.01$) reduced in high-dose males for each of the intervals calculated: weeks 1-4, 5-8, 9-12, and 1-12. High-dose females had significantly ($p \leq 0.01$) reduced food utilization as compared to controls for the weeks 1-4 and 1-12 intervals.

No treatment-related effects were observed on ophthalmology, hematology, or clinical chemistry. In the common bile duct of high-dose males, there were significant increases ($p \leq 0.01$) in the rates of distension (13/47), cholangitis (13/47), thickening of the wall (11/47), and epithelial hyperplasia (9/47); these lesions were not observed in controls (0/34) or the other treated male groups or in females of any group.

Therefore, the systemic toxicity LOEL for males is 750 ppm based on reduced body weights, food consumption and food efficiency, and bile duct lesions (34 mg/kg/day) and the systemic toxicity LOEL for females is 1500 ppm based on reduced body weights (117.1 mg/kg/day). The systemic toxicity NOEL is 300 ppm (18.2 and 22.3 mg/kg/day for males and females, respectively).

There was no evidence of carcinogenic activity in this study. Among female rats, there was a

significant dose-related decrease in the incidence of benign fibroadenomas of the mammary gland with 10/52, 3/52, 2/52 ($p \leq 0.05$), and 1/52 ($p \leq 0.01$) affected in the control, 60, 300, and 1500 ppm groups, respectively.

This combined chronic/oncogenicity toxicity study in the rat is acceptable and satisfies the guideline requirement for a combined chronic/oncogenicity feeding study (83-5a) in rats.

Dose and Endpoint for Establishing RfD: NOAEL of 18.2 mg/kg/day

Uncertainty Factor(s): 100

Comments about Study/Endpoint/Uncertainty Factor:

2.3 Occupational/Residential Exposure

2.3.1 Short-Term (1-7 days) Incidental Oral Exposure

Study Selected: Prenatal Rat Oral Developmental Toxicity Study §870.3700

MRID No.: 43678142

Executive Summary:

In a developmental toxicity study (MRID 43678142) E5504, 95.2% a.i. was administered to 24 Wistar-derived rats/dose by gavage at dose levels of 0, 25, 100 or 300 mg/kg/day from days seven through 16 of gestation.

At 300 mg/kg/d maternal lethality caused the discontinuance of dosing at that level. At 100 mg/kg/d, minimally reduced body weights (< 2%) were observed ($p < 0.05$), although body weight gain and food consumption were not affected. Clinical signs included diarrhea (42%), urinary incontinence (17%) and salivation (71%). At 25 mg/kg/d salivation was observed in 29% of animals. **The maternal LOEL is 25 mg/kg/day, based on increased salivation. The maternal NOEL is not established.**

In the conceptus, no significant adverse developmental effects were observed. **The developmental LOEL is >100 mg/kg/day. The developmental NOEL is 100 mg/kg/day.**

Due to maternal toxicity at the high dose level, this study must be considered a two dose study,

which makes it deficient. However, since valid NOEL and LOEL were obtained from the data, the developmental toxicity study in the rat is classified acceptable and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; §83-3 a) in the rat.

Dose and Endpoint for Risk Assessment: Maternal NOAEL of 25 mg/kg based on increased diarrhea, urinary incontinence, and salivation among dams administered the next higher dose of 100 mg/kg/day (LOAEL).

Comments about Study/Endpoint: The study is appropriate because the exposure is short-term and suitable for this exposure scenario. However, the committee questioned the relevance of increased salivation, on its own, as an endpoint for setting NOAEL/LOAEL for this study. No salivation was reported in any other rat toxicity studies including the acute neurotoxicity study up to and including the HTD of 2000 mg/kg (MRID 43678134). Henceforth, the HIARC was of the opinion that the NOAEL/LOAEL should be 25/100 mg/kg/day, based on the maternal clinical signs of increased diarrhea, urinary incontinence, and salivation. The findings of diarrhea at 100 mg/kg/day in this study is consistent with the similar findings at 200 mg/kg in the acute neurotoxicity study (MRID 43678134).

2.3.2 Intermediate-Term (7 Days to Several Months) Incidental Oral Exposure

Study Selected: 90-Day Feeding in Rats §870-3100

MRID No.: 43678135

Executive Summary:

In a subchronic toxicity study (MRID 43678135), ICIA5504 (95.2% a.i., Lot No. P32) was administered to 12 Alpk:APfSD rats/sex/dose in the diet at concentrations of 0, 200, 2000 or 4000 ppm (0, 20.4, 211.0 or 443.8 mg/kg/day for males and 0, 22.4, 223.0 or 448.6 mg/kg/day for females) for 13 weeks. The 4000 ppm treatment groups were initially administered 6000 ppm in the diet, but this concentration was reduced after 15 days due to reduced food consumption and a marked reduction in growth.

Final body weights of males and females receiving 4000 ppm in the diet were reduced by 32 and 18%, respectively, and final body weights of males and females receiving 2000 ppm in the diet were reduced by 18 and 11%, respectively. Food consumption and food efficiency were reduced in both sexes receiving 4000 ppm, particularly during weeks 1-2 or weeks 1-4. However, by the end of the study, food efficiency of females in the 4000 ppm treatment was not significantly reduced compared with that of controls. In addition to small body size, distended abdomens, attributable to reduced nutritional status, were observed in both sexes in these two exposure groups. Minimal reductions in hemoglobin, MCV, MCH (females) and reduced cholesterol (males), glucose (females), increased triglycerides (both sexes), and some plasma enzyme activities (both sexes) were increased at 4000 ppm were also attributable to reduced nutritional status. Elevated white cell counts and decreased platelets in both sexes may be treatment related,

but were not accompanied by histopathological findings, indicating they were not toxicologically significant. All of these findings were less marked in the groups receiving 2000 ppm and were absent in the groups receiving 200 ppm. Increases in liver and kidney weights adjusted for body weight in the 2000 and 4000 ppm treatment groups were attributable to treatment. Changes in organ weights were accompanied by histopathological findings in two males in the 4000 ppm treatment group. Treatment-related effects in these males included marked elevations in total bilirubin, cholesterol, triglycerides, and plasma enzyme activities. The effect on the liver of these two animals was observed microscopically as proliferation of the intrahepatic bile duct/ductiles and oval cells. Hepatocellular hyperplasia and an enlarged hepatic lymph node was observed in one of the two males. **The LOEL is 2000 ppm (211.0 and 223.0 mg/kg/day for males and females) based on decreased weight gain in both sexes, clinical observations of distended abdomens and reduced body size, and clinical pathology findings attributable to reduced nutritional status. The NOEL is 200 ppm (20.4 and 22.4 mg/kg/day for males and females).**

This subchronic toxicity study is classified acceptable because it generally satisfies the guideline requirement for a subchronic oral study (82-1a) in rats. The study was properly conducted and a NOEL and LOEL were determined. No deficiencies were noted.

