5-29-97

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAY 29 1997

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **Azoxystrobin - 128810**: Health Effects Division Risk Characterization Document for the First Food Uses of Azoxystrobin in/on Grapes (5F4541), Pecans (6F4642), Bananas, Peaches, Peanuts and Tomatoes (6F4762).

PRATS Case Numbers: 286725, 287191, 287972, 005533
PRATS DP Barcode numbers: D230682, D221750, D228688, D235792, and D232805

FROM: Barbara Madden, Chemical Manager
Registration Section
Risk Characterization and Analysis Branch
Health Effects Division (7509C)

THROUGH: Michael Metzger, Chief
Risk Characterization and Analysis Branch
Health Effects Division (7509C)
and
for Margaret J. Stasikowski, Director
Health Effects Division (7509C)

TO: John Bazuin/Cynthia Giles-Parker PM Team 22
Fungicide Herbicide Branch
Registration Division (7505C)

The Health Effects Division (HED) of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The Registration Division (RD) of OPP has requested that HED evaluate toxicology and residue chemistry data and conduct dietary, occupational, and residential risk assessments, as needed to estimate the risk to human health that will result from the use of azoxystrobin in/on bananas, grapes, peaches, peanuts, pecans and tomatoes.

A summary of the findings and an assessment of human risk resulting from the proposed uses for azoxystrobin are provided in this document. The hazard assessment was provided by Myron S. Ottley, Ph.D. of Toxicology Branch I, the product and residue chemistry data review by Joel Garbus, Ph.D. and Linda Kutney of Chemistry Branch 1 - Tolerance Support, and the dietary risk assessment by Brian Steinwand of the Science Analysis Branch.

I. EXECUTIVE SUMMARY

HED has reviewed toxicology and residue chemistry data submitted by Zeneca Ag Products in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and 40 CFR §158. The data were submitted to support the registration of three end-use product formulations containing the active ingredient (ai) azoxystrobin as well as the establishment of permanent tolerances for grapes (5F4541), pecans (6F4642), bananas, peaches, peanuts and tomatoes (6F4762). The 6F4762 permanent tolerance petition originally included a request to establish tolerances for peanut hay, wheat, meat, fat, meat byproducts and milk. The registrant has since requested the removal of these tolerances from consideration at this time. The registrant has also included a feeding restriction of peanut hay on the proposed end-use product labels. Therefore, the crops proposed in these petitions do not concern raw agricultural commodities (RAC's) that are used as animal feeds.

Azoxystrobin is a fungicide. Technical Azoxystrobin is to be formulated into three end-use product formulations, a 22.9% soluble concentrate (10182-URL), a 50% wettable granular (10182-408), and a 80% wettable granular (10182-URA). Azoxystrobin is currently registered for use on turf. HED cannot recommend for the establishment of permanent tolerances for residues of azoxystrobin in/on bananas, peaches, peanuts, pecans and tomatoes resulting from the use of the soluble concentrate formulation. Residue data for these agricultural commodities were generated using the wettable granular formulations. The question arises whether residues and residue levels resulting from the use of the soluble concentrate formulation on agricultural commodities would be the same as those arising from the use of the wettable granular formulations. The guidelines for conducting field trials (OPPTS 860.1500) state that for pesticides used in late season foliar applications (as is the case with azoxystrobin) separate residue trials or bridging data are needed for different formulations.

The petitioner has not provided comparable data as to residue levels on grapes from trials where the soluble concentrate and the wettable granular formulations were applied at equivalent rates. However, residue data is available from trials where the soluble concentrate formulation was applied, due to a manufacturing error, at a rate two-thirds that of the wettable granular formulation. HED concluded from these results that the use of the soluble concentrate formulation would not result in residue levels in/on grapes greater than those that would be incurred from the use of the wettable granular formulation. Therefore, for grapes only, HED has no objections to the use of the soluble concentrate formulation.

The HED RfD/Peer Review Committee recommended that a reference dose (RfD) for azoxystrobin be established based on a no observable effect level (NOEL) of 18.2 mg/kg/day from the rat chronic toxicity/carcinogenicity feeding study (MRID 43678139). An uncertainty factor of 100 was used to allow for interspecies sensitivity and intraspecies variability. There was no evidence of increased susceptibility of infants or children to azoxystrobin. Therefore, no additional uncertainty factors are considered necessary at this time. On this basis, the RfD was calculated to be 0.18 mg/kg/day.

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

The Toxicology Endpoint Selection (TES) Committee met to evaluate the existing toxicology database for azoxystrobin and to assess appropriate toxicology endpoints and dose levels of concern that should be used for risk assessment purposes. Dermal absorption data (MRID 43678155) indicate that absorption is less than or equal to 4%. No appropriate endpoints were identified for acute dietary or short term, intermediate term, and chronic term (noncancer) dermal and inhalation occupational or residential exposure. Therefore, risk assessments are not required for these exposure scenarios. Therefore, there are no residential risk assessments to aggregate with the chronic dietary (food) risk assessment.

HED recommends the following tolerances be used for dietary risk assessments:

banana pulp[1]	0.05	ppm
grape, fresh	1.0	ppm
grape, raisins	1.0	ppm
grape, juice	1.0	ppm
peach	0.8	ppm
peanut, nutmeat	0.01	ppm
peanut, oil	0.03	ppm
pecan	0.01	ppm
tomato, fresh	0.2	ppm
tomato, juice	0.2	ppm
tomato, puree	0.2	ppm
tomato, paste	0.6	ppm
tomato, catsup	0.6	ppm

[1] The Agency does not currently require a separate tolerance for banana pulp. However, residue data for azoxystrobin and its Z isomer in/on banana pulp (prepared from unbagged and bagged bananas) indicate that a tolerance of 0.05 ppm would be appropriate. Though a tolerance of 0.5 ppm will be established for banana (whole fruit including peel), 0.05 ppm is recommended for use in dietary risk assessments.

A chronic dietary risk assessment was conducted using the recommended tolerances. The dietary analysis also included emergency exemption applications (Section 18s) for use of azoxystrobin in/on rice, milk, meat, eggs and poultry. The chronic analysis indicates that exposure from the proposed tolerances, for use of azoxystrobin in/on bananas, grapes, peaches, peanuts, pecans, and tomatoes, for the U.S. population would account for less than 1% of the RfD. For non-nursing infants, the subgroup with the highest exposure, 1% of the RfD would be utilized. Exposure to rice, milk, meat, eggs and poultry, as a result of the Section 18 registrations, as well as the proposed uses accounts for 1% of the RfD for the U.S. population and 5% of the RfD for non-nursing infants.

This chronic analysis for azoxystrobin is an upper-bound estimate of dietary exposure with all residues at tolerance level and 100 percent of the commodities assumed to be treated with azoxystrobin. Therefore, even without refinements, HED does not consider the chronic dietary risk, from use of azoxystrobin in/on bananas, grapes, peaches, peanuts, pecans, and tomatoes to exceed HED's level of concern.

There is no established Maximum Concentration Level for residues of azoxystrobin in drinking water. Data indicate moderate potential for soil mobility or leaching and azoxystrobin is moderately persistent. In examining aggregate exposure, the Food Quality Protection Act (FQPA) directs EPA to consider available information concerning exposures from the pesticide residue in food and all other non-occupational exposures. The primary non-food sources of exposure the Agency looks at include drinking water (whether from groundwater or surface water), and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor uses).

Because the Agency lacks sufficient water-related exposure data to complete a comprehensive drinking water risk assessment for many pesticides, EPA has commenced and nearly completed a process to identify a reasonable yet conservative bounding figure for the potential contribution of water related exposure to the aggregate risk posed by a pesticide. In developing the bounding figure, EPA estimated residue levels in water for a number of specific pesticides using various data sources. The Agency then applied the estimated residue levels, in conjunction with appropriate toxicological endpoints (RfD's or acute dietary NOEL's) and assumptions about body weight and consumption, to calculate, for each pesticide, the increment of aggregate risk contributed by consumption of contaminated water. While EPA has not yet pinpointed the appropriate bounding figure for consumption of contaminated water, the ranges the Agency is continuing to examine are all below the level that would cause azoxystrobin to exceed the RfD if the proposed food uses were granted. The Agency has therefore concluded that the potential

exposures associated with azoxystrobin in water, even at the higher levels the Agency is considering as a conservative upper bound, would not prevent the Agency from determining that there is a reasonable certainty of no harm if the proposed uses of bananas, grapes, peaches, peanuts, pecans, and tomatoes were granted.

The residue chemistry and toxicological database are adequate to support a conditional registration for the use of azoxystrobin in/on bananas, grapes, peaches, peanut, pecans, and tomatoes in terms of human health risk. To fully satisfy storage stability data requirements, the final results of the ongoing 2-year storage stability study must be submitted upon completion.

The registrant must also submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether azoxystrobin share(s) a common mechanism of toxicity with any other substance and, if so, whether any tolerances for azoxystrobin need to be modified or revoked.

EPA is required to develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect..." The Agency is currently working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists in developing a screening and testing program and a priority setting scheme to implement this program. Congress has allowed 3 years from the passage of FQPA (August 3, 1999) to implement this program. At that time, EPA may require further testing of azoxystrobin and end-use product formulations for endocrine disruptor effects.

