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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: September 22, 2000

SUBJECT: PP# 9F06058. **Azoxystrobin. Human Health Risk Assessment for Residues in/on Barley, Bulb Vegetables, Cilantro, Citrus Fruits, Corn, Cotton, Leafy Vegetables (except *Brassica*), Leaves of Root and Tuber Vegetables, Peanuts, Root and Tuber Vegetables, Soybeans, and Wild Rice; Higher Tolerances for the Fat and Meat Byproducts of Cattle, Goats, Horses, and Sheep; and, Apples (Inadvertent Residues).**

Chemical Number:	128810
40CFR:	§180.507
Chemical Class:	Fungicide
Trade Names:	Abound (EPA Registration No. 10182-415) Heritage (EPA Registration No. 10182-408)
DP Barcode:	D267563
Submission No.:	S568437

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INTRODUCTION

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 hazard and exposure data and conduct dietary, occupational/residential, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from the registered and proposed uses of azoxystrobin on barley, bulb vegetables, citrus fruits, field corn, sweet corn, cotton, root and tuber vegetables and tops, leafy vegetables and cilantro, peanuts, soybeans, and wild rice. The registrant has requested permanent tolerances for these new uses, and higher tolerances for the fat and meat byproducts of cattle, goats, horses, and sheep.

A summary of the findings and an assessment of human risk resulting from the new uses of azoxystrobin are provided in this document.

Recommendation for Tolerances

The submitted data (toxicological, product and residue chemistry) and this human health risk assessment support the establishment of the proposed tolerances listed in the Executive Summary.

1.0 EXECUTIVE SUMMARY

Zeneca Ag Products has requested the establishment of permanent tolerances for residues of the fungicide azoxystrobin (methyl (E)-2-[2-[6-(2-cyanophenoxy)pyrimidin- 4-yloxy]phenyl]-3-methoxyacrylate) and its Z isomer (methyl (Z)-2-[2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl]-3-methoxyacrylate) in/on barley, bulb vegetables, citrus fruits, field corn, sweet corn, cotton, root and tuber vegetables and tops, leafy vegetables and cilantro, peanuts, soybeans, and wild rice, and higher tolerances for the fat and meat byproducts of cattle, goats, horses, and sheep. Azoxystrobin is a broad spectrum, systemic fungicide which acts by inhibiting electron transport. Tolerances are established for residues of azoxystrobin (methyl (E)-2-[2-[6-(2-cyanophenoxy)pyrimidin- 4-yloxy]phenyl]-3-methoxyacrylate) and its Z isomer (methyl (Z)-2-[2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl]-3-methoxyacrylate) (40 CFR 180.507) at 0.01 to 20.0 ppm in/on a number of plant and for azoxystrobin *per se in* animal commodities. In addition, there are registered outdoor residential and recreational use sites. There are no Codex, Canadian, or Mexican maximum residue limits. New uses for multiple applications (foliar, banded, or in-furrow) by ground, air, or chemigation to a wide variety of crops (listed below) are being requested for a 50% water-dispersible granular formulation and a 2.08 lbs ai/gal flowable concentrate. Typically on these crops, applications will begin at the onset of, or prior to, disease development and continue throughout the season. The per application rate is up to 0.40 lb ai/A, with a maximum seasonal rate of 1.5-2.0 lbs ai/A. Retreatment is usually on a 1-2 week schedule, and the minimum preharvest interval (PHI) is typically 0-14 days.

PROPOSED (HED RECOMMENDED VERSION) NEW TOLERANCES FOR 40 CFR 180.507					
COMMODITY	PPM	COMMODITY	PPM	COMMODITY	PPM
Barley, bran	0.20	Corn, sweet, K + CWHR	0.050	Soybean, seed	0.50
Barley, grain	0.10	Corn, sweet, stover	25.0	Vegetable, leafy, except *Brassica*, group	30.0
Barley, hay	15.0	Cotton, gin byproducts	0.020	Vegetable, leaves of root and tuber, group	50.0
Barley straw	4.0	Cotton, undelinted seed	0.020	Vegetable, root, subgroup	0.50
Citrus, dried pulp	2.0	Fruit, citrus, group	1.0	Vegetable, tuberous and corm, subgroup	0.030
Citrus, oil	4.0	Grain, aspirated grain fractions	30.0	Cattle, fat	0.030
Coriander, leaves	30.0	Onion, dry bulb	1.0	Cattle, meat byproducts	0.070
Corn, field, forage	12.0	Onion, green	7.50	Goat, fat	0.030
Corn, field, grain	0.050	Peanut	0.20	Goat, meat byproducts	0.070
Corn, field, refined oil	0.30	Peanut, refined oil	0.60	Horse, fat	0.030
Corn, field, stover	25.0	Peanut, hay	15.0	Horse, meat byproducts	0.070
Corn, pop, grain	0.050	Soybean, forage	25.0	Sheep, fat	0.03
Corn, pop, stover	25.0	Soybean, hay	55.0	Sheep, meat byproducts	0.070
Corn, sweet, forage	12.0	Soybean, hulls	1.0		

Note: This listing has been revised by the chemistry reviewer to reflect correct nomenclature and appropriate tolerance levels, and to delete the proposed tolerances for wild rice (for which no supporting residue data were provided); for sugar beet, dried pulp (since a separate tolerance was not warranted); and, for apple (inadvertent residues; since it is not OPP policy to establish a tolerance for inadvertent residues based upon concerns about the possibility of spray drift or contaminated equipment).

No residue problems are expected from impurities in the technical grade active ingredient in conjunction with the proposed uses. The metabolic pathway is similar in plants and animals, and hydrolysis is the major biotransformation process. The HED Metabolism Assessment Review Committee (MARC) has determined that the regulable residue in plant commodities (and that for risk assessments in plant commodities and drinking water) is combined residues of azoxystrobin and its Z isomer; in animal commodities, the regulable residue (and that for risk assessments) is azoxystrobin *per se*.

Adequate enforcement methods for plant (GLC/NPD) and animal (GLC/TSD) commodities are available from PIRIB/IRSD (7502C) and ACB/BEAD (7503W). These have passed successful BEAD validation trials. Azoxystrobin is not recovered by the FDA multiresidue protocols.

The data supporting the proposed tolerances are from crop field trials, processing studies, and a ruminant (dairy cattle) feeding study. Tolerances are not currently required for poultry tissues and eggs; 40 CFR 180.6(a)(3). There are minor residue chemistry data gaps to be addressed as conditions of registration.

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Hazard and Dose Response Assessment

On August 15, 2000, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for azoxystrobin with regard to the acute Reference Dose (RfD) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The Toxicology Endpoint Selection (TES) Committee has previously assessed appropriate toxicology endpoints and dose levels of concern for earlier risk assessment purposes (HED doc. No. 013102, dated 12/10/96).

As required by the Food Quality Protection Act (FQPA) of 1996, the potential for increased susceptibility of infants and children from exposure to azoxystrobin, was also previously evaluated. The HED FQPA Safety Factor Committee, in its meeting of August 24, 1998, recommended that the 10-fold safety factor for increased susceptibility of infants and children should be removed (i.e., reduced to 1x) for azoxystrobin (HED doc. no. 012844, dated 9/3/98, Attachment 1). The HIARC, in its meeting of 8/15/00, reaffirmed the FQPA SF Committee's determination that there are no data gaps for the assessment of the effects of azoxystrobin following *in utero* and/or postnatal exposure; the HIARC also reaffirmed a previous decision that a developmental neurotoxicity study in rats is not required (Memo, HED doc No. 014329, dated 9/25/2000, Attachment 2).

The HED RfD/Peer Review Committee, in its meeting of November 7, 1996, determined that azoxystrobin should be classified as "Not Likely" to be a human carcinogen according to the revised Cancer Guidelines, based on lack of evidence of carcinogenicity in the long-term rat and mouse feeding studies (HED doc. no. 012133, dated 1/14/97).