Dose and Endpoint for Risk Assessment: NOAEL = 200 ppm (21 mg/kg/day) based on reduced body weight gain and other clinical signs.

Comments about Study/Endpoint: The study is appropriate because the exposure is intermediate-term and suitable for this exposure scenario.

2.3.3 Dermal Absorption

At the time the TES report was issued, a dermal absorption study was not available (Appdx. I). A dermal absorption study was later submitted and evaluated by the Agency as follows.

Dermal Absorption Factor: 2 - 4 % based on Rat Dermal Absorption Study (MRID 43678155)

MRID No.: 43678155
Executive Summary:

In a dermal absorption study, (MRID 43678155) 24 male Alpk:APfSD rats were administered ICIA5504 ([^{14}C]-pyrimidinyl ICIA5504 and unlabeled ICIA5504) at doses of 0.01, 0.1, 0.9, or 13.3 mg/kg.

No animals died as a result of the treatment. Percutaneous absorption was minimal ($\leq$ 4.2%) and did not appear to exhibit a dose-response relationship. Limited absorption precluded accurate assessment of distribution and metabolite characterization. Both fecal and urinary excretion were quantified, the former representing ≈6% or less of total absorption and the latter accounting for <0.1% of the absorbed dose over a 24-hr period. Overall recovery of administered radioactivity

was 95-105%.

This study meets the requirements for a dermal absorption study in the rat (§85-2).

Comments about Dermal Absorption: An indirect approach confirms this finding by combining the 21-day rat dermal study (MRID 43678137) with either of a rat developmental toxicity study (MRID 43678142), or a 90-day rat study (MRID 43678135). The NOAEL of the developmental toxicity study is 25 mg/kg/day based on maternal clinical signs of increased diarrhea, urinary incontinence, and salivation at the LOAEL of 100 mg/kg/day. The 90-day study showed a LOEL of 211 mg/kg/d based on decreased body weight gain, with a NOEL of 20.4 mg/kg/day. The 21-day dermal study showed a NOEL of 1000 mg/kg/day, the Limit Dose. When these data are combined, an apparent absorption rate of 2 - 2.5% is calculated in agreement with the above value of 2 - 4% from the dermal absorption study.

2.3.4 Short-Term Dermal (1-7 days) Exposure

Study Selected: Refer to attached TES Report (Appdx. I) §

MRID No.:

Executive Summary:

Dose and Endpoint for Risk Assessment:

Comments about Study/Endpoint: The HIARC concurred with the TES document that this risk assessment is not required since no systemic effects were seen at the limit dermal dose (1000 mg/kg) in a 21-day rat dermal toxicity study (MRID 43678137). This finding of apparently low dermal toxicity is consistent with the low dermal absorption rate of 2 - 4% (see above).

2.3.5 Intermediate-Term Dermal (7 Days to Several Months) Exposure

Study Selected: Refer to attached TES Report (Appdx. I) §

MRID No.:

Executive Summary:

Dose/Endpoint for Risk Assessment:

Comments about Study/Endpoint: The HIARC concurred with the TES document that this risk assessment is not required since no systemic effects were seen at the limit dermal dose (1000 mg/kg) in a 21-day rat dermal toxicity study (MRID 43678137). This finding of apparently low dermal toxicity is consistent with the low dermal absorption rate of 2 - 4% (see above).

2.3.6 Long-Term Dermal (Several Months to Life-Time) Exposure

Study Selected: None §

MRID No.: N/A

Executive Summary: N/A

Dose and Endpoint for Risk Assessment: N/A

Comments about Study/Endpoint: This risk assessment is not required. As previously indicated in the TES report (Appdx. I), and based on the use patterns, this exposure scenario is not expected to be a concern.

2.3.7 Inhalation Exposure (All Durations)

a) Short-Term

Study Selected: Prenatal Rat Oral Developmental Toxicity Study §870.3700

MRID No.: 43678142

Executive Summary: Under Short-Term Incidental Oral Exposure (Section 2.3.1)

Dose/Endpoint for Risk Assessment: Maternal toxicity NOAEL of 25 mg/kg/day based on increased diarrhea, urinary incontinence and salivation in dams administered azoxystrobin at 100 mg/kg/day.

Comments about Study/Endpoint: Azoxystrobin is considered Toxicity Category III (LC_{50} males/females = 1.0/0.7 mg/L) based on an acute inhalation toxicity study of a four hour nose-only exposure to a dust aerosol of the chemical (MRID 43678126). However, there is no inhalation toxicity study available for this risk assessment. **Due to concern for exposure via this route based on the use pattern, the HIARC recommended the submission of a 28-day nose-only inhalation toxicity study using the same form of azoxystrobin to which workers are exposed.** The HIARC also recommended using route-to-route extrapolation and a 100% absorption rate (default value). The following steps should be considered for this inhalation risk assessment:

Step I. Convert the inhalation exposure component (i.e., μg a.i./day) using a 100% absorption rate (default value) and an application rate to an **equivalent oral dose** (mg/kg/day).

Step II. Convert the dermal exposure component (i.e. mg/kg/day) using a 4% dermal

absorption rate and an application rate to an **equivalent oral dose** (mg/kg/day).

Step III. Combine the oral equivalent doses (steps I and II) to obtain a total dose and compare the oral equivalent dose to the oral NOAEL of 25 mg/kg/day to calculate the MOE for the Short-term exposure scenario.

b) Intermediate-Term

Study Selected: 90-Day Feeding in Rats §870-3100

MRID No.: 43678135

Executive Summary: Under Intermediate-Term Incidental Oral Exposure (Section 2.3.2)

Dose/Endpoint for Risk Assessment: NOAEL = 200 ppm (21 mg/kg/day) based on reduced body weight gain and other clinical signs.

