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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: I.D. Nos.: 5F4541, 10182-UNI, 6F04642, 6F04762. Azoxystrobin. Evaluation of Product Labeling Data Submitted and Identification of Outstanding Toxicology Data Requirements

Tox. Chem. No.	None	
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I. CONCLUSIONS

The existing database supports the following uses for Azoxystrobin:

Product I.D.	Submission	Formulation	Application
5F04541	Tolerance Petition	Azoxystrobin	For use on grapes and turf.
10182-UNI	Registration	Azoxystrobin	For use on grapes and turf
6F34642	Tolerance Petition	Azoxystrobin	for use on pecans

Product I.D.	Submission	Formulation	Application
6F04762	Tolerance Petition	Azoxystrobin	For use on bananas, peanuts peaches, tomatoes and wheat

The data submitted (DERs attached) are acceptable except the required acute neurotoxicity study (81-8, MRID 43678134) and subchronic neurotoxicity study (82-5, MRID 43678136) are Supplementary--Upgradeable due to incomplete data reporting, and a developmental toxicity study in the rabbit (MRID 43678143) was unacceptable because NOEL/LOEL determinations could not be made (Executive Summary in Section VIII). This developmental toxicity study was superseded by a subsequent study (MRID 44058701) which was acceptable.

Data Gap(s)

The only data gaps at this time are for acute (81-8) and subchronic (82-7) neurotoxicity. These gaps for neurotoxicity data are not adequate by themselves to hold up registration. The additional requested data for these studies should be considered as confirmatory.

II. ACTION REQUESTED

TB-1 received for evaluation 1) a petition for permanent tolerance for azoxystrobin for grapes and turf; 2) an application for registration of azoxystrobin for food/non-food use on grapes and turf, respectively; 3) a petition for tolerance for azoxystrobin for pecans; and 4) a petition for tolerance for azoxystrobin for peanuts, peaches, tomatoes and wheat. TB-1 was asked to evaluate these against the existing data base on azoxystrobin to determine if it is adequate to fulfill relevant data requirements. The data available were submitted Zeneca AG Products.

III. REQUIREMENTS

The requirements (CFR 158.135) for Food/Feed Use for the Technical, as of January 2, 1997, are listed in the following table.

Table 1. as of January 2, 1997

Test		Technical		Formulations§	
		Required	Satisfied	Required	Satisfied
81-1	Acute Oral Toxicity	Y	Y	Y	Y
81-2	Acute Dermal Toxicity	Y	Y	Y	Y
81-3	Acute Inhalation Toxicity	Y	Y	Y	Y
81-4	Primary Eye Irritation	Y	Y	Y	Y
81-5	Primary Dermal Irritation	Y	Y	Y	Y
81-6	Dermal Sensitization	Y	Y	Y	Y
81-7	Acute Delayed Neurotox. (Hen)	N	-	N	-
81-8-ss	Acute Neurotox. Screening Battery (Rat)	Y	N[1]	N	-
82-1	Oral Subchronic (Rodent)	Y	Y	N	-
82-1	Oral Subchronic (Non-Rodent)	Y	Y	N	-
82-2	21-Day Dermal	Y	Y	N	-
82-3	90-Day Dermal	N	-	N	-
82-4	90-Day Inhalation	N	N	N	-
82-5	90-Day Neurotoxicity (hen)	N	-	N	-
82-7	90 Day Neurotoxicity Screening Battery (Rat)	Y	N[1]	N	-
83-1	Chronic Toxicity (Rodent)	Y	Y	N	-
83-1	Chronic Toxicity (Non-rodent)	Y	Y	N	-
83-2	Oncogenicity (Rat)	Y	Y	N	-
83-2	Oncogenicity (Mouse)	Y	Y	N	-
83-3	Developmental Toxicity (two species—rodent & non-rodent)	Y	Y	N	-
83-4	Reproduction	Y	Y	N	-
83-5	Chronic/Oncogenicity	Y	Y	N	-
84-2	Mutagenicity—Gene Mutation	Y	Y	N	-
84-2	Mutagenicity—Structural Chromosomal Aberrations	Y	Y	N	-
84-4	Mutagenicity—Other Genotoxic Effects	Y	Y	N	-
85-1	General Metabolism	Y	Y	N	-
85-2	Dermal Penetration	N	-	N	-
86-1	Domestic Animal Safety	N	-	N	-
Special Studies for Ocular Effects					
	Acute Oral (Rat)	N	-	N	-
	Subchronic Oral (Rat)	N	-	N	-
	Six-month Oral (Dog)	N	-	N	-

Y Yes
N no
§ WG formulation
1 Study upgradeable; required data is considered confirmatory.