There are no data gaps for the standard Subdivision F Guideline requirements for a food-use chemical by 40 CFR Part 158. However, the metabolism study in rats is considered supplementary "upgradeable" pending the submission of additional information. The study is not required for the proposed food use.

The scientific and regulatory quality of the toxicology data base is considered sufficient, at this time, to clearly define the toxicity of azoxystrobin. There is a good degree of confidence in the hazard and dose-response assessments conducted. With the exception of the exposure via the inhalation route, there are suitable toxicity studies with the same routes of exposure and the proper duration as dictated by the risk assessments scenarios. For the short- and mid-term inhalation exposure scenarios, a prenatal developmental rat toxicity study and a 90-day toxicity study, respectively, were selected by the HIARC which recommended using a route-to-route extrapolation and a 100% absorption rate (default value). **Due to concern for exposure via this route based on the use pattern, the HIARC also recommended the submission of a 28-day nose-only inhalation toxicity study using the same form of azoxystrobin to which workers are exposed** (Memo, HED doc No. 014329, dated 9/25/2000, Attachment 2).

Azoxystrobin generally has a low acute oral toxicity (Toxicity Category IV) and is neither a dermal irritant nor a sensitizer. No treatment-related effects were noted in the 21-day repeated dose dermal toxicity study in rats up to and including the limit dose of 1000 mg/kg/day. Among the most common toxicity findings from oral administration of azoxystrobin to rats were decreased body weight, decreased food intake/utilization, increased diarrhea, and other clinical toxicity observations such as, increased urinary incontinence, hunched postures and distended abdomens. Based on oral feeding studies in rats and dogs, the primary target organs are the liver and bile duct as evidenced by clinical chemistry data, increased organ weight, gross pathology and/or microscopic changes in the liver and biliary tracts. In accordance with the 1996 Cancer Risk Assessment Guidelines, azoxystrobin was classified as "**not likely**" to be carcinogenic to humans via relevant routes of exposure based on the lack of evidence of carcinogenicity in mice or rats (RfD/Peer Review Report dated 1/14/97, HED Doc. No. 012133). There is no evidence of neurotoxicity in any of the guideline studies, including the acute and subchronic neurotoxicity studies in rats. Based on guideline studies in rats and rabbits, azoxystrobin is not a developmental or reproductive toxicant and there is no evidence for increased susceptibility of rat or rabbit fetuses to *in utero* exposure or rat pups to *post-natal* exposure to azoxystrobin.

Following the administration of a single oral low or a high dose or repeated doses to rats, azoxystrobin was widely distributed with the liver and kidneys having the highest concentrations; however, less than 0.5% of the administered dose was detected in the tissues at seven days postdosing. The primary route of excretion was via the feces (≈73-89%) followed by urine (≈9-18%). There was no apparent sex- or dose-related differences in the distribution or in the pattern of excretion. After a single oral high-dose, the biliary excretion profile suggested that, of the administered dose, nearly 70% was absorbed with approximately 32% remaining as the parent compound. The absorbed azoxystrobin appeared to undergo extensive metabolism with minor sex-related qualitative and quantitative differences in biliary metabolites. A metabolic pathway was proposed showing hydrolysis and subsequent glucuronide conjugation.

The HIARC selected an **acute RfD of 0.67 mg/kg/day** for the acute dietary risk assessment. The acute RfD is based on the acute neurotoxicity study in rats in which the LOAEL of 200 mg/kg was based on the occurrence of diarrhea in both sexes at two hours post-dosing. The designated Uncertainty Factor (UF) for assessing acute dietary risk was 300, which includes a factor of 3 since the NOAEL was not identified. Because the FQPA safety factor was removed (i.e., reduced to 1x), the acute population adjusted dose (aPAD) also equals 0.67 mg/kg/day.

For assessing chronic dietary risk, the HIARC selected a **chronic RfD of 0.18 mg/kg/day** by applying an UF of 100 to the NOAEL of 18 mg/kg/day (300 ppm) from the 2-year combined chronic feeding/carcinogenicity study in rats. The systemic toxicity LOAEL for males is 750 ppm (34 mg/kg/day) based on reduced body weights, food consumption and food efficiency, and bile duct lesions and the systemic toxicity LOAEL for females is 1500 ppm (117 mg/kg/day) based on reduced body weights, food consumption and food efficiency. Because the FQPA safety factor was removed (i.e., reduced to 1x), the chronic population adjusted dose (cPAD) also equals 0.18 mg/kg/day.

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For the short-term (1-7 days) incidental oral exposure assessment, the HIARC selected the prenatal rat oral developmental toxicity study with the maternal toxicity NOAEL of 25 mg/kg/day based on increased diarrhea, urinary incontinence and salivation in dams administered the next higher dose of 100 mg/kg/day (LOAEL). For the intermediate-term (7 days to several months) incidental oral exposure assessment, the HIARC selected the 90-day rat toxicity feeding study with the systemic NOAEL of 200 ppm (20 mg/kg/day) based on reduced body weight gain and other clinical signs in both sexes at the LOAEL of 2000 ppm (211mg/kg/day).

The HIARC did not select a toxicological endpoint for the short- or intermediate-term dermal risk assessments. Therefore, these risk assessments are not required. In a 21-day repeated dose dermal toxicity study in rats, no systemic or dermal toxicity was observed at the limit dose of 1000 mg/kg/day. The systemic and dermal NOAEL is the limit dose of 1000 mg/kg/day and LOAEL is unidentified. This finding of apparently low dermal toxicity is consistent with the low dermal absorption rate of 2 - 4%. The proposed use pattern for azoxystrobin indicates there is no potential for long-term dermal exposure. Thus, the HIARC concluded that a long-term dermal exposure assessment is not required.

The HIARC selected toxicological endpoints for the short- and intermediate-term inhalation risk assessments. The HIARC recommended using route-to-route extrapolation and a 100% absorption rate (default value). For the short-term inhalation risk assessment, the HIARC selected the prenatal rat oral developmental toxicity study with the maternal toxicity NOAEL of 25 mg/kg/day based on increased diarrhea, urinary incontinence and salivation in dams administered the next higher dose of 100 mg/kg/day (LOAEL). For the intermediate-term inhalation risk assessment, the HIARC selected a 90-day rat toxicity feeding study with the systemic NOAEL of 200 ppm (20 mg/kg/day) based on reduced body weight gain and other clinical signs in both sexes at the LOAEL of 2000 ppm (211mg/kg/day). A margin of exposure (MOE) of 100 or greater is adequate for occupational exposure risk assessments. The proposed use pattern for azoxystrobin indicates that there is no potential for long-term inhalation exposure and, therefore, this risk assessment is not required. Nonetheless, if this risk assessment becomes necessary in the future, the HIARC recommended using the 2-year combined chronic feeding/ carcinogenicity study in rats which was also selected for the chronic dietary risk assessment. The HIARC also recommended using a route-to-route extrapolation and a 100% absorption rate (default value).

Dietary Risk Estimates from Food Sources

Tier 1 acute and chronic dietary exposure analyses for azoxystrobin were performed using the Dietary Exposure Evaluation Model (DEEM™). At the 95th percentile, the acute exposure estimate for the general U.S. population accounted for 11% of the aPAD. The subpopulation with the highest acute exposure estimate is children 1-6 years old (19% aPAD). The chronic exposure estimate for the general U.S. population accounted for 12% of the cPAD. The most highly exposed subgroup was children 1-6 years old at 18% of the cPAD.

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Dietary Risk Estimates from Drinking Water Sources

EFED provided a drinking water assessment of azoxystrobin. The Estimated Environmental Concentration (EEC) for ground water (from SCI-GROW modeling) is 0.064 ppb. The EEC for surface water (from GENEEC modeling) is 141 ppb for the acute (peak) concentration and 127 ppb for the chronic (56- to 60-day) concentration. With the 3x adjustment factor allowed by OPP policy for 56-day GENEEC estimates, the chronic surface water EEC is 42 ppb.