II. BACKGROUND

Zeneca Ag Products has proposed permanent tolerances for residues of azoxystrobin from use on grapes (5F4541), pecans (6F4642), bananas, peaches, peanuts and tomatoes (6F4762). The 6F4762 permanent tolerance petition originally included a request to establish tolerances for peanut hay, wheat, meat, fat, meat byproducts and milk. The registrant has since requested the removal of these tolerances from consideration at this time. The registrant has also included a feeding restriction of peanut hay on the proposed end-use product labels. Therefore, the crops proposed in these petitions do not concern RAC's that are used as animal feeds.

Azoxystrobin is currently registered for use as a fungicide

on turf. Technical Azoxystrobin is to be formulated into three end-use product formulations, a 22.9% soluble concentrate (10182-URL), a 50% wettable granular (10182-408), and a 80% wettable granular (10182-URA). HED cannot recommend for the establishment of permanent tolerances for residues of azoxystrobin in/on bananas, peaches, peanuts, pecans and tomatoes resulting from the use of the soluble concentrate formulation. Residue data for these agricultural commodities were generated using the wettable granular formulations. The question arises whether residues and residue levels resulting from the use of the soluble concentrate formulation on agricultural commodities would be the same as those arising from the use of the wettable granular formulations. The guidelines for conducting field trials (OPPTS 860.1500) state that for pesticides used in late-season foliar applications (as is the case with azoxystrobin) separate residue trials or bridging data are needed for different formulations.

The petitioner has not provided comparable data as to residue levels on grapes from trials where the soluble concentrate and wettable granular formulations were applied at equivalent rates. However, residue data is available from trials where the soluble concentrate formulation was applied, due to a manufacturing error, at a rate two-thirds that of the wettable granular formulation. HED concluded from these results that the use of the soluble concentrate formulation would not result in residue levels in/on grapes greater than those that would be incurred from the use of the wettable granular formulation. HED has no objections to the use of the soluble concentrate formulation on grapes only.

Azoxystrobin is recommended for the control of black and yellow sigatoka on bananas. It is to be applied as a foliar application to banana trees at rates of 0.09-0.135 lb ai/A/application. Eight applications for a total of 1.08 lb ai/A can be applied per 12-month period. Applications should be started prior to disease development and retreatments made at 12- to 14-day intervals throughout the season. Applications may be made on the day of harvest.

Azoxystrobin is recommended for the control of mildews, black rot, and cane and leafspot on grapes. It is to be applied at rates of 0.11 to 0.25 lb ai/A in a minimum of 50 to 100 gallons per acre depending on the density of the foliage. Six applications for a total of 1.5 lb ai/A can be applied per year. There is a post harvest interval (PHI) of 14 days.

Azoxystrobin is recommended for the control of blossom blight, fruit brown rot and scab on peaches. It is to be applied as a foliar application at rates of 0.07-0.15 lb ai/A/application. Eight applications for a total of 1.2 lb ai/A can be applied per year. Applications may begin at early bloom, and may be made at 12- to 14-day retreatment intervals. There is

a PHI of 14 days.

Azoxystrobin is recommended for the control of early leafspot and late leafspot, Rhizoctonis peg and pod rot and stem rot/white mold (*Sclerotim rolfsii*) on peanuts. It is to be applied as a foliar application at rates of 0.1-0.4 lb ai/A/application. Two applications for a total of 0.8 lb ai/A can be applied per year. Applications should be made at 60 and 90 days after planting for control of soil borne diseases. There is a 50-day PHI. A restriction on the feeding of peanut hay is required at this time.

Azoxystrobin is recommended for the control of scab and anthracnose on pecans. It is to be applied at rates of 0.1 to 0.2 lb ai/A in a sufficient volume of water to ensure adequate coverage. A non-ionic surfactant at the rate of 1 pint per 100 gallons of water should be used to improve coverage. Multiple applications for a total of 1.2 lb ai/A can be applied per year. There is a PHI of 42 days.

Azoxystrobin is recommended for the control of anthracnose, early blight and Septoria leafspot on tomatoes. It is to be applied as a foliar application at rates of 0.025-0.10 lb ai/A/application. Eight applications for a total of 0.8 lb ai/A can be applied per year. Applications should be made at 7- to 21-day intervals. For control of late blight, no more than two consecutive applications of the product are to be made before alternating with other fungicides, and retreatments should be made at 5- to 10-day intervals. There is a PHI of 1 day.

III. SCIENCE ASSESSMENT

A. Physical and Chemical Properties Assessment

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

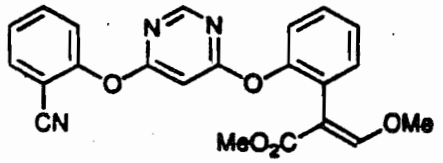
CA NAME: methyl (E)-2-[[6-(2-cyanophenoxy)-4-pyrimidinyl]oxy]- alpha-(methoxymethylene)benzeneacetate

Common Name: azoxystrobin

Caswell Number: 131860-33-8

Synonymous Name: ICIA5504

Structure:



Physical and Chemical Properties for Azoxystrobin Technical Grade Active Ingredient (TGAI) (MRIDs 43678102,-03,-04,-05,-06,-07)	
Color	Pale Brown
Physical State	Powdery Solid
Odor	None
Melting Point	114-116°C
Density, Bulk Density, or Specific Gravity	1.25 g/cm³
Solubility	Water: (20°C) 6.7 mg/l pH 5.2 6.7 mg/l pH 7.0 5.9 mg/l pH 9.2 Hexane: 0.057 g/l Octanol: 1.4 g/l Methanol: 20 g/l Toluene: 55 g/l Acetone: 86 g/l Ethyl Acetate: 130 g/l Acetonitrile: 340 g/l Dichloromethane: 400 g/l
Vapor Pressure (PAI)	1.1×10^{-13} kPa = 8.2×10^{-13} mm Hg (at 20°C)
Dissociation Constant	Not Dissociable
Octanol/Water Partition Coefficient (PAI)	log P_{ow} = 2.5
pH	6.4
Stability	thermal: Stable at least 14 days at 54°C to metals and ions: Unreactive to sunlight: potential for degradation
Oxidizing or Reducing Action	Compatible with oxidizing and reducing agents
Storage Stability	Stable for at least a year at ambient temps.

B. Human Risk Assessment

1. HAZARD ASSESSMENT

a. Acute Toxicity

The acute toxicity data on technical grade azoxystrobin is summarized below.

TEST	RESULTS	CATEGORY
Acute Oral Toxicity – Rat (MRID 43678122)	LD50: Males and Females: >5000 mg/kg (Limit Dose)	IV
Acute Dermal Toxicity – Rat (MRID 43678124)	LD50: >2000 mg/kg (Limit Dose)	III
Acute Inhalation Toxicity - Rat (MRID 43678126)	LC50: 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	III
Primary Eye Irritation – Rabbit (MRID 43678128)	Primary Irritation Index: 4.3 Toxic Signs: slight to moderate erythema and slight chemosis, clearing within 48 hours.	III
Primary Dermal Irritation – Rabbit (MRID 43678130)	Toxic Signs: Slight erythema and edema	IV
Dermal Sensitization – Guinea Pig (MRID 43678132)	Not a Sensitizer	- -

b. Subchronic Toxicity

i. Subchronic Oral Toxicity Feeding in Rats

In a subchronic toxicity study (MRID 43678135), azoxystrobin was administered to rats in the diet at concentrations of 0, 200, 2000 or 4000 ppm (equivalent to 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, mean corpuscular volume (MCV), mean corpuscular hemoglobin (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/ductules and oval cells. Hepatocellular hyperplasia and an enlarged hepatic lymph node was observed in one of the two males. The lowest observable adverse effect level (LOEL) is 211.0 mg/kg/day (2000 ppm) 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 20.4 mg/kg/day (200 ppm).

ii. Subchronic Oral Toxicity Study in Dogs

In a subchronic toxicity study (MRID 43678136) azoxystrobin was administered to dogs by capsule at doses of 0, 10, 50, or 250 mg/kg/day for 92 or 93 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. Total body weight gains were lower than controls in high dose males and females, respectively. Hematological alterations at 250 mg/kg/day in one or both sexes were small compared to concurrent controls and/or pre-treatment values and not toxicologically relevant. Clinical chemistry parameters that were altered significantly from controls at the high dose in both sexes during one or more weeks include plasma cholesterol, triglycerides, alkaline phosphatase, and plasma albumin. Cholesterol was increased in mid- and low-dose males. These results were accompanied by increased absolute liver weight in mid- and high-dose females, and are consistent with an adverse

Guidelines. This classification is based on the lack of evidence of carcinogenicity in long-term rat and mouse feeding studies.

c. Toxicological Endpoints for Risk Assessment

On November 12, 1996, the TES Committee met to evaluate the existing toxicology database for azoxystrobin, discussed in the HAZARD ASSESSMENT section above, and to assess appropriate toxicology endpoints and dose levels of concern that should be used for risk assessment purposes for the following exposure scenarios: acute dietary (one day), short term dermal occupational or residential (1 to 7 days), intermediate term dermal occupational or residential (1 week to several months), chronic term (noncancer) dermal occupational or residential (several months to lifetime), and inhalation (any time period).