IV. SUMMARY OF THE TOXICITY DATA BASE FOR AZOXYSTROBIN TECHNICAL (as of January 2, 1997)

A. ~~ACUTE~~ TOXICITY

Adequacy of data base for acute toxicity (Series 81-1 to 81-6): The data base for acute toxicity is considered complete No additional studies are required at this time.

The Acute toxicity data on the Technical is summarized below in Table 2A. Table 2B summarizes the acute toxicity data on the 51% Formulation.

TABLE 2A. SUMMARY OF ACUTE TOXICITY OF AZOXYSTROBIN TECHNICAL

TEST	RESULTS	CATEGORY
81-1 Acute Oral Toxicity—Rats Study No.: CTL/P/3555 Date: November 12, 1991 MRID No.:43678122	LD50: Males and Females: >5000 mg/kg (Limit Test) Study is Acceptable Toxic Signs: No significant treatment-related signs, necropsy findings or changes in body weight	IV
81-2 Acute Dermal Toxicity—Rat Study No.: CTL/P/3556 Date: November 12, 1991 MRID No.: 43678124	LD50: >2000 mg/kg (Limit Dose) Study is Acceptable Toxic Signs: slight erythema at application site	III
81-3 Acute Inhalation Toxicity—Rat Study No.: CTL/P/3908 Date: December 15, 1992 MRID No.: 43678126	LC50: Males: 0.962 mg/L (95% C.I. = 0.674 Fmls : 0.698 Mg/L (95% C.I. = 0.509, 2.425 The combined LC50 was not calculated Study is Acceptable Toxic Signs: slow, deep breathing, auditory hypesthesia, breathing irregularities, splayed gait, reduced splay reflex, death. No effects on body weight observed	III
81-4 Primary Eye Irritation—Rabbit Study No.: CTL/P/3558 Date: November 6, 1991 MRID No.: 43678128	Primary Irritation Index: 4.3 Study is Acceptable Toxic Signs: slight to moderate erythema and slight chemosis, clearing within 48 hours.	III
81-5 Primary Dermal Irritation—Rabbit Study No.: CTL/P/3557 Date: November 6, 1991 MRID No.: 43678130	Study is Acceptable Toxic Signs: Slight erythema and edema	IV

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TEST	RESULTS	CATEGORY
81-6 Dermal Sensitization—Guinea Pig Study No.: CTL/P/3559 Date: November 13, 1991 MRID No.: 43678132	Not a Sensitizer using Study is Acceptable Toxic Signs: None except in positive controls	--

TABLE 2B. SUMMARY OF ACUTE TOXICITY OF AZOXYSTROBIN 51% WO FORMULATION

CITATION	RESULTS	CATEGORY
Acute Oral/Rat CTL/P/4327 March 23, 1994 MRID 43678123	LD_{50}: Males & Females: > 5000 mg/kg, Limit Test Study is Acceptable Toxic Signs: No significant treatment related signs, necropsy findings or changes in body weight. No deaths.	IV
Acute Dermal/Rat CTL/P/4326 March 23, 1994 MRID 43678125	LD_{50}: >2000 mg/kg (Local & Systemic) NOEL: <2000 mg/kg (Limit Test) Study Is Acceptable Toxic Signs: slight edema at application site	III
Acute Inhalation/Rat CTL/P/4370 May 6, 1994 MRID 43678127	LC_{50} Males and Females: > 4.67 mg/L (Limit test) Study is Acceptable Toxic Signs: no treatment related signs, necropsy findings or body weight changes.	IV
Eye Irrit./Rabbit CTL/P/4335 March 29, 1994 MRID 43678129	Conclusion: Moderate Eye Irritation, persisting up to 72 hr Study is Acceptable Toxic Signs: slight to moderate corneal irritation, slight iridal effects,moderate erythema, slight edema.	III
Primary Dermal Irritation/ Rabbit CTL/P/435 March 1, 1994 MRID 43678131	Conclusion: slight dermal irritant Study is Acceptable Toxic Signs: slight erythema and edema persisting up to three days.	IV

CITATION	RESULTS	CATEGORY
Dermal Sensitization/ Guinea pig CTL/P/4349 March 23, 1994 MRID 43678133	Conclusion: Not a Sensitizer Study is Acceptable Toxic Signs: None	N/A

B. SUBCHRONIC TOXICITY

Adequacy of data base for subchronic toxicity (Series 82): The data base for subchronic toxicity is considered complete. No additional studies are required at this time.

82-1a Subchronic Oral Toxicity Feeding - Rat

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.