Residential Exposure and Risk Estimates

Products containing azoxystrobin are registered for application to turf and ornamentals. They may be applied 1-5 times per year at rates up to 0.95 lb active ingredient per acre. The current registered labels permit homeowners to mix/load/apply both flowable (i.e., liquid) and water-dispersible granule formulations.

Residential handlers may be exposed to azoxystrobin for short-term durations. Toddlers may receive short- and intermediate-term oral exposure from incidental non-dietary ingestion (i.e., hand-to-mouth, turfgrass transfer, and soil ingestion) during post-application activities. HED's Draft Standard Operating Procedures (SOPs) for Residential Exposure Assessments were used as the basis for all residential handler exposure calculations. The post-application risk assessment is based on generic assumptions as specified by the newly proposed Residential SOPs and recommended approaches by HED's Exposure Science Advisory Committee (ExpoSAC). Revisions to the Residential SOPs have been proposed that alter the residential post-application scenario assumptions. The proposed assumptions are expected to better represent residential exposure and are still considered to be high-end, screening level assumptions. HED management has authorized the use of the revised residential SOPs that were presented to the FIFRA SAP in September 1999. Therefore, HED has deviated from the current Residential SOP assumptions and uses the proposed assumptions to calculate exposure estimates.

The short- and intermediate-term NOAELs of 25 mg/kg/day and 20 mg/kg/day, respectively, were used in the inhalation and incidental ingestion risk assessment of residential exposure. As no dermal endpoint was selected, a dermal risk assessment was not required for residential exposure. For residential inhalation and oral risk assessments, the target margin of exposure (MOE) is 100, which incorporates the FQPA Safety Factor of 1x.

MOEs calculated for residential handler's inhalation exposure and children's oral exposure were well above the target of 100.

Aggregate Exposure and Risk Assessment/Characterization

Acute risk estimates resulting from aggregate exposure to azoxystrobin in food and drinking water are below HED's level of concern. Peak surface and ground water EECs were used to compare against back-calculated Drinking Water Levels of Comparison (DWLOCs) for

aggregate risk assessments. For the acute scenario, the DWLOC for the U.S. population is 21,000 ppb and the DWLOC for the most highly exposed subpopulation (children 1-6 years) is 5,400 ppb. The peak EECs of azoxystrobin in surface and ground water are less than HED's DWLOCs for azoxystrobin in drinking water as a contribution to acute aggregate exposure. Therefore, HED concludes with reasonable certainty that residues of azoxystrobin in drinking water do not contribute significantly to the acute aggregate human health risk at the present time considering the present uses and uses proposed in this action.

For the U.S. population and children 1-6 years old, the total food and residential short-term aggregate MOEs are 1,200 and 520, respectively. The total food and residential intermediate-term aggregate MOE for children 1 to 6 years old is 420. As these values are greater than the target of 100, the short-term food and residential aggregate risks for the general U.S. population and the intermediate-term food and residential risks for children 1-6 are below HED's level of concern. The chronic surface water EEC of 42 ppb is less than HED's DWLOCs in drinking water as a contribution to short- or intermediate-term aggregate exposure. Therefore, HED concludes with reasonable certainty that residues of azoxystrobin in drinking water do not contribute significantly to the short- or intermediate-term aggregate human health risk at the present time.

Chronic risk estimates resulting from aggregate exposure to azoxystrobin in food and water are below HED's level of concern. Surface and ground water EECs were used to compare against back-calculated DWLOCs for aggregate risk assessments. For the chronic scenario, the DWLOCs are 5,600 ppb for the U.S. population and 1,500 for the most highly exposed subpopulation (children 1-6 years). The average EECs of azoxystrobin in surface and ground water are less than HED's DWLOCs in drinking water as a contribution to chronic aggregate exposure. Therefore, HED concludes with reasonable certainty that residues of azoxystrobin in drinking water do not contribute significantly to the chronic aggregate human health risk at the present time considering the present uses and uses proposed in this action.

Occupational Exposure and Risk Estimates

As no dermal endpoint was selected, a dermal risk assessment was not required for occupational exposure. The target MOE for the occupational inhalation risk assessment is 100.

Occupational handler inhalation exposures were estimated using unit exposures from the Pesticide Handler Exposure Database (PHED), maximum application rates, and HED standard values for other inputs (i.e. number of acres treated per day, body weight, etc.). The handler inhalation exposures calculated are central to high-end values. Both short- and intermediate-term inhalation MOEs calculated for handlers were well above the target MOE of 100.

The azoxystrobin technical material has been classified in Toxicity Category III for acute dermal and primary eye irritation, and Toxicity Category IV for primary skin irritation. Per the Worker Protection Standard (WPS), a 12-hr restricted entry interval (REI) is required for chemicals

classified under Toxicity Category III or IV, which is the shortest waiting period permitted under the WPS. However, per Pesticide Regulation Notice 95-3 (6/7/95), REIs may be further reduced from 12 hours if certain criteria are met. In a previous risk assessment (Memo, D. Dotson, D248888, 1/28/99), HED determined that the criteria established by Pesticide Regulation Notice 95-3 have been met for azoxystrobin formulated as a water-dispersible granule, and that a 4-hour REI is acceptable on the Heritage® label. However, it is not clear whether the criteria have subsequently been met for the flowable concentrate formulation. This needs to be addressed by the Registration Division (e.g., obtain acute toxicity data for the end-use product) to determine whether the Abound® label may indicate a reduction in REI to 4 hours.

Recommendation for Tolerances

The submitted data (toxicological, product and residue chemistry) and this human health risk assessment support the establishment of the proposed tolerances, as listed above.

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2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

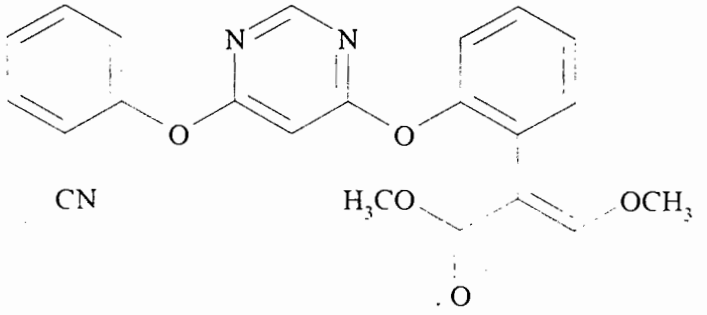
2.1 Chemical Identity and Structure

Chemical Name: methyl (E)-2-[2-[6-(2-cyanophenoxy)pyrimidin- 4-yloxy]phenyl]-3-methoxyacrylate

CAS Registry No.: 131860-33-8
Chemical Class: β - methoxyacrylate fungicide
Empirical formula: $C_{22}H_{17}N_3O_5$

Chemical Structure:

Azoxystrobin



2.2 Physical/Chemical Properties

Physical/Chemical Properties of Azoxystrobin	
Color	white
Physical State	powdery solid
Odor	odorless
Molecular Weight	403.4
Melting Point	114-116° C
Boiling Point	N/A; azoxystrobin is a solid
Density	1.25 g/cm^3
Vapor Pressure	1.1 x 10^{-13} kPa = 8.2 x 10^{-13} mg Hg @ 25° C
Dissociation Constant	Not dissociable

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Physical/Chemical Properties of Azoxystrobin		
Solubility	solvent	solubility @ 20° C
	water, pH 5.2	6.7 mg/L
	water, pH 7	6.7 mg/L
	water, pH 9.2	5.9 mg/L
	n-hexane	0.057 mg/mL
	methanol	20 mg/mL
	ethyl acetate	130 mg/mL
	toluene	55 mg/mL
	acetone	86 mg/mL
	dichloromethane	400 mg/mL
Octanol/Water Partition Coefficient	log P_{0w} = 2.5	
pH	6.4	
Stability	Thermal; stable at least 14 days at 54° C to metals and ions; unreactive to sunlight	
Oxidizing or Reducing Action	Compatible with oxidizing and reducing agents	
Flammability	N/A	
Explodability	N/A	
Storage Stability	Stable for at least a year at ambient temperatures	
Viscosity	N/A	
Miscibility	N/A	
Corrosion Characteristics	N/A	

Azoxystrobin has an isomeric form, the Z isomer. No residue problems are expected from impurities in the technical grade active ingredient in conjunction with the proposed uses.