Comments about Study/Endpoint: Azoxystrobin is considered Toxicity Category III (LC_{50} males/females = 1.0/0.7 mg/L) based on an acute inhalation toxicity study of a four hour nose-only exposure to a dust aerosol of the chemical (MRID 43678126). However, there is no inhalation toxicity study available for this risk assessment. **Due to concern for exposure via this route based on the use pattern, the HIARC recommended the submission of a 28-day nose-only inhalation toxicity study using the same form of azoxystrobin to which workers are exposed.** The HIARC also recommended using route-to-route extrapolation and a 100% absorption rate (default value). The following steps should be considered for this inhalation risk assessment:

Step I. Convert the inhalation exposure component (i.e., μg a.i./day) using a 100% absorption rate (default value) and an application rate to an **equivalent oral dose** (mg/kg/day).

Step II. Convert the dermal exposure component (i.e. mg/kg/day) using a 4% dermal absorption rate and an application rate to an **equivalent oral dose** (mg/kg/day).

Step III. Combine the oral equivalent doses (steps I and II) to obtain a total dose and compare the oral equivalent dose to the oral NOAEL of 21 mg/kg/day to calculate the MOE for the Intermediate-term exposure scenario.

c) Long-Term

The long-term inhalation exposure is not applicable to the use scenario. Nonetheless, the HIARC selected the Combined Chronic Toxicity/Carcinogenicity Rat Feeding study (MRID 43678139, under above item 2.2) if this risk assessment becomes necessary in the future. The HIARC also recommended using a route-to-route extrapolation, a 100% absorption rate (default value), and the three steps as outlined above with the oral NOAEL

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of 18.2 mg/kg/day.

2.3.8 Margins of Exposure for Occupational/Residential Risk Assessments

An MOE of 100 is adequate for both the occupational and residential risk assessments. The FQPA SF committee has previously recommended that the 10-fold safety factor for increased susceptibility of infants and children be removed for azoxystrobin (FQPA report dated 9/3/98, HED doc. No. 012844).

2.4 Recommendation for Aggregate Exposure Risk Assessments

For **acute** aggregate exposure risk assessment, combine the high-end exposure values from food + water and compare it to the acute RfD (0.7 mg/kg) established for the general population.

For **chronic** aggregate exposure risk assessment, combine the average exposure values from food + water and compare it to the chronic RfD (0.25 mg/kg/day).

For **short** aggregate exposure risk assessment, the short-term dermal and inhalation exposures should be converted to oral equivalent doses (using 4% dermal absorption rate and 100% inhalation absorption rate), and these should be added to the oral exposures (from food + water) and compared to the oral NOAEL of 25 mg/kg to calculate the aggregate risk MOE.

For **intermediate** aggregate exposure risk assessment, the intermediate-term dermal and inhalation exposures should be converted to oral equivalent doses (using 4% dermal absorption rate and 100% inhalation absorption rate), and these should be added to the oral exposures (from food + water) and compared to the oral NOAEL of 21 mg/kg/day to calculate the aggregate risk MOE.

No **long-term** aggregate risk is required due to lack of chronic exposure.

3 CLASSIFICATION OF CARCINOGENIC POTENTIAL

3.1 Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID No. 43678139, under Chronic RfD (Section 2.2) Guideline #: 870.4300

Discussion of Tumor Data There was no evidence of carcinogenicity.

Adequacy of the Dose Levels Tested The tested dose levels were 0, 60, 300, and 750 ppm/1500 ppm (males/females) (males: 0, 3.6, 18.2, and 34.0 mg/kg/day; females: 0, 4.5, 22.3, and 117.1 mg/kg/day). The highest dose levels tested were adequate for assessing carcinogenicity based on body weight reduction in both sexes, bile duct lesions in males, and excessive mortality among males before they were switched from the 1500 ppm to the 750 ppm dietary

level at week 52. The NOAEL/ LOAEL for the chronic toxicity phase were considered to be 18.2/34.0 mg/kg/day in males and 22.3/117.1 mg/kg/day in females based on reduced body weights in both sexes and bile duct lesions in males. The HED-RfD/Peer Review Committee also considered the study and doses adequate for testing carcinogenicity (RfD/Peer Review Report dated 1/14/97).

3.2 Carcinogenicity Study in Mice § 870.4200

MRID No. 43678141

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).**

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.

Discussion of Tumor Data There was no treatment-related increase in tumor incidence compared to controls.

Adequacy of the Dose Levels Tested The highest dose level tested was considered to be adequate for carcinogenicity testing based on body weight reduction in both sexes (RfD/Peer Review Report dated 1/14/97).

3.3 Classification of Carcinogenic Potential

In accordance with the 1996 Cancer Risk Assessment Guidelines, the HED-RfD/Peer Review Committee classified azoxystrobin as "**not likely**" to be carcinogenic to humans

via relevant routes of exposure based on the lack of evidence of carcinogenicity in mice or rats (RfD/Peer Review Report dated 1/14/97, HED Doc. No. 012133).

4 MUTAGENICITY

The following assessment is from the RfD/Peer Review Report (dated 1/14/97, HED Doc. No. 012133).

"Several mutagenicity studies (84-2) were available for review by the Committee. The following is a summary of the studies and Committee's conclusions for each study:

1) Salmonella typhimurium/Escherichia coli reverse gene mutation assay (MRID No. 43678146, HED Doc. No. 012115): The test is negative up to 5000 µg/plate +/-S9, the highest dose tested using both plate incorporation and preincubation protocols. Cytotoxicity and compound precipitation were seen at the high dose.

2) Mouse lymphoma L5178Y $TK^{+/-}$ forward gene mutation assay (MRID No. 43678145, HED Doc. No. 012115): Nonlinear, slight but significant increases in the mutation frequency (MF) were seen at 15-60 µg/mL +/-S9. Despite the absence of a dose response, increased MFs were reproducible; therefore, Azoxystrobin is considered positive in this test system. Colony sizing was not performed.

3) In vitro chromosome aberrations in human lymphocytes assay (MRID No. 43678147, HED Doc. No. 012115): The test was positive for the induction of chromosomal aberrations in both the presence and absence of S9 activation at doses (5-50 µg/mL -S9; 100-200 µg/mL +S9) that were moderately to severely cytotoxic (i.e., ≥16-70% reductions in mitotic cells, respectively).