82-1b Subchronic Oral Toxicity [capsule] - Dog

EXECUTIVE SUMMARY: In a subchronic toxicity study (MRID 43678136) ICIA5504 (96.2% w/w) was administered to 4 beagle dogs/sex/dose by capsule at doses of 0, 10, 50, or 250 mg/kg/day for 92 or 93 days (equal numbers of dogs in each dose group were treated for each number of days).

No animals died during the study. Treatment-related clinical observations in both sexes included increases in salivation at dosing, fluid feces, vomiting, and regurgitation primarily at 250 mg/kg/day (statistical analysis was not performed). These signs may have contributed to the lowered animal weights. The weekly body weights of both sexes differed statistically from controls for most weeks at 250 mg/kg/day and in females at 50 mg/kg/day, though values were within 9% of controls ($p \leq 0.05$ or 0.01). Total body weight gains were 34% and 38% lower than controls in high dose males and females, respectively. Hematological alterations at 250 mg/kg day in one or both sexes were small (< 9% change) compared to concurrent controls and/or pre-treatment values and not toxicologically relevant. Clinical chemistry parameters that were altered significantly from controls ($p \leq 0.05$ or 0.01) at the high dose in both sexes during one or more weeks include plasma cholesterol (13-26% increase), triglycerides (42-89% increase), alkaline phosphatase (24-87% increase), and plasma albumin (7.9-11.6% decrease). Cholesterol was increased in mid- and low-dose males (17-25%). These results were accompanied by increased absolute liver weight in mid- and high-dose females (6.3%, $p \leq 0.05$; 9.3%, $p \leq 0.01$, respectively), and are consistent with an adverse effect on liver and possibly biliary function. The lack of histopathological correlates and of a clearly dose- and time-related response in some cases, indicated the clinical and liver weight changes were an adaptive liver response. Other clinical chemistry changes ($p \leq 0.05$ or 0.01) did not appear to be treatment-related (plasma sodium,

creatinine, and total protein). There were no treatment-related effects on gross or microscopic pathology, food consumption, ophthalmology, or urinalysis. The increased thyroid weight, in the absence of histologic change, in high-dose females (37%, $p \leq 0.01$) was of uncertain toxicological significance. **The LOAEL (lowest observable adverse effect level) is 250 mg/kg/day for both male and female dogs under the conditions of this study, based on treatment-related clinical observations and clinical chemistry alterations at this dose. The NOAEL is 50 mg/kg/day.**

This subchronic toxicity study is classified acceptable and satisfies the guideline requirement for a subchronic oral study (82-1b) in dogs.

82-2 Repeated Dose Dermal – Rat

EXECUTIVE SUMMARY: 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.

This study is classified as **acceptable** and satisfies the guideline requirements for a 21-day dermal study (82-2) in rats.

C. CHRONIC TOXICITY

Adequacy of data base for subchronic toxicity (Series 83-1, 83-5): The data base for chronic toxicity is considered complete. No additional studies are required at this time.

83-5 Combined Chronic/Oncogenicity Feeding – Rat

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.

83-1b Chronic Oral Toxicity [capsule] - Dog

EXECUTIVE SUMMARY: In a chronic toxicity study (MRID 43678140) ICIA5504 (96.2% w/w) was administered to 4 beagle dogs/sex/dose by capsule at doses of 0, 3, 25, or 200 mg/kg/day for 52 weeks.

No animals died prior to the scheduled termination date. The most notable treatment-related clinical observation was an increase in the incidence of fluid feces in both sexes at 200 mg/kg/day: there were 414 occurrences in 4/4 males and 115 in 4/4 females compared to 3 occurrences in 2/4 males and 6 in 2/4 females in controls (statistical analysis was not performed). High-dose females had minor increases in salivation compared to control females, although their combined frequency was similar to that of concurrent control males. Treatment-related clinical chemistry changes at 200 mg/kg/day ($p \leq 0.05$ or 0.01) during one or more weeks included increased levels of plasma cholesterol (14-48%, both sexes), triglycerides (65-124%, both sexes), alkaline phosphatase (17-156%, both sexes), gamma-glutamyl transferase (74%-112%, females) and lowered plasma albumin (9.4-13%, males). Mid-dose males had increased cholesterol (23-27%) and triglycerides (65%). These results suggest an effect on liver and possibly biliary function. Minor and/or transient alterations ($p \leq 0.05$ or 0.01) in the total plasma protein, bilirubin, calcium, phosphorus, urea, potassium, and sodium were observed in one or both sexes. There was a small decrease in absolute brain weight in high-dose males (6.5%, $p \leq 0.05$) that is of uncertain biological significance, and a dose-related increase in liver weight in high-dose males (15%, $p \leq 0.01$) and in mid- and high-dose females (12%, $p \leq 0.05$ and 19%, $p \leq 0.01$, respectively). The increased liver weight and clinical chemistry changes observed in both sexes lacked histopathological correlates. There were no treatment-related effects on body weight, food consumption, ophthalmology, urinalysis, and gross or microscopic pathology in either sex of dogs.