2.3 Physical/Chemical Properties Characterization

The vapor pressure and solubility (in water) of azoxystrobin are low, which may limit the inhalation and dermal exposure potential to handlers (mixer/loader/applicators), other occupationally exposed workers (from postapplication activities), and to non-occupationally exposed persons (e.g., homeowners, children, and those engaged in outdoor recreational activities).

3.0 HAZARD CHARACTERIZATION

A stand alone document or summary of the toxicological data base for azoxystrobin (such as a Toxicology Chapter) is not currently available. However, the following hazard characterization is extracted from the recent HED-HIARC report on azoxystrobin (Memo, HED doc No. 014329, dated 9/25/2000, Attachment 2).

3.1 Hazard Profile

Azoxystrobin is structurally related to the naturally occurring strobilurins, compounds derived from some fungal species, and is also in the same chemical class as Trifloxystrobin (PC Code 129112). The biochemical mode of action of these compounds is inhibition of electron transport in pathogenic fungi. The scientific and regulatory quality of the toxicology data base is considered sufficient, at this time, to clearly define the toxicity of azoxystrobin. There is a good degree of confidence in the hazard and dose-response assessments conducted. With the exception of the exposure via the inhalation route, there are suitable toxicity studies with the same routes of exposure and proper duration as dictated by the risk assessments scenarios. The HED-HIARC, in their meeting of August 15, 2000, recommended the submission of a 28-day nose-only inhalation toxicity study using the same form of azoxystrobin to which workers are exposed (Memo, HED doc No. 014329, dated 9/25/2000, Attachment 2).

The overall toxicity profile for azoxystrobin is summarized in Tables 1 and 2. There is one study (pharmacokinetics and metabolism) that is considered **supplementary (upgradable)** pending the submission of additional information. Nonetheless, the missing information is not considered critical and should not compromise the overall confidence in the data base, nor should it invalidate the findings of the respective studies.

Table 1. Acute Toxicity Data on Azoxystrobin Technical

Guideline No.	Study Type	MRID #	Results	Toxicity Category
870.1100	Acute Oral - Rat	43678122	LD_{50} > 5000 mg/kg (Limit Test) in Males & Females	IV
870.1200	Acute Dermal - Rat	43678124	LD_{50} > 2000 mg/kg (Limit Test) in Males & Females	III
870.1300	Acute Inhalation - Rat	43678126	LC_{50} Males = 0.962 mg/L (95% C.I. = 0.674) Females = 0.698 mg/L (95% C.I. = 0.509, 2.425) The combined LC50 was not calculated due to mortality pattern	III
870.2400	Primary Eye Irritation - Rabbit	43678128	Slight to moderate erythema and slight chemosis in all rabbits within one hour, but effects resolved within 48 hours of treatment.	III
870.2500	Primary Skin Irritation - Rabbit	43678130	Very slight erythema and edema that persisted for three days on one rabbit and for one hour on another.	IV
870.2600	Dermal Sensitization - Guinea Pig	43678132	No erythema or edema were found 38 or 48 hrs after challenge with test material.	Not a dermal sensitizer

Table 2. Toxicity Profile of Azoxystrobin	
Guideline No./ Study Type	**Results**
870.3100 90-Day oral toxicity in rats	**NOAEL = 20 mg/kg/day** **LOAEL = 211 mg/kg/day** 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.
870.3150 90-Day oral toxicity in dogs	**NOAEL = 50 mg/kg/day** **LOAEL = 250 mg/kg/day** based on treatment-related clinical observations and clinical chemistry alterations indicative of effects on liver/biliary function in both sexes.
870.3200 21-Day dermal toxicity in rats	**NOAEL = 1000 mg/kg/day** (limit dose) **LOAEL > 1000 mg/kg/day**.
870.3250 90-Day dermal toxicity	Not available
870.3465 90-Day inhalation toxicity	Not available
870.3700a Prenatal developmental in rats	**Maternal NOAEL = 25 mg/kg/day** **LOAEL = 100 mg/kg/day** based on the maternal clinical signs of increased diarrhea, urinary incontinence, and salivation. **Developmental NOAEL = 100 mg/kg/day** **LOAEL > 100 mg/kg/day**.
870.3700b Prenatal developmental in rabbits	**Maternal NOAEL = 150 mg/kg/day** **LOAEL = 500 mg/kg/day** based on decreased body weight gain. **Developmental NOAEL = 500 mg/kg/day** **LOAEL > 500 mg/kg/day**.
870.3800 Reproduction and fertility effects in rats	**Parental/Systemic NOAEL = 32 mg/kg/day** **LOAEL = 165 mg/kg/day** based on reduced body weight, reduced food consumption, and increased adjusted liver weights in both sexes in addition to gross and histopathologic lesions of the bile duct and liver in males. **Reproductive NOAEL = 165 mg/kg/day** **LOAEL > 165 mg/kg/day**. **Offspring NOAEL = 32 mg/kg/day** **LOAEL = 165 mg/kg/day** based on reduced pup body weight and increased adjusted liver weights.
870.4100 Chronic toxicity in dogs	**NOAEL = 25 mg/kg/day** **LOAEL = 200 mg/kg/day** based, in both sexes, on clinical observations, increased liver weight, and clinical chemistry changes indicative of effects on liver/biliary function.
870.4200 Carcinogenicity in mice	**NOAEL = 38 mg/kg/day** **LOAEL = 272 mg/kg/day** based on reduced body weights in both sexes. **There was no evidence of carcinogenicity.**

Table 2. Toxicity Profile of Azoxystrobin	
Guideline No./ Study Type	**Results**
870.4300 Combined Chronic toxicity/ Carcinogenicity in rats	**NOAEL = 18 mg/kg/day** **LOAEL = 34 mg/kg/day in males and 117 mg/kg/day in females** based on reduced body weights in both sexes and bile duct lesions in males. **There was no evidence of carcinogenicity.**
870.5100 Bacterial reverse gene mutation	**Negative in increasing revertant colonies up to 5000 µg/plate +/-S9** using both plate incorporation and preincubation protocols and Salmonella strains TA98, TA100, TA1535, and TA1537 as well as the E. Coli strains WP2P and WP2PuvrA. Cytotoxicity and compound precipitation were seen at the high dose.
870.5300 Mammalian cell forward gene mutation	**Nonlinear, slight but significant increases in the mutation frequency (MF) of mouse lymphoma L5178Y TK$^{+/-}$ at 15-60 µg/mL +/-S9**. Despite the absence of a dose response, increased MFs were reproducible; therefore, Azoxystrobin is considered positive in this test system. Colony sizing was not performed.
870.5375 Cytogenetics chromosomal aberration	**The in vitro test in human lymphocytes was positive for the induction of chromosomal aberrations in both the presence and absence of S9** at doses (5-50 µg/mL -S9; 100-200 µg/mL +S9) that were moderately to severely cytotoxic (i.e., ≥16-70% reductions in mitotic cells, respectively)
870.5385 Cytogenetics bone marrow	**The in vivo mouse bone marrow micronucleus assay was negative at 5000 mg/kg** when administered once by oral gavage. Overt toxicity and depression of erythropoiesis seen in addition to cytotoxic effects on the target cell in the males.
870.5550 Other: Unscheduled DNA synthesis	**The in vivo/in vitro unscheduled DNA synthesis test in rat hepatocytes was negative**. No toxicity to the treated animals or cytotoxic effects on recovered hepatocytes up to the limit dose for acute testing (2000 mg/kg) when administered once by oral gavage.
870.6200a Acute neurotoxicity screening battery in rats	**NOAEL < 200 mg/kg/day** **LOAEL = 200 mg/kg/day** based on transient diarrhea in both sexes.
870.6200b Subchronic neurotoxicity screening battery in rats	**NOAEL = 39 mg/kg/day.** **LOAEL = 161 mg/kg/day** based on decreased body weight/weight gain and food utilization in both sexes.
870.6300 Developmental neurotoxicity	Not available