No appropriate endpoints were identified for any of these exposure scenarios. Therefore, acute dietary, short term, intermediate term, chronic term, and inhalation risk assessments are not required.

Dermal absorption data (MRID 43678155) received subsequent to the TES Committee meeting indicate that absorption is less than or equal to 4%.

3. DIETARY EXPOSURE AND RISK CHARACTERIZATION

a. Dietary Exposure - Food Sources

i. Plant Metabolism

Grape metabolism studies (MRID 43678193) were submitted. Azoxystrobin, ^{14}C labelled separately in either the cyanophenol, pyrimidinyl, or phenylacrylate ring, was applied to developing grape vines. Sixty-two to seventy-nine percent of the residue was identified. Azoxystrobin (and its isomer) were the major components of the residue accounting for 37 to 66% of the total radioactive residue (TRR). Ten other metabolites were identified with Compound 13 accounting for 5.7 % of the TRR. On the basis of this study the petitioner has proposed the residue of concern in plants as azoxystrobin and its Z-isomer.

The petitioner has submitted data (MRID 44058721) investigating the metabolism of [^{14}C]azoxystrobin in peanuts. The petitioner conducted studies with [^{14}C]azoxystrobin separately labelled in the cyanophenyl ring (uniformly labelled), the pyrimidinyl ring (labelled in a single position), and the phenylacrylate ring (uniformly labelled). Peanuts were dug from the ground 10 days following the final application. Approximately 50% of the vines were collected as fresh vines, and the remaining vines and pods were allowed to dry in the field for 1 day and in a greenhouse for 3 days (due to rain) prior to

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 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 was of uncertain toxicological significance. The LOEL 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 NOEL is 50 mg/kg/day.

iii. Repeated Dose Dermal Toxicity Study in Rats

In a 21-day repeated dose dermal toxicity study (MRID 43678137), rats were treated with azoxystrobin 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 equal to or greater than 1000 mg/kg/day; a LOEL was not determined.

c. Chronic Toxicity and Carcinogenicity

i. Chronic Oral Toxicity Study in Dogs

In a chronic toxicity study (MRID 43678140) azoxystrobin was administered to dogs 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. 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 during one or more weeks included increased levels of plasma cholesterol, triglycerides, alkaline phosphatase (both sexes), gamma-glutamyl transferase (females) and lowered plasma albumin (males). Mid-dose males had increased cholesterol and triglycerides. These results suggest an effect on liver and possibly biliary function. Minor and/or transient alterations 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 that is of uncertain biological significance, and a dose-related increase in liver weight in high-dose males and in mid- and high-dose females. 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.

ii. Chronic/Carcinogenicity Feeding Study in Rats

In a combined chronic/carcinogenicity study (MRID 43678139) azoxystrobin was administered to rats in the feed at concentrations of 0, 60, 300, and 750 ppm/1500 ppm (males/females) (equivalent to 0, 3.6, 18.2, and 34.0 mg/kg/day for males and 0, 4.5, 22.3, and 117.1 mg/kg/day for females) for 104 weeks. 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. Hunched posture was observed in males in a dose-related manner. 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 as compared to controls beginning at week 2 and continuing until week 101 (except for week 87 when no difference occurred). The differences in absolute body weights were due to reduced body weight gains of these animals during the first 25 weeks. High-dose females had significantly lower body weights than the controls beginning at week 2 and continuing until study termination. 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 at weeks 1-20, 48, and 96 as compared to controls. Food consumption for high-dose females was significantly less than controls at weeks 1, 3-11, 13-36, 44, 56, and 68. Food utilization was significantly 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 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 in the rates of distension, cholangitis, thickening of the wall, and epithelial hyperplasia; these lesions were not observed in controls or the other treated male groups or in females of any group. Therefore, the systemic toxicity LOEL for males is 34 mg/kg/day, based on reduced body weights, food consumption and food efficiency, and bile duct lesions and the systemic toxicity LOEL for females is 117.1 mg/kg/day based on reduced body weights. The systemic toxicity NOEL is 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.

iii. Carcinogenicity Feeding Study in Mice

In a carcinogenicity toxicity study (MRID 43678141), azoxystrobin was administered in the feed to mice at concentrations of 0, 50, 300, or 2000 ppm (equivalent to 0, 6.2, 37.5, or 272.4 mg/kg/day for males and 0, 8.5, 51.3, or 363.3 mg/kg/day for females) 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 lower than the weights of controls beginning at study week 2 and continuing until the end of the study. Females receiving 2000 ppm had significantly lower mean body weights 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 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 272.4 mg/kg/day, based on reduced body weights of males and females. The systemic toxicity NOEL is 37.5 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.

d. Developmental Toxicity

i. Prenatal Developmental Study in Rats

In a developmental toxicity study (MRID 43678142) azoxystrobin was administered to rats 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/day maternal lethality caused the discontinuance of dosing at that level. At 100 mg/kg/day, minimally reduced body weights were observed, although body weight gain and food consumption were not affected. Clinical signs included diarrhea, urinary incontinence and salivation. At 25 mg/kg/day salivation was observed. The maternal LOEL is 25 mg/kg/day, based on increased salivation. The maternal NOEL is not established, but would be less than 25 mg/kg/day.

In the conceptus, no significant adverse developmental effects were observed. The developmental LOEL is greater than 100 mg/kg/day. The developmental NOEL is equal to or greater than 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 in the rat.

ii. Prenatal Developmental Study in Rabbits

In a developmental toxicity study (MRID 43678143), azoxystrobin was administered to rabbits 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 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 (1 litter). The developmental LOEL and NOEL for this study could not be determined.

This developmental toxicity study in the rabbit is classified unacceptable and does not satisfy the guideline requirement for a developmental toxicity study 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 results are not appropriate for toxicity risk assessments since in subsequent studies (MRIDs 44058702, 44058703, 44058705, 44073201, 44073202, discussion below) the registrant has shown that corn oil, at the dose volume it was used here, is toxic to the dams, and also enhances the toxicity of azoxystrobin. A subsequent developmental toxicity study (MRID 44058701, discussion below) showed that when the dose volume of

corn oil is 1 ml/kg, the above toxic effects are not seen in dams or fetuses.

iii. Prenatal Rangefinding and Developmental Studies in Rabbit

Prenatal rangefinding and developmental studies (MRIDs 44058702, 44058703, 44058705, 44073201, 44073202) in the rabbit 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 azoxystrobin at dose volumes of 2 ml/kg and above. These data support the registrant'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).

iv. Prenatal Developmental Study in Rabbits

In a developmental toxicity study (MRID 44058701) azoxystrobin, was administered to rabbits 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/day and 500 mg/kg/day significant but transient reductions in food consumption were observed during the first three days of dosing. At 500 mg/kg/day, decreased body weight gain 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 greater than 500 mg/kg/day. The developmental NOEL is 500 mg/kg/day.

e. Reproductive Toxicity

i. Two-generation Reproduction Study in Rats

In a 2-generation reproduction study (MRID 43678144), azoxystrobin was administered to rats at concentrations 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 and food consumption 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 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. The LOEL for systemic toxicity in males is 165.4 mg/kg/day (1500 ppm), based on reduced adjusted body weight means. A systemic NOEL in males is 32.3 mg/kg/day (300 ppm). The LOEL for systemic toxicity in females is 175.0 mg/kg/day (1,500 ppm), based on reduced adjusted body weight and feed consumption means and increased adjusted liver weights. The systemic NOEL in females is 33.8 mg/kg/day (300 ppm).

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. The LOEL for reproductive toxicity is 165.4 mg/kg/day (1500 ppm), based on reduced adjusted pup body weights. The reproductive NOEL is 32.3 mg/kg/day (300 ppm).

f. Mutagenicity

1. Mammalian Cells in Culture Gene Mutation Assay in L5178Y Mouse Lymphoma Cells

In a forward mutation study at the tk locus in L5178Y mouse lymphoma cells in culture (MRID 43678145) cells were exposed to azoxystrobin 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.

Azoxystrobin 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 highest dose tested (HDT) (60 µg/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 (2.5×10^{-4}) is not significantly different than the solvent control value of 2.1×10^{-4} while the mutation frequencies at 15, 30 and 60 µg/mL (3.7, 3.9 and 3.5×10^{-4}) are virtually the same and significantly increased over the solvent control. 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.

ii. Salmonella/Mammalian Activation Gene Mutation Assay

In a reverse gene mutation assay in bacteria (MRID 43478146), strains TA98, TA100, TA1535 and TA1537 of *Salmonella typhimurium* and strains WP2P and WP2PuvrA of *Escherichia coli* were exposed to azoxystrobin in DMSO at concentrations of 100, 200, 500, 1000, 2500 or 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 rat liver.

Azoxystrobin 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.

iii. *In vitro* Mammalian Cytogenetics Assay in Human Lymphocytes

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 azoxystrobin in DMSO at concentrations of 0.5, 1, 5, 10, 20, 30, 40, or 50 µg/mL in the absence of an exogenous metabolic activation system (S9-mix) and to 1, 5, 25, 50, 75, 100, 200, or 300 µg/mL in the presence of S9-mix. The S9 preparation was obtained from Aroclor 1254 induced male rat liver.