The LOEL is 200 mg/kg/day, based on clinical observations, clinical chemistry changes, and liver weight increase occurring in both sexes at this dose. The NOEL is 25 mg/kg/day based on lack of significant treatment-related effects.

This chronic toxicity study is acceptable and satisfies the guideline requirement for a chronic oral study (83-1(b)) in dogs.

D. CARCINOGENICITY

Adequacy of data base for Carcinogenicity (Series 83-2, 83-5): The data base for carcinogenicity is considered complete. No additional studies are required at this time.

83-2b Carcinogenicity [feeding] - Mouse

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.

83-5 Combined Chronic/Oncogenicity Feeding – Rat

This study (MRID 43678139) is presented in the Chronic Toxicity Section.

E. DEVELOPMENTAL TOXICITY

Adequacy of data base for Developmental Toxicity (Series 83-3): The data base for developmental toxicity is considered complete. No additional studies are required at this time.

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83-3a Prenatal Developmental Study - Rat

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.

83-3b Prenatal Developmental Study - Rabbit

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

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

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

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

83-3 Prenatal Rangefinding and Developmental Studies - Rabbit

EXECUTIVE SUMMARY: The studies in the rabbit (MRIDs 44058702, 44058703, 44058705, 44073201, 44073202) were not necessarily conducted according to guidelines, but were supporting, fact-finding studies performed in connection with other guideline developmental toxicity studies in the rabbit. These data show that corn oil is not an innocuous vehicle, but can be toxic to rabbit dams at volumes of 2 ml/kg and above, and can enhance the toxicity of ICIA5504 at dose volumes of 2 ml/kg and above. These data support the Submitter's conclusion that the toxicity seen at 50 mg/kg in the 1994 rabbit developmental toxicity study (MRID 43678143) may be due to high volumes of corn oil vehicle (2 ml/kg).

F. REPRODUCTIVE TOXICITY

Adequacy of data base for Reproductive Toxicity (Series 83-34: The data base for reproductive toxicity is considered complete. No additional studies are required at this time.

83-4 2-generation Reproduction Study in the Rat

EXECUTIVE SUMMARY: In a 2-generation reproduction study (MRID 43678144), ICIA5504 (96.2% a.i.) was administered to 26 Alpk:Apfsd (Wistar-derived) rats/sex/dose at dose levels of 0, 60, 300, and 1,500 ppm in the diet. The average (F_0 and F_1) achieved test substance intake during the premating interval was as follows: 0 6.4, 32.3, or 165.4 (males) and 0, 6.8, 33.8, or 175.0 mg/kg/day (females). Exposure to the F_0 parental animals began at 4 weeks of age and lasted for 10 weeks before they were mated to produce the F_{1a} litters. The F_1 parental animals were selected from the F_{1a} litters at 29 days of age and were mated 10 weeks after selection to produce the F_{2a} litters. All animals were mated on a 1:1 ratio. Exposures to the test material for all animals were continuous in the diet throughout the study.

At 1,500 ppm, systemic toxicity in the F_0 and F_1 adults (both sexes) was demonstrated as reduced adjusted body weights (↓3-12%, $p \leq 0.01$ or 0.05) and food consumption (↓5-14%, $p \leq 0.05$ or 0.01) during the pre-mating intervals. In addition, treatment-related increases in liver weights adjusted for final body weights were noted in the F_0 and F_1 males and females (↑15-38%, $p \leq 0.01$ or 0.05) at the 1,500 ppm dose level. Treatment-related distention of the common bile duct was also noted grossly in 12 and 42% of the F_0 and F_1 males dosed at 1,500 ppm, respectively: Treatment-related histopathologic lesions of the common bile duct in the adult high-dose males were characterized as epithelial hyperplasia of the intraduodenal portion, cholangitis, ulceration of the dilated region, and small basophilic deposits in the lumen. Treatment-related increases in severity of proliferative cholangitis were also observed in the livers of the F_0 and F_1 males dosed at 1,500 ppm. Both sexes in the F_{1a} and F_{2a} 1,500 ppm dose groups had treatment-related increases in the adjusted (for final body weight) liver

weights (↑10-13%, $p \leq 0.01$). **The LOEL for systemic toxicity in males is 1500 ppm (163.2 mg/kg/day), based on reduced adjusted body weight means. A systemic NOEL in males was 300 ppm (33 mg/kg/day). The LOEL for systemic toxicity in females is 1,500 ppm (170.6 mg/kg/day), based on reduced adjusted body weight and feed consumption means and increased adjusted liver weights. The systemic NOEL in females is 300 ppm (33.2 mg/kg/day).**