4) In vivo bone marrow micronucleus assay (MRID No. 43678148, HED Doc. No. 012115): The test is negative in C57BL/6JfBL10/Alpk mice up to 5000 mg/kg, the highest dose tested, when administered once by oral gavage. Overt toxicity and depression of erythropoiesis seen in the high-dose group; cytotoxic effects on the target cell were significant in the males.

5) In vivo/in vitro unscheduled DNA synthesis in rat hepatocytes (MRID No. 43678149): The test is negative in Alderley Park rats. No toxicity to the treated animals or cytotoxic effects on recovered hepatocytes up to the proposed new limit dose for acute testing (2000 mg/kg) when administered once by oral gavage.

The Committee overall concluded that Azoxystrobin in the presence and absence of exogenous metabolic activation induced a weak mutagenic response in the mouse lymphoma assay. Although colony sizing was not performed in the mouse lymphoma assay, it is likely that the increased MFs seen in this study were associated with a chromosomal rather than point mutational event. This interpretation is based on the similarity of the response uncovered in the mouse lymphoma assay to the clastogenic response seen with and without S9 activation in human lymphocytes. However, the negative genotoxicity associated with bone marrow cytotoxicity in the micronucleus assay provides confidence that Azoxystrobin is not an in vivo genotoxicant. This assumption is further supported by the negative findings of the UDS assay, the lack of an oncogenic effect in rat or mouse long-term

feeding studies and the absence of significant reproductive or developmental toxicity attributable to a mutagenic mode of action (i.e., decreased total implants, increased resorptions). Hence, it can be concluded that Azoxystrobin is active in vitro but this genotoxicity is not expressed in whole animals.

The submitted test battery satisfies the new mutagenicity initial testing battery guidelines. No other genetic toxicology data requirements have been identified at this time."

5 FQPA CONSIDERATIONS

5.1 Adequacy of the Data Base

The FQPA SF Committee considered the available toxicology data base adequate for an FQPA assessment and recommended that the 10-fold safety factor for increased susceptibility of infants and children should be removed for azoxystrobin (FQPA Report dated 9/3/98, HED Doc. No. 012844). The following rationale was provided in the FQPA Report. "The Committee recommended that the 10x Safety Factor should be removed. since: 1) the toxicology data base is complete; 2) the developmental and reproductive toxicity data did not indicate increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure; 3) unrefined chronic dietary exposure estimates (assuming all commodities contain tolerance level residues) will overestimate dietary exposure; 4) modeling data are used for ground and surface source drinking water exposure assessments resulting in estimates considered to be upper-bound concentrations; and 5) there are currently no registered residential uses for Azoxystrobin."

5.2 Neurotoxicity

— ***Acute Neurotoxicity*** - § 870.6200 (81-8), MRID 43678134

EXECUTIVE SUMMARY: In an acute neurotoxicity study (MRID 43678134), ICIA5504 (Azoxystrobin, 96.2% a.i.) was administered once in corn oil (10 ml/kg body wt) by gavage to 3 groups of 10 Alpk:ApfSD rats/sex/dose at doses of 0, 200, 600 or 2000 mg/kg. All animals were evaluated in functional observational battery (FOB) and motor activity (MA) testing on Days -7, 1 (2 hr post-dosing), 8 and 15. Five control and high dose animals/sex perfused in situ were evaluated for microscopic neuropathology.

At 200 mg/kg and higher, diarrhea/signs of diarrhea were observed at 2 hr post-dosing in both sexes (males, 1, 4, 5 and 10; females, 0, 9, 9 and 6). Tip-toe gait and upwardly curved spine at 2 hr were also observed in treated but not control animals (no dose-response observed). No treatment-related effects on survival, food consumption, motor activity, brain weight/dimensions, or gross/ microscopic pathology were observed. Body weights of males at 2000 mg/kg were slightly decreased (2.9% and 2.6% at day 8 and 15). Statistically significant increases in landing foot splay on Day 8 in females at 600 and 2000 mg/kg are noted (23.7% and 20.5% higher than controls, respectively; on Day 1 females at 600 and 2000 mg/kg had nonstatistically significantly increased values of 11.8 and 12.5%, respectively). These were not considered indicative of neurotoxicity due

to lack of effect on day of dosing (only marginal non-significant increase seen) and to lack of a clear dose-response and indications of other effects. These effects are also exacerbated by the observed gastric distress, a non-neurotoxic response. **The systemic toxicity LOEL is 200 mg/kg, based on occurrence of transient diarrhea in both sexes. The systemic toxicity NOEL is < 200 mg/kg. There was no indication of neurotoxicity at the doses tested.**

This acute neurotoxicity study in the rat is classified as **Supplementary (upgradable)** and does not satisfy the guideline requirement for an acute oral study (81-8). The study may be upgraded to Acceptable pending submission of: (1) validation studies demonstrating proficiency of the testing laboratory in conduct of neurobehavioral testing procedures, (2) provision of data supporting selection of 2 hr post-dosing as the time of peak effect and (3) clarification of parameters evaluated in the FOB (see "Discussion" for details).

— ***Subchronic Neurotoxicity*** - § 870.6200 (82-7), MRID 43678138

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

At 2000 ppm, mean body weights of males were statistically significantly decreased throughout the study (at week 13, 12.6% less than controls). Mean body weights of females were slightly decreased (at week 13, 5.1% less than controls; significant only at week 2). Cumulative body weight gains were 18% lower (males) and 10% lower (females). Food consumption was statistically significantly lower in males (5.4% to 15.4%) but not females. Food utilization in males at 2000 ppm was statistically significantly decreased during Weeks 1-4 (9.7%) and 1-13 (11.7%) and was non-significantly less in females during the same periods (11.8% and 14.4%, respectively). There were no consistent indications of treatment-related neurotoxicity (clinical signs, qualitative or quantitative neurobehavioral effects, brain weight/ dimensions, or gross/microscopic pathology). [Statistically significant decreases in landing foot splay in males (week 5, 19%, 16.4% and 24.1%, low to high dose; week 9, 18% at high dose), forelimb grip strength (males week 5, 14.3%, 14.3% and 19%, low to high dose and females week 14, 12.9%, high dose), hindlimb grip strength in males (week 5, 13.3%, 15.3% and 12.9%, low to high dose) and motor activity in females (21%, week 9) are noted but not considered treatment-related due to lack of dose-response, inconsistency of observations at different time points, variability of pretreatment values and/or small magnitude of response; see review for details]. **The systemic toxicity LOAEL is 2000 ppm (161 mg/kg/day), based on decreased body weight/weight gain and food utilization in both sexes (marginal in females). The NOAEL is 500 ppm (38.5 mg/kg/day).** A NOEL was not established due to the occurrence of gastric disturbances at all levels.