Azoxystrobin 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 azoxystrobin 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. Comparable values in cultures from the female donor were 4.50% at 5 µg/mL, 8.00% at 20 µg/mL and 6.00% at 50 µg/mL compared to the solvent control value of 1.00%. In the presence of S9-mix, the mean percent of aberrant cells was significantly increased at 200 µg/mL in cultures from both the male and female donor. The mean percent of aberrant cells was also significantly increased at 100 µg/mL in cultures from the male donor. 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.

iv. Mouse Micronucleus

In a mouse bone marrow micronucleus assay (MRID 43678148), mice treated once orally with azoxystrobin 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 maximum tolerated dose (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 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 and again by an independent evaluator. 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.

v. Other Genotoxicity: Unscheduled DNA Synthesis in Rat Hepatocytes/Mammalian Cells

In an *in vivo/in vitro* unscheduled DNA synthesis (UDS) assay in rat hepatocytes (MRID 43678149), azoxystrobin, at doses of 1250 or 2000 mg/kg, was administered to rats 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 maximum lethal dose (MLD) value of greater than 5000 mg/kg azoxystrobin had been previous demonstrated at this laboratory. Because azoxystrobin 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 azoxystrobin 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.

g. Metabolism

i. Metabolism Study in Rats

In a metabolism study (MRID 43678150, 43678151, 43678152, 43678153, 43678154), azoxystrobin (unlabeled or with pyrimidinyl, phenylacrylate, or cyanophenyl label) was administered to rats 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 azoxystrobin. 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 azoxystrobin 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 azoxystrobin 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 versus 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 azoxystrobin 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 may be upgraded once 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 are reviewed. Information (MRID 44265601) to upgrade the studies was recently submitted to the Agency and have been forwarded to HED for review.

h. 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 review of required additional information. These data are considered as confirmatory. Information to upgrade the studies was recently submitted to the Agency and have been forwarded to HED for review.

i. Acute Oral Neurotoxicity Study in Rats

In an acute neurotoxicity study (MRID 43678134), azoxystrobin was administered once in corn oil (10 ml/kg body wt) by gavage to rats 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. Tip-toe gait and upwardly curved spine at 2 hr were also observed in treated but not control animals (no dose response [illegible] 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. Statistically significant increases in landing foot splay on Day 8 in females at 600 and 2000 mg/kg were noted. 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 less than 200 mg/kg. There was no indication of neurotoxicity at the doses tested.

This acute neurotoxicity study in the rat is classified as Supplementary (upgradeable) and does not satisfy the guideline requirement for an acute oral study (81-8). The study may be upgraded to Acceptable pending review 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.

ii. Subchronic Neurotoxicity Feeding Study in Rats

In a subchronic neurotoxicity study (MRID 43678138), azoxystrobin was administered to rats 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 FOB and 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. Mean body weights of females were slightly decreased. Cumulative body weight gains were lower. Food consumption was statistically significantly lower in males but not females. Food utilization in males at 2000 ppm was statistically significantly decreased during weeks 1-4 and 1-13 and was non-significantly less in females during the same periods. 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, forelimb grip strength in males and females, hindlimb grip strength in males, and motor activity in females were 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 161 mg/kg/day, based on decreased body weight/weight gain and food utilization in both sexes (marginal in females). The NOEL is 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 review 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.

i. Other Toxicological Considerations

i. Dermal Absorption Study in Rats

In a dermal absorption study, (MRID 43678155) male rats were administered azoxystrobin ([^{14}C]-pyrimidinyl azoxystrobin and unlabeled azoxystrobin) 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 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 less than 0.1% of the absorbed dose over a 24-hr period. Overall recovery of administered radioactivity was 95-105%.

2. DOSE RESPONSE ASSESSMENT

a. Reference Dose and Safety Considerations for Infants and Children Under FQPA

The RfD represents the level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risks to human health. The RfD is determined by using the toxicological end-point of the NOEL for the most sensitive mammalian toxicological study. The HED RfD/Peer Review Committee met on November 7, 1996 to evaluate the existing toxicology database for azoxystrobin, discussed in the HAZARD ASSESSMENT section above, and to assess the RfD for azoxystrobin.

The HED RfD/Peer Review Committee recommended that a RfD for azoxystrobin be established based on a NOEL of 18.2 mg/kg/day from the rat chronic toxicity/carcinogenicity feeding study (MRID 43678139) in which decreased body weight and bile duct lesions were observed in male rats at the LOEL of 34 mg/kg/day. An uncertainty factor of 100 was used to allow for interspecies sensitivity and intraspecies variability.

FQPA, recently enacted as an amendment to FIFRA, requires that pesticide regulatory review incorporate an assessment of potential hazards to infants and children and include additional safety factors, of up to 10 fold when warranted, for the protection of these sensitive subpopulations. The toxicology database for azoxystrobin for developmental and reproductive toxicity is considered to be complete and no additional studies are required. In the developmental toxicity studies in rat and rabbit, no developmental toxicity was observed at doses that elicited maternal toxicity. The HED TES Committee determined that there is no evidence of increased susceptibility of infants or children to azoxystrobin (November 12, 1996). Therefore, no additional uncertainty factors are considered necessary at this time.

On this basis, the RfD was calculated to be 0.18 mg/kg/day for azoxystrobin.

b. Carcinogenicity Classification and Risk Quantification

The HED RfD/Peer Review Committee (November 7, 1996) determined that azoxystrobin should be classified as "Not Likely" to be a human carcinogen according to the proposed revised Cancer

collection of dried hay and pods. The petitioner concluded that this represented a 14-day PHI.

The qualitative nature of the residue in peanuts is adequately understood. The TRRs were 0.24-0.65 ppm in nutmeats, 0.68-0.87 ppm in hulls, 39.2-46.6 ppm in hay, and 16.4-19.6 ppm in vines harvested 10 days following the last of three sequential applications of [^{14}C]azoxystrobin, labeled in the cyanophenyl, pyrimidinyl, or phenylacrylate ring, at ~0.7, 0.8, and 0.3 lb ai/A (total application rate of 1.8 lb ai/A; 2.25x the maximum proposed seasonal rate).

In peanut nutmeats, hulls, and hay ~62-72% of TRR were characterized/identified. Azoxystrobin was the major compound identified in hulls (12.5-13.5% of TRR, 0.088-0.109 ppm) and hay (33.0-43.8% of TRR, 13.3-20.4 ppm); the Z isomer was identified in hulls and hay at 1.0-1.2% of TRR (0.008-0.009 ppm) and 2.4-2.8% of TRR (0.965-1.30 ppm), respectively. Azoxystrobin and the Z isomer were not identified in nutmeats. Minor metabolites identified in hulls and hay included compounds 2, 13, 19, 24, 28, 30, 35, 40, 42, and U13; these compounds were present at 0.1-5.1% of TRR. In nutmeats, the majority of the radioactivity was found to be associated with oleic acid (27.5-32.3% of TRR, 0.074-0.210 ppm) and linoleic acid (11.2-16.3% of TRR, 0.027-0.106 ppm). In addition, incorporation of radioactivity into sucrose, glucose, and fructose was observed (1.4-5.6% of TRR) in nutmeats, and the incorporation of radioactivity into glutamic acid was verified in nutmeat treated with [pyrimidinyl-^{14}C]azoxystrobin. Compounds 3, 13, 36, and 42 were found in nutmeats at very minor levels (up to 1.0% of TRR, up to 0.002 ppm). No residues were characterized in vines because the extraction profile of residues was very similar to that for hay; comparative thin layer chromatography (TLC) analyses of one extract indicated that the metabolite profile was the same for vines and hay.

The petitioner also submitted data (MRID 44058720) from a study investigating the metabolism of [^{14}C]azoxystrobin in wheat. As with peanuts, studies were conducted with [^{14}C]azoxystrobin separately labelled in the cyanophenyl ring, the pyrimidinyl ring, and the phenylacrylate ring. Applications were made at Zadoks' growth stages 30-31 (start of stem elongation) and 59-61 (completion of ear emergence). Approximately 10% of the crop was harvested as immature forage 13 days following the second application, and the remainder of the crop was harvested at maturity, 61-62 days following the second application.

The qualitative nature of the residue in wheat is adequately understood. TRRs were 1.02-2.79 ppm in forage harvested 13 days following treatment and 0.075-0.077 ppm in grain and 3.06-9.41 ppm in straw harvested 61-62 days following treatment of winter wheat with [^{14}C]azoxystrobin twice as a foliar spray at ~0.45 lb ai/A/application for a total application rate of 0.9 lb ai/A

(~2.2x the maximum proposed seasonal rate). In wheat grain, forage, and straw, ~53-85% of TRR were characterized/identified. Azoxystrobin was the major compound identified in grain (17.1-22.0% of TRR; 0.013-0.017 ppm), straw (22.1-43.3% of TRR; 0.676-4.08 ppm), and forage (54.9-64.7% of TRR, 0.560-1.81 ppm. The Z isomer was identified in all three commodities in minor amounts (1.4-3.5% of TRR). Minor metabolites identified included compounds 2, 3, 10, 13, 19, 23, 24, 28, 30, 35, U5, U6, and U13 as well as a glucoside conjugate of compound 28; these compounds were present at 0.3-7.6% of TRR. In addition, incorporation of radioactivity into glucose was observed (9.7-20.9% of TRR) in grain.