Reproductive toxicity was demonstrated as treatment-related reductions in adjusted (for initial weight) pup body weights as observed in the F_{1a} and F_{2a} pups dosed at 1500 ppm (↓8 - 21%, $p \leq 0.05$ or $p \leq 0.01$). **The LOEL for reproductive toxicity is 1500 ppm (31.7 mg/kg/day), based on reduced adjusted pup body weights. The reproductive NOEL is 300 ppm (33 mg/kg/day).**

The reproductive study in the rat is classified as **acceptable** satisfies the guideline requirement for a 2-generation reproductive study (OPPTS 870.3800, §83-4).

G. NEUROTOXICITY

Adequacy of data base for Neurotoxicity (Series 81-7, 81-8, 82-7: The data base for neurotoxicity is not considered complete. The submitted studies are considered supplementary at this time, but can be upgraded to acceptable upon receipt of required information. These data are considered as confirmatory.

81-8 Acute Oral Neurotoxicity - Rat

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. **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.

82-7 Subchronic Neurotoxicity Feeding - Rat

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 LOEL is 2000 ppm (161 mg/kg/day), based on decreased body weight/weight gain and food utilization in both sexes (marginal in females). The NOEL is 500 ppm (38.5 mg/kg/day).**

This study is classified as **Supplementary (upgradeable)** 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.

H. MUTAGENICITY

Adequacy of data base for Mutagenicity (Series 84): The data base for Mutagenicity is considered adequate. Based on the available mutagenicity studies, there are no concerns for mutagenicity at this time.

84-2 Mammalian cells in culture gene mutation assay in L5178Y mouse lymphoma cells

EXECUTIVE SUMMARY: In a forward mutation study at the TK locus in L5178Y mouse lymphoma cells in culture (MRID 43678145) cells were exposed to ICIA5504 (96.2% w/w) in the presence and absence of an exogenous metabolic activation system (S9 mix), at concentrations of: 1st assay - 8, 15, 30, 60 μg/mL; 2nd assay - 34, 45, 60, 80 μg/mL and 3rd assay - 26, 33, 41, 51, 64, 80 μg/mL. Preparations for metabolic activation were made from Phenobarbital plus β-Naphthoflavone induced rat liver. The test material was delivered in DMSO.

ICIA5504 was tested to an upper concentration limited by cytotoxicity. The positive controls were acceptable as were the solvent controls in all cases except the second experiment without S9 mix where the solvent control was said to be out of the acceptable range (0.8 - 6.0 x 10^{-4} mutants per survivor). Mean cell survival at the HDT (60 ug/mL) in the first experiment was 30% in the absence of S9 mix and 26% in the presence of S9 mix. The maximum dose of test material was raised to 80 μg/mL in the second and third experiments with mean survival values without and with S9 mix of 10% and 4% in experiment 2 and 12% and 8% in experiment 3, respectively. Small, but statistically significant, increases in mutation frequency were seen in treated cells in all three experiments when S9 mix was present and also in Experiments 1 and 3 when S9 mix was absent. Mutation data from cultures without S9 mix in Experiment 2 were not presented because of the unacceptable solvent control. The mutation frequencies seen, both with and without S9 mix, in experiments 1 - 3 are small and inconsistent within and between experiments. For example, in experiment 1 with S9 mix, the mutation frequency at 8 μg/mL (2.5 x 10^{-4}) is not significantly different than the solvent control value of 2.1 x 10^{-4} while the mutation frequencies at 15, 30 and 60 μg/mL (3.7, 3.9 and 3.5 x 10^{-4}) are virtually the same and significantly increased over the solvent control at the $p < 0.01$ level. Comparable doses tested in experiment 2 with S9 mix, 34 μg/mL and in experiment 3, 26 and 33 μg/mL, with or without S9 did not significantly increase the mutation frequency over solvent control values, but higher (moderately to severely cytotoxic) doses did.

This study is classified as acceptable. Although the study cannot be considered definitive, we agree with the investigator that the test material is positive for forward gene mutation at

the TK-locus in L5178Y mouse lymphoma cells. The study satisfies the requirements for FIFRA Test Guideline 84-2 for *in vitro* mammalian cell gene mutation studies.