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

of the testing laboratory in performing neurobehavioral testing and (2) submission of a complete list of FOB parameters evaluated.

5.3 Developmental Toxicity

-- ***Developmental Toxicity Study in Rats*** - § 870.3700 (83-3), MRID 43678142

The chemical was administered by gavage at dose levels of 25, 100, or 300 mg/kg/day on gestation days 7-16. According to the DER, the maternal toxicity LOEL was considered to be 25 mg/kg/day, the lowest dose level tested, based on increased salivation; the maternal NOEL was not established. At 100 mg/kg/day, diarrhea, urinary incontinence, and salivation were observed. The 300 mg/kg/day dose was discontinued due to maternal deaths. The developmental toxicity LOEL was considered to be > 100 mg/kg/day; the developmental toxicity NOEL was not established.

As stated above (Section 2.3.1), the HIARC questioned the relevance of increased salivation, on its own, as an endpoint for setting NOAEL/LOAEL for this study. No salivation was reported in any other rat toxicity studies including the acute neurotoxicity study up to and including the HTD of 2000 mg/kg (MRID 43678134). Henceforth, the HIARC was of the opinion that the NOAEL/ LOAEL should be 25/100 mg/kg/day, based on the maternal clinical signs of increased diarrhea, urinary incontinence, and salivation. The findings of diarrhea at 100 mg/kg/day in this study is consistent with the similar findings at 200 mg/kg in the acute neurotoxicity study (MRID 43678134).

-- ***Developmental Toxicity in Rabbits*** - § 870.3700 (83-3), MRID 44058701

Azoxystrobin was administered by gavage at the dose levels of 50, 150, or 500 mg/kg/day on gestation days 8-20 at a dose volume of 1 ml corn oil/kg. The maternal toxicity NOEL/LOEL were considered to be 150 and 500 mg/kg/day, based on decreased body weight gain. The developmental toxicity NOEL was considered to be 500 mg/kg/day, the highest dose level tested. This is the second of two developmental toxicity studies in rabbits (the first is MRID 43678143).

The RfD/Peer Review Committee considered the first developmental toxicity study in rabbits (MRID 43678143) to be unacceptable and provided the following excerpted comments (RfD/Peer Review Report dated 1/14/97, HED Doc. No. 012133). The chemical was administered by gavage at dose levels of 7.5, 20, or 50 mg/kg/day on gestation days 8-20. The study, although performed in accordance with the USEPA guidelines, failed to accurately provide an overall NOEL. The Registrant submitted several supplementary nonguideline studies (MRID Nos. 44058702, 44058703, 44058705, 44073202 and 44073201) supporting their claim that the stress resulting from the dosing volume used (2 ml corn oil/kg) and maternal diarrhea caused by corn oil might have contributed to the effects seen in this study. In that particular testing facility, doses of corn oil at 2 mL/kg body weight and above may enhance the toxicity of Azoxystrobin. Because of all the uncertainties regarding the effects and the lack of definite etiology, the Committee considered the first rabbit developmental toxicity study (MRID No. 43678143) unacceptable and concluded that it should not be used for regulatory or risk assessment purposes and NOEL/LOELs should not be set (RfD/Peer Review Report dated 1/14/97, HED Doc. No. 012133). The RfD Report added that the second study

(MRID 44058701) demonstrated a completely different toxicity pattern with respect to maternal and fetal toxicity to Azoxystrobin; therefore, it was judged to be acceptable for regulatory or risk assessment purposes and should supersede the previous developmental toxicity study in rabbits (MRID 43678143).

5.4 Reproductive Toxicity

In the 2-generation reproductive toxicity study in rats (83-4, MRID No. 43678144), azoxystrobin was tested at dietary levels of 60, 300, or 1500 ppm (approx. 6.4, 32.3 or 165.4 mg/kg/day for males and 6.8, 33.8 or 175.0 mg/kg/day for females). The systemic toxicity NOEL/LOEL were considered to be 32.3 and 165.4 mg/kg/day, respectively, based on reduced body weight in both sexes, reduced food consumption and increased adjusted liver weights in females, histopathologically observed cholangitis, and increased weanling liver weights for both generations. The reproductive toxicity NOEL/LOEL were considered to be 32.3 and 165.4 mg/kg/day, respectively, based on decreased body weights for male and female pups of both generations.

5.5 Additional Information from Literature Sources (*if available*)

N/A

5.6 Determination of Susceptibility

The HIARC reaffirmed the FQPA SF Committee's conclusions that the available studies **indicated no increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to azoxystrobin.** In the prenatal developmental toxicity studies in rats and rabbits and the two-generation reproduction study in rats, any observed toxicity to the offspring occurred at equivalent or higher doses than did toxicity to parental animals (FQPA Report dated 9/3/98, HED Doc. No. 012844).

5.7 Recommendation for a Developmental Neurotoxicity Study

The HIARC, in its meeting of 8/15/00, reaffirmed the FQPA SF Committee's determination that " there are no data gaps for the assessment of the effects of azoxystrobin following *in utero* and/or postnatal exposure. Based on the toxicity profile, a developmental neurotoxicity study in rats is not required." (FQPA Report dated 9/3/98, HED Doc. No. 012844)

According to a recent health risk assessment for some food tolerances, the HIARC had also previously addressed this issue and decided not to recommend a developmental neurotoxicity study (see memorandum dated 1/28/99, t:\hed\reviews\128810\risk\d248888.mem). The following is a quotation from that memorandum. "Azoxystrobin was brought to the Hazard Identification Assessment Review Committee (HIARC) on 10/13/98, specifically to address the requirement for a developmental neurotoxicity study. The HIARC did not recommend a requirement for a developmental neurotoxicity study at this time. Neither the acute nor the subchronic mammalian neurotoxicity study gave a clear, consistent indication of neurotoxicity. There was no microscopic

evidence of neuropathology in either of these two studies or in any of the other studies conducted with azoxystrobin. In addition, there were no behavioral effects in pups in the 2-generation reproduction study and there were no alterations in the development of the central nervous system in the developmental studies."