Table 2. Toxicity Profile of Azoxystrobin	
Guideline No./ Study Type	**Results**
870.7485 Metabolism and pharmacokinetics	Following oral administration as a single gavage dose of 1 or 100 mg/kg or 15-day repeated doses of 1 mg/kg, azoxystrobin was widely distributed with the liver and kidneys having the highest concentrations; however, less than 0.5% of the administered dose was detected in the tissues at seven days postdosing. The primary route of excretion was via the feces (≈73-89%) followed by urine(≈9-18%). There was no apparent sex- or dose-related differences in distribution or in the pattern of excretion. In a bile duct cannulated single high-dose group, assessment of biliary excretion suggested approximately 70% absorption with approximately 32% of the administered dose remaining as parent compound in the gastrointestinal tract. Absorbed azoxystrobin appeared to be extensively metabolized with minor sex-related qualitative and quantitative differences in biliary metabolites. A metabolic pathway was proposed showing hydrolysis and subsequent glucuronide conjugation as the major biotransformation process.
870.7600 Dermal penetration	2 - 4 % based on Rat Dermal Absorption Study (MRID 43678155).
Special studies	Not available

Common Toxicity Findings

The most common toxicity findings from oral administration of azoxystrobin to rats were decreased body weight, decreased food intake/utilization, increased diarrhea, and other clinical toxicity observations such as, increased urinary incontinence, hunched postures and distended abdomens. One or more of these effects were reported in most rat studies including subchronic (MRID 43678135), combined chronic toxicity/oncogenicity (MRID 43678139), prenatal developmental toxicity (MRID 43678142), 2-generation reproduction (MRID 43678144), acute neurotoxicity (MRID 43678134, 44182013, 44182015), and subchronic neurotoxicity (MRID 43678138, 44182014). In the repeated dosing rat studies, these effects were not seen at the NOAEL values that ranged from 18 mg/kg/day in the chronic rat dietary feeding study to nearly 32 mg/kg/day (300 ppm) in the 2-generation rat reproduction study. In the rat subchronic neurotoxicity study, for instance, the NOAEL was 38.5 mg/kg/day (500 ppm) based on decreased body weight/weight gain and food utilization.

In addition, increased lethality may occur after repeated oral administration at relatively high doses. Details of these findings are provided under the "Dose-Response Assessment" section (below).

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Target Organs of Toxicity

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

Developmental and Reproductive Toxicity

The pre- and post-natal toxicology data base for azoxystrobin is adequate and includes the rat and rabbit developmental toxicity studies (MRID 43678142 and 44058701) and the 2-generation reproduction toxicity study in rats (MRID 43678144). There were no developmental effects in the rat and rabbit developmental studies. In the reproduction study, both the offspring and parents in the high dose group (165 mg/kg/day) had decreased body weights and increased adjusted liver weights. In addition, the F_0 and F_1 parents in the high dose group, but not their offspring (aged 29 days), had liver and bile duct changes including distention and histopathologic lesions of the common bile duct in addition to increased liver proliferative cholangitis. Therefore, the effects in the young are not more severe than those observed with the parents.

Neurotoxicity

In both the acute and subchronic neurotoxicity studies, there were no consistent indications of treatment-related neurotoxicity including clinical signs, qualitative or quantitative neurobehavioral effects, brain weight/dimensions, or gross/microscopic pathology. In the acute neurotoxicity study, tip-toe gait and upwardly curved spine were observed in treated but not control animals (no dose-response). Statistically significant increases in landing foot splay on day 8 in females at 600 and 2000 mg/kg were noted but were not considered indicative of neurotoxicity because of a lack of effect on day of dosing (only marginal non-significant increase seen) and to the lack of a clear dose-response and indications of other effects. The systemic toxicity LOAEL is considered to be 200 mg/kg (lowest dose tested) based on occurrence of transient diarrhea in both sexes (MRID 43678134, 44182013, 44182015). The NOAEL/LOAEL for the subchronic rat neurotoxicity study is 39/161 mg/kg/day based on decreased body weight/weight gain and food utilization. Statistically significant decreases in landing foot splay in males, forelimb grip strength in males and females, hindlimb grip strength in males, and motor activity in females were noted but were not considered treatment-related because of a lack of dose-response, inconsistency of observations at different time points, variability of pretreatment values and/or small magnitude of response (MRID 43678138, 44182014).

Carcinogenicity

The long-term dietary administration of azoxystrobin did not result in treatment-related increased incidences of tumors. The RfD/Peer Review Committee considered both the rat and mouse carcinogenicity studies and the doses tested adequate based on findings at the highest tested doses of body weight reduction and bile duct lesions in the rat and body weight reduction in the mouse. The RfD/Peer Review Committee, using the current cancer risk assessment guidelines concluded that azoxystrobin is **not likely** to be carcinogenic to humans via relevant routes of exposure (Report by RfD/Peer Review Committee dated 1/14/97, HED doc. No. 012133).

Mutagenicity

The positive findings in some of the mutagenicity studies (Table 2) were evaluated by the RfD/Peer Review Committee which "concluded that Azoxystrobin in the presence and absence of exogenous metabolic activation induced a weak mutagenic response in the mouse lymphoma assay. Although colony sizing was not performed in the mouse lymphoma assay, it is likely that the increased MFs seen in this study were associated with a chromosomal rather than point mutational event. This interpretation is based on the similarity of the response uncovered in the mouse lymphoma assay to the clastogenic response seen with and without S9 activation in human lymphocytes. However, the negative genotoxicity associated with bone marrow cytotoxicity in the micronucleus assay provides confidence that Azoxystrobin is not an in vivo genotoxicant. This assumption is further supported by the negative findings of the UDS assay, the lack of an oncogenic effect in rat or mouse long-term feeding studies and the absence of significant reproductive or developmental toxicity attributable to a mutagenic mode of action (i.e., decreased total implants, increased resorptions). Hence, it can be concluded that Azoxystrobin is active in vitro but this genotoxicity is not expressed in whole animals." (Report by RfD/Peer Review Committee dated 1/14/97, HED doc. No. 012133)

Metabolism and Pharmacokinetics

Based on pharmacokinetics and metabolism studies in rats (MRID 43678150, 43678151, 43678152, 43678153, 43678154), azoxystrobin was widely distributed following administration as a single gavage dose of 1 or 100 mg/kg or 15-day repeated doses of 1 mg/kg/day. The greatest concentrations were detected in organs associated with excretory function, especially the liver and kidneys. However, less than 0.5% of the administered dose was detected in the tissues at seven days postdosing and there was no apparent sex-related differences in distribution and no evidence of potential for bioaccumulation. Excretion via expired air was minimal. The primary route of excretion was via the feces (≈73-89%), although ≈9-18% was detected in the urine of the various dose groups. The fecal vs. urinary route of excretion did not vary considerably with dose or sex. However, a definitive quantitative assessment of absorption was not possible because of fecal sample extraction difficulties. Biliary metabolites were assessed from bile duct cannulated rats which were administered a single 100 mg/kg gavage dose of azoxystrobin. The biliary excretion suggested that approximately 70% of this high dose was absorbed with nearly

32% of the administered radioactivity remaining as the parent compound in the gastrointestinal tract. Absorbed azoxystrobin appeared to undergo extensive metabolism with minor sex-related qualitative and quantitative differences in biliary metabolites. With the exception of metabolite V (a glucuronide conjugate) which represented 29.3% (males) and 27.4% (females) of the administered dose, individual biliary metabolites represented less than 10% of the administered dose. A metabolic pathway was proposed showing hydrolysis and subsequent glucuronide conjugation as the major biotransformation process.