84-2 Salmonella/mammalian activation gene mutation assay

EXECUTIVE SUMMARY: In a reverse gene mutation assay in bacteria (MRID 43678146), strains TA98, TA100, TA1535 and TA1537 of *Salmonella typhimurium* and strains WP2P and WP2PuvrA of *Escherichia coli* were exposed to ICIA5504 (97.2% w/w) in DMSO at concentrations of 100, 200, 500, 1000, 2500 and 5000 μg/plate in the presence and absence of mammalian metabolic activation (S9-mix). S9-mix was prepared from phenobarbital plus β-naphthoflavone induced male Alderley Park (Alpk:Apfsd) rat liver.

ICIA5504 was tested up to 5000 μg/plate, an acceptable upper concentration. Test material precipitation and thinning of the background lawn was seen at this upper concentration. Both a standard plate assay and a pre-incubation assay were used and no significant, dose-related increase in the number of revertants per plate over solvent control values was seen in any strain in the presence or absence of S9-mix. The positive and solvent controls induced the appropriate responses in the corresponding strains. **There was no evidence of induced mutant colonies over background.**

This study is classified as acceptable. It satisfies the requirement for FIFRA Test Guideline 84-2 for *in vitro* mutagenicity [bacterial reverse gene mutation] data.

84-2 *In vitro* mammalian cytogenetics assay in human lymphocytes

EXECUTIVE SUMMARY: In a mammalian cell cytogenetics chromosomal aberration assay (MRID 43678147), cultures of primary human lymphocytes from one male and one female donor were exposed to E5504 (95.2% w/w) in DMSO at concentrations of 0.5, 1, 5, 10, 20, 30, 40, and 50 μg/mL in the absence of an exogenous metabolic activation system (S9-mix) and to 1, 5, 25, 50, 75, 100, 200, and 300 μg/mL in the presence of S9-mix. The S9 preparation was obtained from Aroclor 1254 induced male rat liver.

E5504 was tested up to cytotoxic concentrations as determined by reduced mitotic index or virtual absence of metaphase cells at the highest concentrations tested. Cultures exposed to E5504 at concentrations of 25, 100 and 200 μg/mL in the presence of S9-mix were evaluated for chromosomal aberrations for both cell donors at the 72 hour harvest time. Cultures exposed to concentrations of 1, 10 and 20 μg/mL and to concentrations of 5, 20 and 50 μg/mL in the absence of S9-mix were evaluated for chromosomal aberrations at 72 hours for the male and female donors respectively. Cultures, from the female donor only, exposed to 20 μg/mL test material in the absence of S9-mix and to 200 μg/mL in the presence of S9-mix were also evaluated at 96 hours. At the 72 hour harvest time in the absence of S9-mix, the mean percent of aberrant cells (excluding gaps in all cases) was 4.5% at 20 μg/mL in

cultures from the male donor compared to 0.0% in the solvent control ($p<0.01$). Comparable values in cultures from the female donor were 4.50% at 5 μg/mL ($p<0.05$), 8.00% at 20 μg/mL ($p<0.01$) and 6.00% at 50 μg/mL ($p<0.01$) compared to the solvent control value of 1.00%. In the presence of S9-mix, the mean percent of aberrant cells was significantly increased ($p<0.01$) at 200 μg/mL in cultures from both the male and female donor (11.50% vs 0.00% in solvent control and 6.50% vs 0.50% in solvent control respectively). The mean percent of aberrant cells was also significantly increased ($p<0.05$) at 100 μg/mL in cultures from the male donor (2.50% vs 0.00%). No significant increase in mean percent of aberrant cells was seen, with or without S9-mix, at the 96 hour harvest time. Aberrations were virtually all breaks and fragments or minutes. Positive and solvent controls induced the appropriate response. **There was evidence of a concentration related induction of chromosomal aberrations over background** in the presence of moderate to severe cytotoxicity.

This study is classified as acceptable. It satisfies the requirement for FIFRA Test Guideline 84-2 for in vitro cytogenetic mutagenicity data.

84-2 Mouse Micronucleus

EXECUTIVE SUMMARY: In a C57BL/6JfBL10/Alpk mouse bone marrow micronucleus assay (MRID 43678148), five mice of each sex per harvest time were treated once orally with E5504 (97.2% w/w) at a dose of 5000 mg/kg. Bone marrow cells were harvested at 24 and 48 hours post-treatment. The vehicle was corn oil.