Data (MRIDs 44058715,-16 and -17) from studies investigating the metabolism of [^{14}C]azoxystrobin in rotational crops (lettuce, radishes, wheat) were submitted. As with the peanut and wheat metabolism studies, [^{14}C]azoxystrobin was separately labeled in the cyanophenyl, pyrimidinyl, and phenylacrylate rings. Azoxystrobin was identified in all RACs at 30 days after treatment (DAT) interval at 1.5-43.9% of TRR (<0.01-1.93 ppm). In 30-DAT samples, the Z-isomer was only identified in wheat forage and straw (0.1-0.9% of TRR, <0.01-0.12 ppm). Compound 42 was the major metabolite identified in 30-DAT lettuce and wheat forage and straw (at 12.8-41.0% of TRR). In 30-DAT radish roots, azoxystrobin was the major metabolite and in 30-DAT radish tops, metabolites G_2, N_1, and N_2 were the major metabolites. In 30-DAT wheat grain, ^{14}C-starch was found to account for the largest portion of radioactivity (27.3-44.3% of TRR). Several conjugated metabolites (compound 42 and the M, N, and O metabolites were identified, indicating that azoxystrobin is more extensively metabolized in rotational crops than in primary crops.

The results of the nature of the residue in grapes (MRID 43678193) submitted with PP 5F4641 and summarized in the three plant metabolism studies conducted with wheat, peanuts, and rotational crops, were presented to HED's Metabolism Committee in December of 1995. The four studies indicated that, in primary crops, the residue consisted primarily of the parent together with a small contribution from its Z-isomer. However, with rotational crops, a different pattern of residues was observed.

For rotational crops the Committee concluded that compound 42 is likely to be significantly less toxic than the parent such that it need not be analyzed in field trials. The Committee agrees with the petitioner that the confined rotational crop study resulted in much higher residues than will be found under actual use conditions. Therefore, most individual components (other than compound 42) will likely be present at levels of about 0.01 ppm or less in lettuce, radishes, and wheat forage and grain. However, measurable levels of parent and the conjugated metabolites N1, N2, O2 and O3 could be found in wheat straw, especially at the 30 day plantback interval. At this time the

Committee believes it is acceptable for the petitioner to analyze field rotational crop samples for just the parent compound and its Z-isomer. If quantifiable residues are not found on any of the three representative crops at the desired plantback interval(s), additional field trials and tolerances will not be required for any rotational crops. However, if quantifiable residues are observed in any representative crop, additional field trials and tolerances will be necessary on that crop and closely related crops to which rotation is desired. Also, residue data for crops beyond those closely related to the three typical representative commodities (i.e., leafy vegetables, root and tuber vegetables, small grains) would likely be required if rotation to such crops is desired.

The Metabolism Committee decided that for the purposes of the use of azoxystrobin on grapes, the residue of concern should be considered the parent and its Z-isomer. Bananas, peaches, peanuts, pecans, and tomatoes are also considered primary crops. It is possible that peanuts and tomatoes may have rotational crops, however the proposed label contains a 45 day plantback interval and there are no measurable residues of parent after 45 days. Therefore, HED concludes that, for the purposes of these petitions, the residue of concern consists of azoxystrobin and its Z-isomer.

The residues of concern for other primary and for rotational crops are to be determined as required by additional registration requests.

ii. Animal Metabolism

A goat metabolism study (MRID 43678194) was conducted in which azoxystrobin, ^{14}C labelled separately in either the cyano-phenol, pyrimidinyl, or phenylacrylate ring was administered to lactating goats. The daily dosing level for 7 days was equivalent of 25 ppm azoxystrobin in the diet. Milk, feces, and urine were collected daily. After 7 days, the animals were sacrificed, and tissue samples taken. Samples of the tissues and fluids were combusted and analyzed for total radioactivity. The metabolism of azoxystrobin by ruminants appears to be different from that of plants. In this study Compounds 2, 20, and 28 appear to be the major components of the residue in animal tissues.

Since the proposed label currently has a restriction which prohibits the feeding of peanut hay, and dry grape pomace and raisin waste are no longer considered to be significant items of livestock feed, the crops proposed in these petitions do not concern RAC's that are used as animal feeds. Therefore, the nature of the residue in ruminants is not of concern at this time. The nature of the residue of regulatory concern will be addressed by HED's Metabolism Committee when and if uses on

feedstuffs are proposed.

Data (MRID 44073203) from a study investigating the metabolism of [^{14}C]azoxystrobin in laying hens were submitted. Similar to the plant metabolism studies, the poultry metabolism study was conducted with [^{14}C]azoxystrobin separately labeled in the cyanophenyl ring, the pyrimidinyl ring, and the phenylacrylate ring. The test substances were diluted with unlabeled azoxystrobin and [^{13}C]azoxystrobin (cyanophenyl and phenylacrylate labels only) to specific activities of 1652 Bq/µg (pyrimidinyl label) and 1720 Bq/µg (cyanophenyl and phenylacrylate labels; radiochemical purities of 98.6-99.5%), and were administered orally via gelatin dose capsules to hens for each test substance for 10 consecutive days. The nominal dose rate of 10 ppm for each ring label represents ~67x the maximum theoretical dietary burden. The qualitative nature of the residue in poultry is adequately understood. Following oral administration of [^{14}C]azoxystrobin to hens at 10 ppm (~67x the maximum theoretical dietary burden) in the diet for 10 days, total radioactive residues were 0.050-0.113 ppm in egg yolk, 0.011-0.016 ppm in egg white, 0.068-0.106 ppm in liver, 0.004-0.018 ppm in muscle, 0.013-0.049 ppm in skin with underlying fat, and 0.004-0.012 ppm in peritoneal fat.

The petitioner did not attempt to identify metabolites in egg whites, muscle, skin with underlying fat, or peritoneal fat because residues in extracts for these matrices were less than 0.01 ppm; ~71-90% of TRR were characterized/identified in egg yolk and liver. Azoxystrobin was identified in egg yolk at 0.3-12.4% TRR (<0.001-0.007 ppm), and Compound 28 was identified in egg yolk at 1.8-8.4% TRR (<0.002-0.004 ppm) and in liver at 2.1% TRR (0.002 ppm, pyrimidinyl label only). In addition, the incorporation of radioactivity into the fatty acids stearic acid (5.1% TRR, 0.006 ppm) and palmitic/oleic acid (6.2% TRR, 0.007 ppm) was demonstrated in egg yolk from the pyrimidinyl label. Because residues of azoxystrobin were detected at less than 0.01 ppm at an exaggerated feeding level of 67x, there is no reasonable expectation of finite residues of azoxystrobin in poultry commodities.

iii. Residue Analytical Method - Plants

Samples of banana, peaches, peanut hay, tomatoes, tomato juice, tomato puree, tomato paste, tomato wet and dry pomace, and wheat hay, grain, straw, bran, middlings, shorts, germ, and flour from the submitted field trials and processing studies, as well as the rotational crops from the field rotational crop study, were analyzed for residues of azoxystrobin and its Z isomer using gas chromatography (GC) method SOP RAM 243/03. Samples of peanut nutmeats, hulls, meal, and crude and refined oil from the submitted field trials and processing studies were analyzed for residues of azoxystrobin and its Z isomer using GC method SOP RAM

260/01.

Agency validation of the proposed enforcement methods for these commodities has been satisfactorily completed [telephone message from C. Stafford, Analytical Chemistry Branch (ACL), 5/14/97]. HED awaits the formal response regarding ACL's method validation.

iv. Residue Analytical Method - Animals

The petitioner is proposing GC method 255/01 for the enforcement of tolerances for residues of azoxystrobin in animal commodities. Method SOP RAM 255/01 is concurrently undergoing Agency method validation. We note that if the HED Metabolism Committee determines that any azoxystrobin metabolites need to be regulated in animal commodities, an enforcement method for these additional metabolites will be required.

Since the crops proposed in these petitions do not concern RAC's that are used as animal feeds, a residue analytical method for animals is not necessary at this time.

v. Storage Stability

The petitioner submitted interim storage stability data (MRID 44058722,-23,-24 and -25) for various crops and processed commodities in support of the submitted field trial and processing studies. The storage stability study will be continued for up to 2 years of storage. The interim storage stability data for apples, grapes, grape wine, peaches, peanuts, peanut oil, peanut meal, pecans, rape seed oil, tomatoes, tomato juice, tomato paste, wheat straw, and wheat bran partially satisfy data requirements. The data indicate that fortified residues of azoxystrobin and its R [illegible] for 4 months in/on peanut oil, peanut meal, tomato juice, tomato paste, and wheat bran; 5 months in/on apples and peaches; 6 months in/on rape seed oil; 12 months in/on peanuts, pecans, and tomatoes; and 14 months in/on grapes, grape wine and wheat straw.

The available storage stability data support the storage intervals of the peach, peanut nutmeat, and tomato samples from the submitted field trials. The test commodities used in the study adequately represent fruit/fruiting vegetable crops (apples, grapes, tomatoes, and tomato processed commodities), non-oily grain crops (wheat straw and bran), and oilseed crops (peanuts and peanut processed commodities, pecans, and rape seed oil). To fully satisfy storage stability data requirements, the final results of the ongoing 2-year storage stability study must be submitted upon completion.