3.2 FQPA Considerations

The FQPA Safety Factor Committee (SFC) met on August 24, 1998 to evaluate the hazard and exposure data for azoxystrobin. The SFC considered the available toxicology data base adequate for an FQPA assessment and recommended that the 10-fold safety factor for increased susceptibility of infants and children (as required by Food Quality Protection Act of August 3, 1996) be removed (i.e., reduced to 1x) in assessing the risk posed by this chemical for the following reasons (FQPA Report dated 9/3/98, HED Doc. No. 012844):

- The toxicology data base is complete;
- The developmental and reproductive toxicity data did not indicate increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure;.
- Unrefined chronic dietary exposure estimates (assuming all commodities contain tolerance level residues) will overestimate dietary exposure;
- Modeling data are used for ground and surface source drinking water exposure assessments resulting in estimates considered to be upper-bound concentrations; and
- There are currently no registered residential uses for Azoxystrobin. [Note: Residential turf uses have since been registered, however, as indicated below, the most recent HIARC did not indicate that the safety factor would need to be reexamined.]

The HIARC, in its meeting of 8/15/00, reaffirmed the FQPA SF Committee's determination that there are no data gaps for the assessment of the effects of azoxystrobin following *in utero* and/or postnatal exposure; the HIARC also reaffirmed a previous decision that a developmental neurotoxicity study in rats is not required (Memo, HED doc No. 014329, dated 9/25/2000, Attachment 2).

3.3 Dose Response Assessment

Azoxystrobin generally has a low acute oral toxicity (Toxicity Category IV) and is neither a dermal irritant nor a sensitizer. No treatment-related effects were noted in the 21-day repeated dose dermal toxicity study in rats up to and including the limit dose of 1000 mg/kg/day. Among the most common toxicity findings from oral administration of azoxystrobin to rats were decreased body weight, decreased food intake/utilization, increased diarrhea, and other clinical

toxicity observations such as, increased urinary incontinence, hunched postures and distended abdomens. Based on oral feeding studies in rats and dogs, the primary target organs are the liver and bile duct as evidenced by clinical chemistry data, increased organ weight, gross pathology and/or microscopic changes in the liver and biliary tracts. In accordance with the 1996 Cancer Risk Assessment Guidelines, azoxystrobin was classified as "**not likely**" to be carcinogenic to humans via relevant routes of exposure based on the lack of evidence of carcinogenicity in mice or rats (RfD/Peer Review Report dated 1/14/97, HED Doc. No. 012133). There is no evidence of neurotoxicity in any of the guideline studies, including the acute and subchronic neurotoxicity studies. Based on guideline studies in rats and rabbits, azoxystrobin is not a developmental or reproductive toxicant and there is no evidence for increased susceptibility of rat or rabbit fetuses to *in utero* exposure or rat pups to *post-natal* exposure to azoxystrobin.

The HIARC selected an acute RfD of 0.67 mg/kg for the acute dietary risk assessment. The acute RfD is based on the acute neurotoxicity study in rats in which the LOAEL of 200 mg/kg was based on the occurrence of diarrhea in both sexes at two hours post-dosing. The designated Uncertainty Factor (UF) for assessing acute dietary risk was 300, which includes a factor of 3 since the NOAEL was not identified.

For assessing chronic dietary risk, the HIARC selected a chronic RfD of 0.18 mg/kg/day by applying an UF of 100 to the NOAEL of 18 mg/kg/day (300 ppm) from the 2-year combined chronic feeding/carcinogenicity study in rats. The systemic toxicity LOAEL for males is 750 ppm (34 mg/kg/day) based on reduced body weights, food consumption and food efficiency, and bile duct lesions and the systemic toxicity LOAEL for females is 1500 ppm (117 mg/kg/day) based on reduced body weights, food consumption and food efficiency.

For the short-term (1-7 days) incidental oral exposure assessment, the HIARC selected the prenatal rat oral developmental toxicity study with the maternal toxicity NOAEL of 25 mg/kg/day based on increased diarrhea, urinary incontinence and salivation in dams administered the next higher dose of 100 mg/kg/day (LOAEL). For the intermediate-term (7 days to several months) incidental oral exposure assessment, the HIARC selected the 90-day rat toxicity feeding study with the systemic NOAEL of 200 ppm (20 mg/kg/day) based on reduced body weight gain and other clinical signs in both sexes at the LOAEL of 2000 ppm (211mg/kg/day).

The HIARC did not select a toxicological endpoint for the short- or intermediate-term dermal risk assessments. Therefore, these risk assessments are not required. In a 21-day repeated dose dermal toxicity study in rats, no systemic or dermal toxicity was observed at the limit dose of 1000 mg/kg/day. The systemic and dermal NOAEL is the limit dose of 1000 mg/kg/day and LOAEL is unidentified. This finding of apparently low dermal toxicity is consistent with the low dermal absorption rate of 2 - 4%. The proposed use pattern for azoxystrobin indicates there is no potential for long-term dermal exposure. Thus, the HIARC concluded that a long-term dermal exposure assessment is not required.

The HIARC selected toxicological endpoints for the short- and intermediate-term inhalation risk

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assessments. The HIARC recommended using route-to-route extrapolation and a 100% absorption rate (default value). For the short-term inhalation risk assessment, the HIARC selected the prenatal rat oral developmental toxicity study with the maternal toxicity NOAEL of 25 mg/kg/day based on increased diarrhea, urinary incontinence and salivation in dams administered the next higher dose of 100 mg/kg/day (LOAEL). For the intermediate-term inhalation risk assessment, the HIARC selected a 90-day rat toxicity feeding study with the systemic NOAEL of 200 ppm (20 mg/kg/day) based on reduced body weight gain and other clinical signs in both sexes at the LOAEL of 2000 ppm (211mg/kg/day). A margin of exposure (MOE) of 100 or greater is adequate for occupational exposure risk assessments. The proposed use pattern for azoxystrobin indicates that there is no potential for long-term inhalation exposure and, therefore, this risk assessment is not required. Nonetheless, if this risk assessment becomes necessary in the future, the HIARC recommended using the 2-year combined chronic feeding/ carcinogenicity study in rats which was also selected for the chronic dietary risk assessment. The HIARC also recommended using a route-to-route extrapolation and a 100% absorption rate (default value)

The doses and toxicological endpoints selected for various exposure scenarios are summarized in Table 3.

Table 3. Summary of Toxicological Doses and Endpoints for Azoxystrobin for Use in Human Risk Assessment

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary general population including infants and children	NOAEL < 200 mg/kg/day UF = 300 **Acute RfD** = 0.67 mg/kg/day	FQPA SF = 1X **aPAD** = acute RfD / FQPA SF = 0.67 mg/kg/day	Acute Neurotoxicity - Rat (MRID 43678134, 44182013, 44182015) LOAEL = 200 mg/kg based on diarrhea at two-hours post dose at all dose levels up to and including the LOAEL.
Chronic Dietary all populations	NOAEL= 18 mg//kg/day UF = 100 **Chronic RfD** = 0.18 mg/kg/day	FQPA SF = 1X **cPAD** = chronic RfD / FQPA SF = 0.18 mg/kg/day	Combined Chronic Toxicity/Carcinogenicity Feeding study - Rat (MRID 43678139) LOAEL in males/females = 34/117 mg/kg/day based on reduced body weights in both sexes and bile duct lesions in males.
Short-Term (1-7 days) Incidental Oral (Residential)	NOAEL= 25 mg//kg/day UF = 100	FQPA SF = 1X	Prenatal Developmental Oral Toxicity - Rat (MRID 43678142) LOAEL = 100 mg/kg/day based on increased maternal diarrhea, urinary incontinence, and salivation.