5.7.1 Evidence that suggest requiring a Developmental Neurotoxicity study:

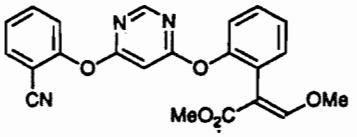
N/A

5.7.2 Evidence that **do not** support a need for a Developmental Neurotoxicity study:

N/A

6 HAZARD CHARACTERIZATION

Azoxystrobin is a β-methacrylate compound that is structurally related to the naturally occurring strobilurins, compounds derived from some fungal species. Azoxystrobin (structure shown below) is also in the same chemical class as Trifloxystrobin (PC Code 129112) which recently was granted a " reduced risk" status as a fungicide on several crops. The biochemical mode of action of these compounds is inhibition of electron transport in pathogenic fungi.



The most common toxicity findings from administration of azoxystrobin to rats, via the oral route, were decreased body weight, decreased food intake/utilization, increased diarrhea, and other clinical toxicity observations such as, increased urinary incontinence, hunched postures and distended abdomens. One or more of these effects were reported in most rat studies including subchronic (MRID 43678135), combined chronic toxicity/oncogenicity (MRID 43678139), prenatal developmental toxicity (MRID 43678142), 2-generation reproduction (MRID 43678144), acute neurotoxicity (MRID 43678134), and subchronic neurotoxicity(MRID 43678138). In the repeated dosing rat studies, these effects were not seen at the NOAEL values that ranged from 18 mg/kg/day in the chronic rat dietary feeding study to nearly 32 mg/kg/day (300 ppm) in the 2-generation rat reproduction study. In one instance (rat subchronic neurotoxicity study), the NOAEL was 38.5 mg/kg/day (500 ppm) based on decreased body weight/weight gain and food utilization; however, the executive summary of this study (section 5.2. above) indicated that a NOEL was not established due to the occurrence of gastric disturbances at all levels (100, 500, or 2000 ppm).

In addition, increased lethality was seen after repeated oral administration at relatively high doses. For instance, in the combined chronic toxicity/oncogenicity study (MRID 43678139), the high dose male group was switched from dietary feeding at 1500 ppm to 750 ppm (34.0 mg/kg/day) due to excessive

mortality beginning at week 52. Also, in the prenatal developmental toxicity study (MRID 43678142), three of the first 12 pregnant rats (25%) died after two days of treatment at the high dose (300 mg/kg/day in 10 ml corn oil/kg); henceforth, the study authors discontinued dosing at this level. It is interesting to note that these results do not appear to be consistent with the rat oral LD_{50} reported to be > 5000 mg/kg (MRID 43678122). In this acute toxicity study, five rats of each sex were gavaged a single dose of azoxystrobin at 5000 mg/kg (in 10 ml/kg corn oil); all rats survived the 14 day follow up with no reported clinical toxicity effects or changes in body weight. It is not clear why the chemical is more lethal in the developmental toxicity study than in the acute toxicity study; however, it is possible that there is enhanced toxicity due to pregnancy.

In the two-generation rat reproduction study (MRID 43678144) and the subchronic and chronic toxicity studies in rat (MRID 43678135 and 43678139) and dog (MRID 43678136 and 43678140), the liver and bile duct are the major target organs for azoxystrobin as evidenced by clinical chemistry, increased weight, gross pathology and/or microscopic changes in the liver and biliary tracts. Minor hematological effects were also reported in the rat and dog subchronic toxicity studies including decreased hemoglobin, MCV, and MCH in both species, increased white blood cells and decreased platelets in rats, and increased platelets in dogs; however, the changes were not considered toxicologically relevant because the magnitude was small (<10%) and there were no dose-response relationship.

The pre- and post-natal toxicology data base for azoxystrobin is adequate and includes the rat and rabbit developmental toxicity studies (MRID 43678142 and 44058701) and the 2-generation reproduction toxicity study in rats (MRID 43678144). There were no developmental effects in the rat and rabbit developmental studies. In the reproduction study, both the offspring and parents in the high dose group (1500 ppm) had decreased body weights and increased adjusted liver weights. In addition, the F_0 and F_1 parents in the high dose group, but not their offspring (aged 29 days), had liver and bile duct changes including distention and histopathologic lesions of the common bile duct (e.g., epithelial hyperplasia, cholangitis, ulceration of the dilated region, and small basophilic deposits in the lumen) in addition to increased liver proliferative cholangitis. Therefore, the effects in the young are not more severe than those observed with the parents.

In both the acute and subchronic neurotoxicity studies, there were no consistent indications of treatment-related neurotoxicity including clinical signs, qualitative or quantitative neurobehavioral effects, brain weight/dimensions, or gross/microscopic pathology. In the acute neurotoxicity study, tip-toe gait and upwardly curved spine were observed in treated but not control animals (no dose-response). Statistically significant increases in landing foot splay on day 8 in females at 600 and 2000 mg/kg were noted but were not considered indicative of neurotoxicity because of a lack of effect on day of dosing (only marginal non-significant increase seen) and to the lack of a clear dose-response and indications of other effects. The systemic toxicity LOAEL is considered to be 200 mg/kg/day (lowest dose tested) based on occurrence of transient diarrhea in both sexes (MRID 43678134). The NOAEL/LOAEL for the subchronic rat neurotoxicity study is 38.5/161 mg/kg/day based on decreased body weight/weight gain and food utilization. Statistically significant decreases in landing foot splay in males, forelimb grip strength in males and females, hindlimb grip strength in males, and motor activity in females were noted but were not considered treatment-related because of a lack of dose-response, inconsistency of observations at different time points, variability of pretreatment values and/or small magnitude of response (MRID 43678138).