No storage stability data for animal commodities were submitted. However, since the crops proposed in these petitions

do not concern RAC's that are used as animal feeds these data are not necessary at this time.

vi. Magnitude of the Residue - Meat, Milk, Poultry & Eggs

Since the crops proposed in these petitions do not concern RAC's that are used as animal feeds, a consideration of secondary residues in animal commodities is not necessary at this time.

vii. Magnitude of the Residue - Crop Field Trials/ Processed Commodities

Residue data for bananas, grapes, peaches, peanuts, pecans and tomatoes were generated using the wettable granular formulations. The guidelines for conducting field trials (OPPTS 860.1500) state that for pesticides used in late-season foliar applications (as is the case with azoxystrobin) separate residue trials or bridging data are needed for different formulations. Therefore, HED cannot recommend for the establishment of permanent tolerances for residues of azoxystrobin in/on bananas, peaches, peanuts, pecans and tomatoes resulting from the use of the soluble concentrate formulation.

The petitioner has not provided comparable data as to residue levels on grapes from trials where the soluble concentrate and the wettable granular formulations were applied at equivalent rates. However, residue data is available from trials where the soluble concentrate formulation was applied, due to a manufacturing error, at a rate two-thirds that of the wettable granular formulation. HED concluded from these results that the use of the soluble concentrate formulation would not result in residue levels in/on grapes greater than those that would be incurred from the use of the wettable granular formulation. HED has no objections to the use of the soluble concentrate formulation on grapes.

Crop Field Trials

Bananas

Data (MRID 44058726) from six crop field trials depicting residues of azoxystrobin in/on bananas were submitted. The banana field trial data are adequate. Data indicate that the combined residues of azoxystrobin and its Z isomer will not exceed the proposed tolerance of 0.5 ppm in/on bananas (whole fruit including peel) at the maximum proposed use level. The combined residues in/on bananas were less than 0.09-0.27 ppm in/on 12 samples of unbagged whole bananas, and less than 0.02-0.16 ppm in/on 12 samples of bagged whole bananas; residues of the Z isomer were less than the limit of quantitation (LOQ) of less than 0.01 ppm in all samples. A tolerance of 0.5 ppm

for residues of azoxystrobin and its Z isomer is appropriate for bananas (whole fruit including peel).

Additional data were provided depicting the residues of azoxystrobin and its Z isomer in/on banana pulp prepared from unbagged and bagged bananas in support of a proposed tolerance of 0.05 ppm for azoxystrobin and its Z isomer in/on pulp. The Agency does not currently require a separate tolerance for banana pulp. As a result, the request for a tolerance for banana pulp was withdrawn. However, residue data for azoxystrobin and its Z isomer in/on banana pulp (prepared from unbagged and bagged bananas) indicate that a tolerance of 0.05 ppm would be appropriate. Though a tolerance of 0.5 ppm should be established for bananas (whole fruit including peel), a tolerance of 0.05 ppm for banana pulp is recommended for use in dietary risk assessments.

A residue decline study was not performed for bananas. Residue decline studies conducted on peaches, peanuts, tomatoes, and wheat indicate that residues of azoxystrobin and its Z isomer do not increase with increasing posttreatment intervals. A residue decline study for bananas will not be required.

Grapes

Data (MRIDs 43694201,-02,-03,-04,-05,-06, and 43678206,-07,-08,-09,-10) from seventeen field trials depicting residues of azoxystrobin in/on grapes were submitted. The trials were conducted at 15 sites located in Europe and the USA. Seven of the trials were conducted in the US. Based on the residue data from the US and a consideration of the European trials, HED concluded that a tolerance of 1 ppm for residues of azoxystrobin and its Z isomer would be appropriate for grapes, provided the post harvest interval (PHI) was increased to 21 days.

The petitioner submitted data (MRID 440022201) from nine additional field trials conducted in 1995 depicting residues of azoxystrobin in/on grapes. The 9 additional residue trials had PHI's of 14 days. Residue levels in all trials were below the proposed tolerance of 1 ppm. HED concludes that the PHI of 14 days is appropriate. HED also concludes that a tolerance of 1 ppm for residues of azoxystrobin and its Z isomer would be appropriate for grapes.

Peaches

Data (MRID 44073205) from fourteen crop field trials depicting residues of azoxystrobin in/on peaches were submitted. Field trial data at the maximum proposed use rate are adequate and indicate combined residues of azoxystrobin and its Z isomer will not exceed the proposed 0.8 ppm tolerance in/on peaches. Combined residues in/on peaches were less than 0.08-0.74 ppm

in/on 28 samples.

Peanuts

Data (MRIDs 44058728 and 44058729) from twelve crop field trials depicting residues of azoxystrobin in/on peanuts were submitted. Field trial data are adequate at the maximum proposed rate and indicate residues of azoxystrobin and its Z isomer were less than the LOQ (<0.01 ppm each) in on peanut nutmeats.

HED in its 4/30/97 review recommended for a tolerance of 0.02 ppm for peanut nutmeats and for a tolerance of 0.05 for peanut oil. These tolerances were based upon the limit of quantitation (LOQ) level for azoxystrobin (0.01 ppm) plus the limit of quantitation level for the Z isomer of azoxystrobin (also 0.01 ppm). In HED's reviews for the use of azoxystrobin on grapes and pecans (PP#5F4541 and PP#6F4642, Memo, J. Garbus, 9/20/96) the LOQ was considered to be 0.01 ppm for the sum of the levels of the parent and its isomer as both are determined simultaneously in a single analytical procedure.

The proposed tolerances of 0.01 for peanut nutmeat is appropriate.

Pecans

Data (MRID 43861204) from four crop field trials depicting residues of azoxystrobin in/on pecans were submitted. Detectable residues of azoxystrobin or of its isomer were not found in any of the eight samples from four locations. The Agency's guidance (June 1994) for the number of residue trials necessary for domestic registration and tolerances requires 5 trials for pecans from sites in 3 areas, Region II (2 trials), IV (1 trial), VI (1 trial) and VIII (2 trials). The petitioner has provided data from 2 trials in Georgia and Alabama (Region II), 1 in Mississippi (Region IV), and 1 in eastern Texas (Region VI). Region VIII is not represented. However, as these trials were initiated prior to the issuance of this guidance and as all samples bore non-detectable residues, HED concludes that the number of residue trials are sufficient.

The residue trials were carried out under the maximum application conditions specified on the proposed label. HED concludes that the results of the residue trials justifies the proposed tolerance of 0.01 ppm, the LOQ of the proposed enforcement method.

Tomatoes

Data (MRIDs 44058730 and 44058731) from sixteen crop field trials depicting residues of azoxystrobin in/on tomatoes were submitted. Field trial data are adequate at the maximum proposed

use rate, and indicate the combined residues of azoxystrobin and its Z isomer in/on tomatoes will not exceed the proposed 0.2 ppm tolerance. Combined residues in/on tomatoes were less than 0.02-0.18 ppm in/on 29 samples.

Processed Commodities

Grapes

The petitioner has submitted the results of processing studies (MRIDs 43694201,-02,-03,-04,-05,-06, and 43678206,-07,-08,-09,-10) to determine residues in the vinification of treated grapes. The grapes were obtained from field trials in France and Italy. Grape juice and raisins are the only commodities for which tolerances may be needed. The results of the European processing studies appear to indicate that a tolerance for grape juice is not needed. However, the study was conducted with fermented juice and does not reflect domestic practice for the processing of grape juice. A California processing study indicates that a tolerance is not needed for raisins.

The petitioner has submitted an additional document providing further details of the grape processing study conducted in France. The process as originally described in MRID 43694206 did not clearly indicate that the juice initially expressed from treated grapes was divided into two processing streams, one for juice and the other for wine. The current document also includes a comparison of the European and US procedures for the commercial production of grape juice. In the petitioner's additional information, the description of the commercial practices for the production of grape juice in Europe and in the US indicates that although the two procedures differ in details, they are sufficiently similar so that the European processing study simulates domestic practices to a considerable degree. HED now accepts the results of the European processing study as showing no concentration of azoxystrobin residues in grape juice.

Peanuts

Data (MRID 44058734) from a single test depicting the potential for concentration of residues of azoxystrobin and its Z isomer in the processed commodities of peanuts were submitted. Data are adequate and indicate combined residues of azoxystrobin and its Z isomer do not concentrate in peanut meal. Data indicate that residues of azoxystrobin concentrate in refined oil at 3.3x. Residues of the Z isomer were less than the LOQ in both the RAC and processed refined oil samples.

The highest average field trial (HAFT) azoxystrobin residue for peanut nutmeat is 0.01 ppm. Maximum expected residues in peanut oil would be 0.033 ppm azoxystrobin (0.01 x 3.3) and less than 0.043 ppm combined residues (0.033 ppm azoxystrobin + <0.01

ppm Z isomer).

As discussed above, HED recommended in its 4/30/97 review, for a tolerance of 0.02 ppm for peanut nutmeats and for a tolerance of 0.05 for peanut oil. HED now recommends a tolerance of 0.03 ppm for peanut oil be established.