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Table 3. Summary of Toxicological Doses and Endpoints for Azoxystrobin for Use in Human Risk Assessment			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**FQPA SF and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Intermediate-Term (1 week to several months) Incidental Oral (Residential)	NOAEL= 20 mg//kg/day UF = 100	FQPA SF = 1X	90-Day Feeding - Rat (MRID 43678135) LOAEL = 211/223 mg/kg/day in males/females based on decreased body weight gain in both sexes and clinical signs indicative of reduced nutrition.
Short-, Intermediate-, and Long-Term Dermal (Occupational/ Residential)	none	No dermal or systemic toxicity was seen at the limit dose (1000 mg/kg/day). This risk assessment is not required.	21-Day Repeated Dose Dermal - Rat (MRID 43678137)
Short-Term (1-7 days) Inhalation (Occupational/ Residential)	oral NOAEL= 25 mg/kg/day Use route-to-route extrapolation (inhalation absorption rate = 100%)	**LOC for MOE** = 100 (Occupational/ Residential)	Prenatal Developmental Oral Toxicity - Rat (MRID 43678142) LOAEL = 100 mg/kg/day based on increased maternal diarrhea, urinary incontinence, and salivation.
Intermediate-Term (1 week to several months) Inhalation (Occupational/ Residential)	oral NOAEL= 20 mg/kg/day Use route-to-route extrapolation (inhalation absorption rate = 100%)	**LOC for MOE** = 100 (Occupational/ Residential)	90-Day Feeding - Rat (MRID 43678135) LOAEL = 211/223 mg/kg/day in males/females based on decreased body weight gain in both sexes and clinical signs indicative of reduced nutrition.
Long-Term (> 180 days) Inhalation	NOAEL = N/A	This risk assessment is not applicable to the use scenario of azoxystrobin.	

UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern.

The studies were well designed and followed the current EPA guideline requirements. The doses in each of the studies were properly spaced to determine the maximum dose (NOAEL) that can be administered without causing any observed adverse effects and the minimum dose (LOAEL) at which adverse effects could be seen.

It should be noted that, while azoxystrobin has a low acute toxicity by the oral route (LD_{50} > 5000 mg/kg), lethality might be enhanced upon repeated administration of the test material at much lower doses than the LD_{50}. For instance, in the combined chronic toxicity/oncogenicity study

(MRID 43678139), the high dose male group was switched from dietary feeding at 1500 ppm to 750 ppm (34.0 mg/kg/day) due to excessive mortality beginning at week 52. Also, in the prenatal developmental toxicity study (MRID 43678142), three of the first 12 pregnant rats (25%) died after two days of treatment at the high dose (300 mg/kg/day in 10 ml corn oil/kg); henceforth, the study authors discontinued dosing at this level. These results seem contrast with the rat oral LD_{50} reported to be > 5000 mg/kg (MRID 43678122). In this acute toxicity study, five rats of each sex were gavaged a single dose of azoxystrobin at 5000 mg/kg (in 10 ml/kg corn oil); all rats survived the 14 day follow up with no reported clinical toxicity effects or changes in body weight. It is not clear why the chemical is more lethal in the developmental toxicity study than in the acute toxicity study; however, in the developmental toxicity study, there might be enhanced toxicity due to pregnancy. Alternatively, chance variations among the studies and/or the small number of animals per group in the rat oral LD_{50} study might have contributed to these inconsistencies.

3.4 Endocrine Disruption

The FQPA of 1996 requires that EPA 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...." EPA has been working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists to develop a screening and testing program as well as a priority setting scheme to implement this program. The Agency's proposed Endocrine Disrupter Screening Program was published in the Federal Register of December 28, 1998 (63 FR 71541). The Program uses a tiered approach and anticipates issuing a Priority List of chemicals and mixtures for Tier 1 screening in the year 2000. As the Agency proceeds with implementation of this program, further testing of azoxystrobin and its end-use products for endocrine effects may be required.

4.0 EXPOSURE ASSESSMENT and CHARACTERIZATION

4.1 Summary of Registered Uses

Azoxystrobin is a broad spectrum, systemic fungicide of the β-methoxyacrylate chemical class. It is related to the naturally occurring strobilurins and functions similarly, by inhibiting electron transport in pathogens. It is to be applied as a 50% water-dispersible granular formulation (Heritage; EPA Reg. No.10182-408) and a 2.08 lbs ai/gal flowable concentrate product (Abound Flowable; EPA Reg. No. 10182-415).

Typically, azoxystrobin will be applied to the target crops by multiple foliar sprays, banded, or in-furrow applications. Ground, aerial, or chemigation equipment may be used. Applications usually begin prior to, or in the early stages of, disease development and continue throughout the season up to, and often including, the day of harvest.

Use rates are typically in the range of 0.1-0.33 lb ai/A/application, with a seasonal maximum of 1.5-2.0 lbs ai/A Retreatment is often made on a 1-2 week schedule. Many of the target crops receive up to 6-8 applications during a season. However, depending on the crop, the use may be as limited as a single, soil-directed spray at-planting (cotton). Of the crops associated with this petition, the maximum use pattern is on the "Vegetable, root, subgroup", which may be treated with up to 6 foliar sprays at a maximum of 0.33 lb ai/A/application, for a seasonal maximum of 2.0 lbs ai/A, at 5-14 day retreatment intervals, and harvested with a 0-day PHI.

There are no non-agricultural use sites associated with the proposed uses of this petition. However, there are registered non-agricultural uses; e.g., outdoor residential (lawns and ornamentals) and recreational (e.g., golf courses, parks, and athletic fields) sites.

4.2 Dietary Exposure/Risk Pathway

The following is a brief summary of the residue chemistry data base for the proposed use in/on barley, bulb vegetables, citrus fruits, field corn, sweet corn, cotton, root and tuber vegetables and tops, leafy vegetables and cilantro, peanuts, soybeans, and wild rice, and higher tolerances for the fat and meat byproducts of cattle, goats, horses, and sheep. A more detailed summary is provided in the residue chemistry review which is included as Attachment 3 to this risk assessment.

4.2.1 Residue Profile

Permanent tolerances are currently established (40 CFR 180.507) for the combined residues of azoxystrobin *and its Z isomer* in/on a number of raw agricultural (bananas, canola, cucurbits, stone fruits, grapes, various nuts, peanuts, potatoes, rice, tomatoes, and wheat) and processed (almond hulls, aspirated grain fractions, peanut oil, rice hulls, tomato paste, and wheat bran) commodities at levels ranging from 0.01 (peanuts, pecans) to 20.0 (rice hulls) ppm.

Permanent tolerances are also established for residues of azoxystrobin *per se* at 0.01 ppm in the meat, fat, and meat byproducts of livestock (except poultry) and at 0.006 ppm in milk. A number of time-limited Section 18 tolerances are also currently in effect.

There are no Codex, Canadian, or Mexican maximum residue limits.