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Based on pharmacokinetics and metabolism studies in rats (MRID 43678150, 43678151, 43678152, 43678153, 43678154), azoxystrobin was widely distributed following oral administration as single gavage doses of 1 or 100 mg/kg or 14-day repeated doses of 1 mg/kg. The greatest amounts of absorbed azoxystrobin were detected in organs associated with excretory function, especially the liver and kidneys. However, less than 0.5% of the administered dose was detected in the tissues at seven days postdosing and there was no apparent sex-related differences in distribution and no evidence of potential for bioaccumulation. Excretion via expired air was minimal. The primary route of excretion was via the feces (≈73-89%), although ≈9-18% was detected in the urine of the various dose groups. The fecal vs. urinary route of excretion did not vary considerably with dose or sex. However, a definitive quantitative assessment of absorption was difficult because of fecal sample extraction difficulties. Biliary metabolites were assessed using rats with cannulated bile ducts given a single 100 mg/kg gavage dose of azoxystrobin. For the single high-dose group, assessment of biliary excretion suggested approximately 70% absorption with approximately 32% of administered radioactivity remaining as parent compound in the gastrointestinal tract. Absorbed azoxystrobin appeared to be extensively metabolized with minor sex-related qualitative and quantitative differences in biliary metabolites. With the exception of metabolite V (a glucuronide conjugate) which represented 29.3% (males) and 27.4% (females) of the administered dose, individual biliary metabolites represented less than 10% of the administered dose. A metabolic pathway was proposed showing hydrolysis and subsequent glucuronide conjugation as the major biotransformation process.

7 DATA GAPS

There were no guideline required data gaps. **However, the HIARC recommended the submission of a 28-day inhalation toxicity study (Section 2.3.7).**

8 ACUTE TOXICITY

Acute Toxicity of Azoxystrobin

Guideline No.	Study Type	MRID #	Results	Toxicity Category
81-1	Acute Oral - Rat	43678122	LD_{50} > 5000 mg/kg (Limit Test) in Males & Females	IV
81-2	Acute Dermal - Rat	43678124	LD_{50} > 2000 mg/kg (Limit Test) in Males & Females	III
81-3	Acute Inhalation - Rat	43678126	LC_{50} **Males = 0.962 mg/L (95% C.I. = 0.674, *)** **Females = 0.698 mg/L (95% C.I. = 0.509, 2.425)** **The combined LC50 was not calculated** * Not calculated due to mortality pattern	III
81-4	Primary Eye Irritation - Rabbit	43678128	Slight to moderate erythema and slight chemosis in all rabbits within one hour, but effects resolved within 48 hours of treatment.	III
81-5	Primary Skin Irritation - Rabbit	43678130	Very slight erythema and edema that persisted for three days on one rabbit and for one hour on another.	IV
81-6	Dermal Sensitization - Guinea Pig	43678132	No erythema or edema were found 38 or 48 hrs after challenge with test material.	Not a dermal sensitizer
81-8	Acute Neurotoxicity	43678134	No indication of neurotoxicity at any dose level tested. NOEL/LOEL based on transient diarrhea in both sexes. NOEL = < 200 mg/kg LOEL = 200 mg/kg	Suppl. Upgradeable

9 SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	NOAEL < 200 mg/kg UF = 300	Diarrhea at two-hours post dose at all dose levels up to and including the lowest tested dose of 200 mg/kg (LOAEL).	Acute Neurotoxicity - Rat (MRID 43678134)
	Acute RfD = 0.7 mg/kg		
Chronic Dietary	NOAEL = 18.2 UF = 100	NOAEL = 300 ppm (males 18.2, females 22.3 mg/kg/day) based on reduced body weights in both sexes and bile duct lesions in males. The LOAEL in males/females = 750/1500 ppm (34/117 mg/kg/day).	Combined Chronic Toxicity/Carcinogenicity Feeding study - Rat (MRID 43678139)
		Chronic RfD = 0.18 mg/kg/day	
Incidental Oral, Short-Term	NOAEL = 25	Increased maternal diarrhea, urinary incontinence, and salivation at 100 mg/kg/day (LOAEL).	Prenatal Developmental Oral Toxicity - Rat (MRID 43678142)
Incidental Oral, Intermediate-Term	NOAEL = 20	NOAEL = 200 ppm (20.4/22.4 mg/kg/day in males/females) based on decreased body weight gain in both sexes and clinical signs indicative of reduced nutrition at the LOAEL of 2000 ppm (211/223 mg/kg/day in males/females).	90-Day Feeding - Rat (MRID 43678135)
Dermal, Short-Term	NOAEL = N/A	This risk assessment is not required since no dermal or systemic effects were seen at the limit dermal dose (1000 mg/kg/day).	21-Day Repeated Dose Dermal - Rat (MRID 43678137)
Dermal, Intermediate-Term	NOAEL = N/A	This risk assessment is not required since no dermal or systemic effects were seen at the limit dermal dose (1000 mg/kg/day).	21-Day Repeated Dose Dermal - Rat (MRID 43678137)
Dermal, Long-Term	NOAEL = N/A	This risk assessment is not required based on the use pattern.	
Inhalation, Short-Term	NOAEL = 25	Increased maternal diarrhea, urinary incontinence, and salivation at 100 mg/kg/day (LOAEL). Use route-to-route extrapolation and 100% absorption rate (default value).	Prenatal Developmental Oral Toxicity - Rat (MRID 43678142)
Inhalation, Intermediate-Term	NOAEL = 20	NOAEL = 200 ppm (20.4/22.4 mg/kg/day in males/females) based on decreased body weight gain in both sexes and clinical signs indicative of reduced nutrition at 2000 ppm (211/223 mg/kg/day in males/females). Use route-to-route extrapolation and 100% absorption rate (default value).	90-Day Feeding - Rat (MRID 43678135)
Inhalation, Long-Term	NOAEL = N/A	This risk assessment is not applicable to the use scenario of azoxystrobin.	

Appendix I

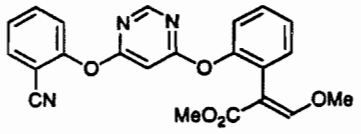
HED DOC. NO. 013102
Document dated 12/10/96

TOXICOLOGY ENDPOINT SELECTION DOCUMENT

Chemical Name: Azoxystrobin

PC Code: 128810

Structure



The Health Effects Division Toxicology Endpoint Selection Committee considered the available toxicology data for Azoxytrobin at a meeting held on Nov 12,1996. Based upon a review of the toxicology database for the chemical listed above, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories below. A brief capsule of the study is presented for use in preparation of risk assessments.

Where no appropriate data have been identified or a risk assessment is not warranted, this is noted. Data required to describe the uncertainties in the risk assessment due to the toxicology database are presented. These include but are not limited to extrapolation from different time frames or conversions due to route differences. If route to route extrapolation is necessary, the data to perform this extrapolation are provided.