Tomatoes

Data (MRID 44058735) from a single test depicting the potential for concentration of residues of azoxystrobin and its Z isomer in the processed commodities of tomatoes were submitted. Processing data are adequate and indicate residues of azoxystrobin and its Z isomer do not concentrate in tomato puree. However, data indicate that azoxystrobin residues concentrate in paste at 2.6x. Residues of the Z isomer were less than the LOQ in the RAC and detected at the LOQ in tomato paste.

The HAFT azoxystrobin residues for tomatoes are 0.16 ppm azoxystrobin and 0.02 ppm Z isomer (0.18 ppm combined residues). The maximum expected residues in tomato paste would be 0.42 ppm azoxystrobin (0.16 ppm x 2.6) and greater than 0.02 ppm Z isomer (0.02 ppm x >1) for combined residues of greater than 0.44 ppm. The proposed tolerances of 0.2 ppm for tomato and 0.5 ppm for tomato paste are appropriate.

Summary of Magnitude of the Residue data - Raw and Processed Commodities

Commodity	Residue levels (ppm)	Formulation type, Rate, Timing	Use Limitations, Frequency
banana (whole fruit including peel)	0.5	50% wettable granular and 80% granular Applied at rates of 0.09-0.135 lb ai/A/application Eight foliar applications to banana trees at 0.09-0.135 lb ai/A/application for a maximum seasonal application of 1.08 lb ai/A/year.	Applications should be made at 12- to 14-day intervals throughout the season 0-day PHI
grape, fresh grape, raisins grape, juice	1.0 1.0 1.0	50% wettable granular, 80% granular, and 22.9% soluble concentrate. Applied at rates of 0.11 to 0.25 lb ai/A in a minimum of 50 to 100 gallons per acre depending on the density of the foliage. Six applications for a total of 1.5 lb ai/A can be applied per year.	PHI 14 days

Commodity	Residue levels (ppm)	Formulation type, Rate, Timing	Use limitations Frequency
peach	0.8	50% wettable granular and 80% granular Up to eight foliar applications to peach trees at 0.07-0.15 lb ai/A/application for a maximum seasonal application of 1.2 lb ai/A/year.	Applications may begin at early bloom, and may be made at 12- to 14-day retreatment intervals. 14-day PHI
peanut, nutmeats peanut, oil	0.01 0.03	50% wettable granular and 80% granular Up to two foliar applications to peanut plants at 0.1-0.4 lb ai/A/application for a maximum seasonal application of 0.8 lb ai/A/year.	Applications should be made at 60 and 90 days after planting for control of soil borne diseases. 50-day PHI Label should contain a restriction prohibiting the feeding of peanut hay.
pecan	0.01	50% wettable granular and 80% granular Apply at rates of 0.1 to 0.2 lb ai/A Multiple applications for a total of 1.2 lb ai/A can be applied per year.	42-day PHI
tomato tomato, puree tomato, juice tomato paste	0.2 0.2 0.2 0.4	50% wettable granular and 80% granular Up to eight foliar applications to tomato plants at 0.025-0.10 lb ai/A/application for a maximum seasonal application of 0.8 lb ai/A/year.	Applications should be made at 7- to 21-day intervals. For control of late blight, no more than two consecutive applications of the product are to be made before alternating with other fungicides, and retreatments should be made at 5- to 10-day intervals.
tomato, catsup	0.6		1-day PHI

viii. Confined Rotational Crops

As discussed in the Plant Metabolism section above, data (MRIDs 44058715, 16 and 17) from studies investigating the metabolism of [^{14}C]azoxystrobin in rotational crops (lettuce, radishes, wheat) were submitted. The submitted limited rotational field trial data are adequate. The data indicate that residues of azoxystrobin and its Z isomer were below the LOQ (<0.01 ppm) in/on leafy vegetables (mustard greens), and root and tuber vegetables (radishes and turnips) planted ~30 days following two foliar applications of the 80% wettable granular formulation to the primary crop wheat at 0.4 lb ai/A/application (2x the maximum proposed seasonal rate for wheat; 1x the maximum

proposed seasonal rate for crops that may be rotated). Residues of azoxystrobin were observed in millet forage from the 30-day plantback interval (at <0.01-0.02 ppm); however, residues of azoxystrobin were below the LOQ in millet hay, straw, and grain at this plantback interval. Residues of azoxystrobin and its Z isomer were less than the LOQ in millet forage at the 45-day plantback interval. The proposed plantback intervals of 45 days for all crops are appropriate.

Summaries of these rotational crop studies were presented to the HED Metabolism Committee which concluded that compound 42 was likely to be significantly less toxic than the parent. It was also concluded that for the purposes of conducting field rotational crop studies, residues of azoxystrobin and the Z-isomer should be determined, and that if quantifiable residues were not found at the desired plantback intervals in the field rotational crop studies, additional field trials and tolerances would not be required for rotational crops.

The HED Metabolism Committee will be meeting to discuss the final reviews of these rotational crop studies in the near future. If the Committee determines that azoxystrobin metabolites are residues of concern in rotational crops, then additional field trial data and methodology may be required.

For these petitions only, since the proposed label contains a 45 day plantback interval for all crops and there are no measurable residues of parent after 45 days, HED concludes that the residue of concern consists of azoxystrobin and its Z-isomer.

ix. Field Rotational Crops

The petitioner submitted data (MRID 44058718) from field trials conducted in 1995 in Illinois and North Carolina to investigate the potential for residue accumulation of azoxystrobin and its Z isomer in/on representative rotational crop commodities. The primary crop, winter wheat, received two foliar applications at 0.4 lb ai/A/application of the 80% wettable granular formulation using ground equipment. Rotational crops were planted following harvest of the primary crop. At the Illinois site, rotational crops of mustard, radishes, and millet were planted. At the North Carolina site, rotational crops of mustard, turnips, and millet were planted.

The submitted limited rotational field trial data are adequate. The data indicate that residues of azoxystrobin and its Z isomer were below the LOQ (<0.01 ppm) in/on leafy vegetables (mustard greens), and root and tuber vegetables (radishes and turnips) planted ~30 days following two foliar applications of the 80% wettable granular formulation to the primary crop wheat at 0.4 lb ai/A/application (2x the maximum proposed seasonal rate for wheat). Residues of azoxystrobin were

observed in millet forage from the 30-day plantback interval (at <0.01-0.02 ppm); however, residues of azoxystrobin were below the LOQ in millet hay, straw, and grain at this plantback interval. Residues of azoxystrobin and its Z isomer were less than the LOQ in millet forage at the 45-day plantback interval. The proposed plantback intervals of 45 days for all crops are appropriate.

If the HED Metabolism Committee determines that additional azoxystrobin metabolites are residues of concern in rotational crops, then additional field trial data and methodology may be required.

b. Dietary Exposure - Drinking Water

There is no established Maximum Concentration Level for residues of azoxystrobin in drinking water. Data indicate moderate potential for soil mobility or leaching and azoxystrobin is moderately persistent. In examining aggregate exposure, FQPA directs EPA to consider available information concerning exposures from the pesticide residue in food and all other non-occupational exposures. The primary non-food sources of exposure the Agency looks at include drinking water (whether from groundwater or surface water), and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor uses).

Because the Agency lacks sufficient water-related exposure data to complete a comprehensive drinking water risk assessment for many pesticides, EPA has commenced and nearly completed a process to identify a reasonable yet conservative bounding figure for the potential contribution of water related exposure to the aggregate risk posed by a pesticide. In developing the bounding figure, EPA estimated residue levels [illegible] specific pesticides using various [illegible] then applied the estimated residue levels, in conjunction with appropriate toxicological endpoints [illegible] NOEL's) and assumptions about body weight and consumption, to calculate, for each pesticide, the increment of aggregate risk contributed by consumption of contaminated water. While EPA has not yet pinpointed the appropriate bounding figure for consumption of contaminated water, the ranges the Agency is continuing to examine are all below the level that would cause azoxystrobin to exceed the RfD if the proposed food uses were granted. The Agency has therefore concluded that the potential exposures associated with azoxystrobin in water, even at the higher levels the Agency is considering as a conservative upper bound, would not prevent the Agency from determining that there is a reasonable certainty of no harm if the proposed uses of bananas, grapes, peaches, peanuts, pecans, and tomatoes were granted.

c. Dietary Risk Characterization

i. Acute Dietary

As part of the hazard assessment process, the TES Committee reviews the available toxicological data base to determine if there are toxicological endpoints of concern (refer to the Toxicological Endpoints for Risk Assessment section above). For azoxystrobin, HED does not have a concern for acute dietary exposure since the available data do not indicate any evidence of significant toxicity from a one day or single event exposure by the oral route. Therefore, an acute dietary risk assessment is not required for azoxystrobin at this time.

ii. Chronic Dietary

A chronic dietary risk assessment is required for azoxystrobin. The RfD of 0.18 mg/kg/day was use for the chronic dietary risk assessment. The following recommended tolerances were also used:

banana pulp	0.05 ppm
grapes, fresh	1.0 ppm
grapes, raisins	1.0 ppm
grapes, juice	1.0 ppm
peaches	0.8 ppm
peanut, nutmeat	0.01 ppm
peanut, oil	0.03 ppm
pecans	0.01 ppm
tomato, fresh	0.2 ppm
tomato, juice	0.2 ppm
tomato, puree	0.2 ppm
tomato, paste	0.6 ppm
tomato, catsup	0.6 ppm

This dietary analysis also includes Section 18 requests on rice, milk, meat, eggs and poultry. Section 18s have been issued for the 1997 growing season in Louisiana and Mississippi for use in/on rice. There are also three additional pending Section 18 applications for use in/on rice in Texas, Missouri and Arkansas.