There were no signs of toxicity during the preliminary MTD determination: however, in the main micronucleus test, treated females showed subdued nature, tiptoe gait, piloerection, signs of diarrhoea and signs of urinary incontinence on the day of dosing. No adverse reactions were seen subsequently. The mean percent of polychromatic erythrocytes (PCE) was significantly reduced in treated males at the 48 hour sampling time ($p < 0.01$) but not at 24 hours or at either time in females. The positive control induced the appropriate response. Slides prepared for micronuclei determination were evaluated twice, once as part of the primary study (1000 PCEs/mouse) and again by an independent evaluator (1000 PCEs/mouse from a different area of the slide than that used in the first evaluation). **There was no evidence of an increased induction of micronuclei over solvent control values in bone marrow PCEs in either sex at either sampling time in either evaluation.**

This study is classified as an acceptable study. It satisfies the requirement for FIFRA Test Guideline 84-2 for *in vivo* cytogenetic mutagenicity data.

84-2 Other Genotoxicity: Unscheduled DNA Synthesis in Rat Hepatocytes/Mammalian Cells - *in vivo/in vitro* Procedure

EXECUTIVE SUMMARY: In an *in vivo/in vitro* unscheduled DNA synthesis (UDS) assay in rat hepatocytes (MRID 43678149), E5504 (97.2% w/w) , at doses of 1250 and 2000 mg/kg, was administered to 5 male Alderley Park (Alpk:Apfsd) rats per test group by oral gavage. The test material was delivered once in corn oil at 10 ml/kg. Hepatocytes from 5 rats per test group were isolated at 2 or 16 hours post-treatment and cultured for determination of tritiated thymidine incorporation into DNA using the autoradiographic technique.

A preliminary toxicity test using doses ranging from 500 to 2000 mg/kg showed no signs of acute toxicity at any dose although diarrhea and urinary incontinence were seen at each dose level. An acute oral MLD value of greater than 5000 mg/kg E5504 had been previous demonstrated at this laboratory. Because E5504 was virtually non-toxic, it was tested to the limit dose of 2000 mg/kg for the UDS assay. No signs of cytotoxicity were seen in hepatocytes isolated from the treated rats. The net nuclear grain count was determined for 60 hepatocytes per animal and the percent of cells in repair recorded. A second independent assay was conducted. **There was no evidence that E5504 at either 1250 or 2000 mg/kg increased the incidence of UDS over solvent control values in hepatocytes isolated from rats 2 or 16 hours post-treatment,** but without any evidence presented that the test material (or its active metabolites) as administered (once orally, and up to a so-called "limit dose" of 2000 mg/kg) reached the target tissue (hepatocytes) in concentrations sufficient to register any effect (cytotoxicity, and/or genotoxicity). In contrast, hepatocytes from animals given the reference mutagens responded appropriately, with the vast majority of cells in repair (i.e., with net nuclear grain counts significantly in excess of +5).

Since signs of clinical toxicity (diarrhea, urinary incontinence) were observed in an initial range-finding study, at doses up to 2000 mg/kg (but not in additional rats given the same dosage, nor in the main study), we may consider the data requirements for this type of in vivo study to be satisfied, according to current FIFRA Test Guidelines.

I. METABOLISM

Adequacy of data base for metabolism (Series 85-1): The data base for metabolism is considered to be complete. No additional studies are required at this time.

85-1 Metabolism - Rat

EXECUTIVE SUMMARY: In a metabolism study (MRID 43678150, 43678151, 43678152, 43678153, 43678154), ICIA5504 (Azoxystrobin, 99% a.i. unlabeled or with pyrimidinyl, phenylacrylate, or cyanophenyl label) was administered to Alpk:Apfsd rats (5-8/sex/group depending on the experiment) as single gavage doses of 1 or 100 mg/kg or 14-day repeated doses of 1 mg/kg. Biliary metabolites were assessed using rats with cannulated bile ducts given a single 100 mg/kg gavage dose of ICIA5504.

No animals died as a result of the treatment. The overall recovery of administered radioactivity in the single low-dose, 14-day repeated low-dose, and single high-dose groups were 91.75-103.99% indicating acceptable mass balance. Less than 0.5% of the administered dose was detected in the tissues and carcass up to seven days postdosing. Absorbed of ICIA5504 following oral administration was widely distributed. However, a definitive quantitative assessment of absorption was difficult due to fecal sample extraction difficulties. The greatest amounts of absorbed ICIA5504 were detected in organs associated with excretory function, especially the liver and kidneys. There was 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, although for fecal excretion in the low-dose groups it was not possible to determine the relative contributions of parent compound and metabolites due to the previously noted extraction difficulties. 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. However, in the biotransformation study, parent compound was not detected in the fecal extracts of the single low-dose and repeated low-dose groups nor were substantial quantities of metabolites detected. Sex-related differences in excretion were minor; slightly greater (≈3-7%) amounts urinary radioactivity with commensurate reductions in fecal radioactivity were noted for female rats in all three treatment regimens. There were no apparent sex-related differences in distribution of administered radioactivity.