TOXICOLOGIST: _____ Date: _____
(Myron S. Ottley, PhD)

SECTION HEAD: _____ Date: _____
(Marion P. Copley, DVM, DABT)

BRANCH CHIEF: _____ Date: _____
(Karl Baetcke, PhD)

DERMAL ABSORPTION DATA

MRID: N/A

% absorbed: N/A

No dermal absorption studies are available. Available are a 21-day rat dermal study, a rat developmental toxicity study and a 90-day rat study. The developmental toxicity study showed a LOEL of 100 mg/kg/d based on urinary incontinence, with a NOEL of 25 mg/kg/day.The 90-day study showed a LOEL of 211 mg/kg/d based on decreased body weight gain, with a NOEL of 20.4 mg/kg/day. The 21-day dermal study showed a NOEL of 1000 mg/kg/day, the Limit Dose. When these data are combined, **an absorption rate of 2% to 2.5% can be postulated.**

****

ACUTE DIETARY ENDPOINT (ONE DAY)

Study Selected - Guideline No.:

N/A

MRID No.:

N/A

Summary: (Enter Standard Executive Summary or equivalent):

N/A

Dose and Endpoint for use in risk assessment:

N/A

Comments about study and/or endpoint:

No appropriate endpoint was identified for this exposure scenario. No developmental toxicity was observed in the rabbit and rat studies reviewed. Effects seen in the acute neurotoxicity study were due to abdominal discomfort, not primary neurotoxicity.

This risk assessment **is not** required.

****

SHORT TERM DERMAL OCCUPATIONAL OR RESIDENTIAL EXPOSURE (1 TO 7 DAYS)

Study Selected - Guideline No.: Repeated Dose Dermal - Rat (82-2)

MRID No.: 43678137

Summary: (Enter Standard Executive Summary or equivalent):

In a 21-day repeated dose dermal toxicity study (MRID 43678137), groups of 5 male and 5 female Wistar rats were treated with ICIA5504 (Azoxystrobin) (96.2% w/w) in a deionized water paste by dermal occlusion at doses of 0, 200, 500, or 1000 mg/kg/day, 6 hours/day for 21 days over a 30 day period.

No mortality was observed and there were no significant treatment-related clinical abnormalities. There were no treatment-related effects on bodyweight, food consumption, organ weights, clinical biochemistry, or hematology. There were no treatment-related pathological abnormalities. Abdominal scabs and scabs at the edge of the application area were observed in all groups of females and were attributed to the bandaging method and were not of toxicological significance.

The **NOEL for Azoxystrobin was 1000 mg/kg/day; a LOEL was not determined.**

Dose and Endpoint for use in risk assessment: Not applicable

Comments about study and/or endpoint: At 1000 mg/kg/day (Limit Dose), no dermal or systemic effects were seen.

This risk assessment **is not** required because testing above the limit dose is not required.

****

INTERMEDIATE TERM DERMAL OCCUPATIONAL OR RESIDENTIAL EXPOSURE (1 WEEK TO SEVERAL MONTHS)

Study Selected - Guideline No.: Repeated Dose Dermal - Rat (82-2)

MRID No.: 43678137

Summary:

See SHORT-TERM DERMAL OCCUPATIONAL OR RESIDENTIAL EXPOSURE

Dose and Endpoint for use in risk assessment: Not applicable

Comments about study and/or endpoint: At 1000 mg/kg/day (Limit Dose), no dermal or systemic effects were seen.

This risk assessment **is not** required.

****

CHRONIC DERMAL OCCUPATIONAL OR RESIDENTIAL EXPOSURE (SEVERAL MONTHS TO LIFETIME)

Study Selected - None

MRID No.: N/A

Summary: N/A

Dose and Endpoint for use in risk assessment: Not applicable

Comments about study and/or endpoint: Based on use patterns and a lack of any observed effects in the 21-day dermal study, chronic exposure is not expected to be a concern at this time.

This risk assessment **is not** required at this time.

****

INHALATION EXPOSURE (ANY TIME PERIOD)

Study Selected - Guideline No.: Acute Inhalation Study (81-3)

MRID No.: 43678126

Summary:

N/A

Dose and Endpoint for use in risk assessment: Not applicable

Comments about study and/or endpoint: The acute inhalation Toxicity Category of this study is III, therefore risk assessment for inhalation exposure **is not** required at this time.

****

CANCER CLASSIFICATION AND BASIS:

Classified as NOT LIKELY, according to the proposed new guidelines
Q_1^* = N/A

****

RfD AND BASIS: The RfD is 0.18 mg/kg/day based on a NOEL of 18.2 mg/kg/d and an Uncertainty Factor of 100. Effects seen at the LOEL, 34 mg/kg/day were reduced body weight and bile duct lesions in males.

NOEL for critical study: 18.2 mg/kg/day

Study Type - Guideline No.: 83-5a

MRID: 43678139

****

FQPA Evidence of increased susceptibility in infants not identified. cf. RfD Report, meeting date: 12/5/96

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ACUTE TOXICITY ENDPOINTS:

Acute Toxicity of Azoxystrobin

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral	43678122	LD_{50} > 5000 mg/kg (Limit Test) in Males & Females	IV
81-2	Acute Dermal		LD_{50} > 2000 mg/kg (Limit Test) in Males & Females	III
81-3	Acute Inhalation	43678126	LC_{50} **Males = 0.962 mg/L (95% C.I. = 0.674, *) Females = 0.698 mg/L (95% C.I. = 0.509, 2.425) The combined LC50 was not calculated** * Not calculated due to mortality pattern	III
81-4	Primary Eye Irritation	43678128	Slight to moderate erythema and slight chemosis in all rabbits within one hour, but effects resolved within 48 hours of treatment.	III
81-5	Primary Skin Irritation	43678130	Very slight erythema and edema that persisted for three days on one rabbit and for one hour on another.	IV
81-6	Dermal Sensitization	43678132	No erythema or edema were found 38 or 48 hrs after challenge with test material.	Not a dermal irritant
81-8	Acute Neurotoxicity	43678134	Systemic toxicity not observed at any dose level tested NOEL = 200 mg/kg LOEL = < 200 mg/kg.	Suppl. Upgradeable

SignOff Date:	12/10/96
DP Barcode:	D000000
HED DOC Number:	013102
Toxicology Branch:	SAB