The chronic exposure analysis was performed using tolerance level residues and 100 percent crop treated information to estimate the Theoretical Maximum Residue Contribution (TMRC) for the general population and 22 subgroups.

The chronic analysis indicates that exposure from the proposed tolerances, for use of azoxystrobin in/on bananas, grapes, peaches, peanut, pecans, and tomatoes, for the U.S. population would account for less than 1% of the RfD. For non-nursing infants, the subgroup with the highest exposure, 1% of the RfD would be utilized. Exposure to rice, milk, meat, eggs

and poultry, as a result of the Section 18 registrations, as well as the proposed uses account for 1% of the RfD for the U.S. population and 5% of the RfD for non-nursing infants.

This chronic analysis for azoxystrobin is an upper-bound estimate of dietary exposure with all residues at tolerance level and 100 percent of the commodities assumed to be treated with azoxystrobin. Therefore, even without refinements, HED does not consider the chronic (food source) dietary risk, from use of azoxystrobin in/on bananas, grapes, peaches, peanuts, pecans, and tomatoes to exceed HED's level of concern.

4. OCCUPATIONAL AND RESIDENTIAL EXPOSURE AND RISK CHARACTERIZATION

As part of the hazard assessment process, the TES Committee reviews the available toxicological database to determine if there are toxicological endpoints of concern (refer to the Toxicological Endpoints for Risk Assessment section above). For azoxystrobin, HED does not have a concern for short-term, intermediate-term, or chronic-term (noncancer) occupational or residential exposure since the available toxicology data indicates minimal toxicity only at a very high dose by the dermal or inhalation routes. Therefore, occupational or residential risk assessments are not required for azoxystrobin at this time. Therefore, there is no chronic residential risk assessment to aggregate with the chronic dietary (food source) risk assessment.

5. CUMULATIVE EFFECTS

Section 408 of FQPA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." While the Agency has some information in its files that may be helpful in determining whether a pesticide shares a common mechanism of toxicity with any other substances, EPA does not at this time have the methodology to resolve the scientific issues concerning common mechanism of toxicity in a meaningful way. EPA has begun a pilot process to study this issue further through the examination of particular classes of pesticides. The Agency hopes that the results of this pilot process will enable it to develop and apply policies for evaluating the cumulative effects of chemicals having a common mechanism of toxicity. At present, however, the Agency does not know how to apply the information in its files concerning common mechanism issues to most risk assessments.

In the case of azoxystrobin, HED has not yet determined whether or how to include this chemical in a cumulative risk assessment. This tolerance determination therefore does not take into account common mechanism issues. After EPA develops a

methodology for applying common mechanism of toxicity issues to risk assessments, the Agency will develop a process (either as part of the periodic review of pesticides or otherwise) to reexamine those tolerance decisions made earlier.

On this basis, the registrant must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether azoxystrobin share(s) a common mechanism of toxicity with any other substance and, if so, whether any tolerances for azoxystrobin need to be modified or revoked.

6. ENDOCRINE DISRUPTION

EPA is required to develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect..." The Agency is currently working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists in developing a screening and testing program and a priority setting scheme to implement this program. Congress has allowed 3 years from the passage of FQPA (August 3, 1996) to implement this program. At that time, EPA may require further testing of azoxystrobin and end-use product formulations for endocrine disruptor effects.

IV. DATA REQUIREMENTS

A. Residue Chemistry

To fully satisfy storage stability data requirements, the final results of the ongoing 2-year storage stability study must be submitted upon completion.

HED cannot recommend for the establishment of permanent tolerances for residues of azoxystrobin in/on bananas, peaches, peanuts, pecans and tomatoes resulting from the use of the soluble concentrate formulation. Residue data for these agricultural commodities were generated using the wettable granular formulations. The question arises whether residues and residue levels resulting from the use of the soluble concentrate formulation on agricultural commodities would be the same as those arising from the use of the wettable granular formulations. The guidelines for conducting field trials (OPPTS 860.1500) state that for pesticides used in late-season foliar applications (as is the case with azoxystrobin) separate residue trials or bridging data are needed for different formulations. Separate residue trials or bridging data are needed in support of late

season uses of the soluble concentrate formulation.

V. LABEL REQUIREMENTS

The label should contain a crop rotation restriction prohibiting the planting of crops, other than those included in these petitions, within 45 days after the last application.

A feeding restriction, prohibiting the feeding of peanut hay, should be included on the label.

References

Garbus, J. 1997. PP#6F4762. Azoxystrobin. Permanent Tolerance Petition for Use on Bananas, Peaches, Peanuts, Tomatoes and Wheat. Petitioner's Response to Deficiencies Noted In CBTS Memo of 4/30/1997. Memo to Cynthia Giles-Parker and John Bazuin, PM Team 22 and Barbara Madden. May 20, 1997.

Garbus, J. 1996. PP No. 6F4642: New Chemical: Azoxystrobin (ICIA5504) in/on Pecans. Chemical No. 128810. Revised Section F. Memo to D. McCall/C. Eiden. September 24, 1997.

Garbus, J. 1996. PP No. 5F4541: New Chemical: Azoxystrobin (ICIA5504) in/on Grape RAC's and Rotational Crops. Conclusions of HED's Metabolism Committee. Memo to D. McCall, Acting Section Head. August 6, 1996.

Garbus, J. 1996. PP No. 5F4541: New Chemical: Azoxystrobin (ICIA5504) in/on Grape Rac's. Chemical No. 128810. Revised Sections B and F and Additional Field Trial Residue Data. Memo to D. McCall / B. Madden. June 26, 1996.

Garbus, J. 1996. PP No. 6F4642: Azoxystrobin (ICIA5504) in/on Pecans. Chemical No. 128810. Evaluation of Analytical Methods and Residue Data. Memo to D. McCall, Acting Section Head. June 26, 1996.

Garbus, J. 1996. PP Nos. 5F4541 and 6F4642: New Chemical: Azoxystrobin in/on Grape Rac's and Pecans. Amendment of Label Adding Use of New End Use Formulations. Memo to Deborah McCall, Acting Section Head. May 14, 1996.

Garbus, J. 1996. PP No. 5F4541: New Chemical: Azoxystrobin (ICIA5504) in/on Grape Rac's. Evaluation of Analytical Methods and Residue Data. Memo to J. Bazuin / C. Giles-Parker, PM 22. April 1, 1996.

Ghali, G.Z. 1997. RfD/Peer Review report of azoxystrobin, January 14, 1997.

Hansen, L. 1997. AZOXYSTROBIN. PC CODE 128810. HED Risk Assessment for Use of the New Chemical Fungicide Azoxystrobin on Turf. Memo to Cynthia Giles-Parker, Manager, PM Team 22 and John Bazuin, Reviewer, PM Team 22, January 30, 1997.

Kutney, L.L. 1997. PP#6F4762. Azoxystrobin. Permanent Tolerance Petition for Use on Bananas, Peaches, Peanuts, Tomatoes and Wheat. Evaluation of Analytical Methodology and Residue Data. Memo to Cynthia Giles-Parker and John Bazuin, PM Team 22 and Barbara Madden. April 30, 1997.

Kutney, L.L. 1997. PP#6F4762. Azoxystrobin, Telephone Request for Information from California Department of Pesticide Regulation. Chemical# 128810. Memo to Cynthia Giles-Parker and John Bazuin, PM Team 22. March 27, 1997.

Loranger, R. 1996. Residues of Concern for Azoxystrobin in Grapes and Rotational Crops. Results of the HED Metabolism Committee Meeting Held 12/95. Memo to Health Effects Division Metabolism Committee. September 12, 1996.

Ottley, M.S. 1997. I.D. Nos.: 5F4541, 10182-UNI, 6F04642, 6F04762. Azoxystrobin Follow-up. Correction of the Executive Study of the Reproduction Study (MRID 43678114) in HED Doc. 012115. Memo to Deborah McCall. February 11, 1997.

Ottley, M.S. 1997. I.D. Nos.: 5F4541, 10182-UNI, 6F04642, 6F04762. Azoxystrobin. Evaluation of Product Labeling Data Submitted and Identification of Outstanding Toxicology Data Requirements. Memo to Deborah McCall. January 10, 1997.

Ottley, M.S. 1996. Toxicology Endpoint Selection Document. December 12, 1996.

Steinwand, B. 1997. Dietary Exposure Analysis for Azoxystrobin in/on Bananas, Peaches, Peanuts, and Tomatoes (PP# 6F4762). Memo to M. Metzger, Chief. May 27, 1997.

Steinwand, B. 1997. Dietary Exposure Analysis for Azoxystrobin in/on Grapes (PP# 5F4541) and Pecans PP# 6F4642). Memo to M. Metzger, Chief. April 21, 1997.