Absorbed ICIA5504 appeared to be extensively metabolized. Minor qualitative and quantitative differences in biliary metabolites were observed for males and females. 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, consistent with the data on metabolite identification and quantitation, was proposed showing hydrolysis and subsequent glucuronide conjugation as the major biotransformation process.

This metabolism study in the rat is classified supplementary and does not satisfy the guideline requirement for a metabolism study (85-1) in rats. The studies can be upgraded upon acceptable additional explanations of fecal excretion data and how they pertain to assessing absorption in the single low-dose and 14-day repeated low-dose groups.

85-2 Dermal Absorption - Rat

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 (≤ 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 study in the rat (§85-2).

V. ENDPOINTS FOR RISK ASSESSMENT

The HED Toxicity Endpoint Selection (TES) committee met on November 12, 1996 to select appropriate endpoints for acute dietary and short-, intermediate-, and long-term occupational exposure (dermal and inhalation) to azoxystrobin. No dermal absorption studies were available at that time. However, available were 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% was postulated. Subsequent to this meeting a dermal absorption study (85-2, MRID 43678155) showed **dermal absorption to be ≤4.2%.**

a. Acute Dietary Exposure (one day)

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.

b. Short Term Dermal Exposure (1 to 7 days)

No dermal or systemic effects were seen at the Limit Test of 1000 mg/kg/day in a 21-day dermal study. Therefore, this risk assessment is not required.

c. Intermediate Term Dermal Exposure (1 week to several months)

See SHORT-TERM DERMAL OCCUPATIONAL OR RESIDENTIAL EXPOSURE Dose and Endpoint for use in risk assessment: 1000 mg/kg/day. No dermal or systemic effects were seen at the Limit Test. No risk assessment is required.

d. Chronic Dermal Exposure (Several Months to Lifetime)

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.

e. Inhalation Exposure (Any time period)

The acute inhalation Toxicity Category of this study is III, therefore risk assessment for inhalation exposure is not required at this time.

f. Reference Dose

The RfD Document (dated 12/9/96) assigned an RfD of 0.18 mg/kg/day established by this committee (Study MRID 43678139, 83-5a), 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.

g. Carcinogenicity Classification

Classified by the RfD Document (dated 12/9/96) as NOT LIKELY, according to the proposed new guidelines.

h. FQPA

Evidence of increased susceptibility in infants not identified. cf. RfD Document, dated 12/09/96.

VI. ISSUES

TB1 received one rabbit developmental toxicity study for review (MRID 43678143), and it was found to be Unacceptable--Not Upgradeable (see Executive Summary below). However, we received a second rabbit developmental toxicity study for review (MRID 44058701) and found it acceptable for use in risk assessment. The second study, therefore, supersedes the first.

EXECUTIVE SUMMARY (unacceptable study): In a developmental toxicity study (MRID 43678143) ICIA5504, 96.2% a.i. was administered to 20 New Zealand White rabbits/dose by gavage in corn oil at 2 mg/kg bw at dose levels of 0, 7.5, 20, or 50 mg/kg/day from days eight through 20 of gestation.

At 20 mg/kg/d and higher, decreased body weight gain (< 5%) was observed, as well as negligible food consumption in some animals (not fully quantified due to excessive food wastage), which led to their sacrifice in moribund condition. **The maternal LOEL and NOEL for this study could not be determined.**

In the conceptus, increased fused sternebrae (3rd and 4th, and/or 4th and 5th) was observed in the high dose group, along with open eye and cleft palate (litter). **The developmental LOEL and NOEL for this study could not be determined.**

The developmental toxicity study in the rabbit is classified **unacceptable** and does not satisfy the guideline requirement for a developmental toxicity study (OPPTS 870.3700; §83-3 b) in the rabbit. The study was compromised due to excessive food wastage, maternal death and other unidentified factors. A NOEL/LOEL could not be established. The RfD committee concurred with these conclusions. The RfD committee has concurred with these conclusions at the Nov. 7, 1996 meeting.

The results are not appropriate for toxicity risk assessments since in subsequent studies (MRIDs 44058702, 44058703, 44058705, 44073201, 44073202) the Submitter has shown that corn oil, at the dose volume it was used here, is toxic to the dams, and also enhances the toxicity of ICIA5504. A subsequent developmental toxicity study (MRID 44058701) showed that when the dose volume of corn oil is 1 ml/kg, the above toxic effects are not seen in dams or fetuses.