Additional tolerances are being proposed in this risk assessment for the following raw agricultural, processed, and animal commodities (for a complete evaluation of the residue chemistry data in support of these tolerances, please refer to Attachment 3):

PROPOSED (HED RECOMMENDED VERSION) NEW TOLERANCES FOR 40 CFR 180.507					
COMMODITY	PPM	COMMODITY	PPM	COMMODITY	PPM
Barley, bran	0.20	Corn, sweet, K + CWHR	0.050	Soybean, seed	0.50
Barley, grain	0.10	Corn, sweet, stover	25.0	Vegetable, leafy, except *Brassica*, group	30.0
Barley, hay	15.0	Cotton, gin byproducts	0.020	Vegetable, leaves of root and tuber, group	50.0
Barley straw	4.0	Cotton, undelinted seed	0.020	Vegetable, root, subgroup	0.50
Citrus, dried pulp	2.0	Fruit, citrus, group	1.0	Vegetable, tuberous and corm, subgroup	0.030
Citrus, oil	4.0	Grain, aspirated grain fractions	30.0	Cattle, fat	0.030
Coriander, leaves	30.0	Onion, dry bulb	1.0	Cattle, meat byproducts	0.070
Corn, field, forage	12.0	Onion, green	7.50	Goat, fat	0.030
Corn, field, grain	0.050	Peanut	0.20	Goat, meat byproducts	0.070
Corn, field, refined oil	0.30	Peanut, refined oil	0.60	Horse, fat	0.030
Corn, field, stover	25.0	Peanut, hay	15.0	Horse, meat byproducts	0.070
Corn, pop, grain	0.050	Soybean, forage	25.0	Sheep, fat	0.030
Corn, pop, stover	25.0	Soybean, hay	55.0	Sheep, meat byproducts	0.070
Corn, sweet, forage	12.0	Soybean, hulls	1.0		

Note: This listing has been revised by the chemistry reviewer to reflect correct nomenclature and appropriate tolerance levels, and to delete the proposed tolerances for wild rice (for which no supporting residue data were provided); for sugar beet, dried pulp (since a separate tolerance was not warranted); and, for apple (inadvertent residues; since it is not OPP policy to establish a tolerance for inadvertent residues based upon concerns about the possibility of spray drift or contaminated equipment).

The nature of the residue in plants has been adequately delineated, based upon metabolism studies in cotton, grapes, peanuts, and wheat. Residues are systemic. The HED Metabolism Assessment Review Committee (MARC) has determined (Memo, W. Wassell, 12/30/98, D251683) that the residue to be regulated in plant commodities (and used in risk assessments for plant commodities and drinking water) is the combined residues of azoxystrobin and its Z isomer.

The nature of the residue in animals has been adequately delineated, based upon ruminant (goat) and poultry metabolism studies. The metabolic pathway in plants and animals is qualitatively similar, although the Z isomer was not identified in animals; the major biotransformation process is hydrolysis. The MARC has determined (*op. cit.*) that the residue to be regulated (and used in risk assessments) in animal commodities is parent azoxystrobin only.

The data supporting the proposed tolerances are from crop field trials, processing studies, and a ruminant (dairy cattle) feeding study. Based on poultry metabolism and feeding studies, tolerances continue to be unnecessary in poultry tissues and eggs; 40 CFR 180.6(a)(3).

Adequate analytical methods are available to enforce the proposed tolerances. The methods (RAM 243 and RAM 260) for plant commodities use gas-liquid chromatography (GLC) with nitrogen-phosphorous detection. The one (RAM 255) for animal commodities uses GLC with thermionic-specific detection, nitrogen mode. These methods have previously undergone successful validation trials by BEAD. The limit of quantitation (LOQ) for each analyte is 0.01 ppm. These methods are available from PIRIB/IRSD (7502C) and ACB/BEAD (7503W) until published in the FDA Pesticide Analytical Manual, Volume II. Azoxystrobin was not recovered through the FDA multiresidue protocols.

4.2.2 Acute Dietary Exposure Analysis

HED conducts dietary risk assessments (food only) using DEEM™, which incorporates consumption data generated in USDA's Continuing Surveys of Food Intake by Individuals (CSFII), 1989-1992. For acute dietary risk assessments, one-day consumption data are summed and a food consumption distribution is calculated for each population subgroup of interest. The consumption distribution can be multiplied by a residue point estimate for a deterministic (Tier I/II type) exposure/risk assessment, or used with a residue distribution in a probabilistic (Monte Carlo) type risk assessment. Acute exposure estimates are expressed in mg/kg bw/day and as a percent of the aPAD.

The Tier 1 acute dietary exposure analysis for azoxystrobin was performed using DEEM™ (Memo, D267564, D. Dotson, Attachment 4). In conducting this acute dietary exposure analysis, HED has made very conservative assumptions: all commodities having established or proposed azoxystrobin tolerances will contain azoxystrobin residues (i.e., 100% crop treated), and those residues will be at the level of the tolerance. These assumptions result in an overestimate of human dietary exposure. All established tolerances (permanent and Section 18 tolerances) are also included in this dietary risk assessment. Processing studies show that residues do not concentrate in the following foods: citrus juice, grapes-raisins, plums-prunes (dried), potatoes-white (dry), grape juice, tomato juice, and tomatoes-puree. As a result, DEEM™ default processing factors (adjustment factors #1) were set to 1.0 for these commodities. The concentration factors for the following juice concentrates were changed to preserve the concentration ratio from juice to concentrate: grapes (3.6 to 3.0), grapefruit (8.3 to 3.9), lemons (11.4 to 5.7), limes (6 to 3), oranges (6.7 to 3.7), and tangerines (7.4 to 3.2) (Memo, PP# 9F06058, D267564, 9/06/2000).

Tier 1 acute analyses were performed for the U.S. population and 26 population subgroups. As these were Tier 1 analyses, the acute risk is reported at the 95th percentile of exposure. The aPAD for the U.S. population and all population subgroups is 0.67 mg/kg/day. The results reported in Table 4 below are for the U.S. Population (total); those for infants and children; the other subgroup(s), if any, for which the percentage of the acute PAD occupied is greater than that occupied by the subgroup U. S. Population (total); and, the most highly exposed of the females subgroups (in this case, Females, 13+, nursing). The complete analysis is included as Attachment 4.

4.2.3 Chronic Dietary Exposure Analysis

A Tier 1 chronic analysis was performed for the general U.S. population and 26 population subgroups. The same conservative assumptions used in the acute dietary exposure analysis (i.e., 100% crop treated and tolerance-level residues) were employed for the chronic DEEM analysis. For chronic risk assessments, residue estimates for foods or food-forms of interest are multiplied by the averaged consumption estimate of each food/food-form of each population subgroup. Chronic exposure estimates are expressed in mg/kg bw/day and as a percent of the cPAD. The cPAD for the general U.S. population and all subgroups is 0.18 mg/kg/day. The results reported in Table 4 are for the U.S. Population (total); those for infants and children; the other subgroup(s), if any, for which the percentage of the chronic PAD occupied is greater than that occupied by the subgroup U. S. Population (total); and, the most highly exposed of the females subgroups (in this case, Females, 13+, nursing). The complete analysis is included as Attachment 4.

Table 4. Summary of Dietary Exposure Analysis Results

Population Subgroup	Acute Dietary		Chronic Dietary	
	Exposure (mg/kg/day) 95th Percentile	% aPAD	Exposure (mg/kg/day)	% cPAD
U.S. Population (total)	0.076	11	0.021	12
All Infants (< 1 year)	0.047	7.0	0.017	9.5
Nursing Infants	0.031	4.6	0.0055	3.1
Non-nursing Infants	0.059	8.8	0.022	12
Children 1-6 Years	0.13	19	0.033	18
Children 7-12 Years	0.091	14	0.024	13
U.S. Population (spring season)	0.081	12	0.023	13
U.S. Population (winter season)	0.078	12	0.021	12
Northeast Region	0.078	12	0.023	13
Southern Region	0.078	12	0.021	12
Western Region	0.080	12	0.024	13
Non-hispanic Blacks	0.098	15	0.024	13
Non-hispanic/Non-white/Non-black	0.11	17	0.030	17
Females 20+ (not pregnant or nursing)	0.077	12	0.021	12
Females 13+ (nursing)	0.083	12	0.026	14
Seniors 55+ Years	0.080	12	0.022	13
Pacific Region	0.085	13	0.025	14

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4.2.4 Cancer Dietary Exposure Analysis

Azoxystrobin was classified by the HED RfD/Peer Review Committee as not likely to be a human carcinogen (11/07/1996). Therefore, a cancer dietary exposure analysis was not performed.

4.3 Water Exposure/Risk Pathway

HED does not have monitoring data available to perform a quantitative drinking water risk assessment for azoxystrobin at this time. EFED provided Estimated Environmental Concentrations (EECs) for azoxystrobin under the proposed uses on barley, bulb vegetables, citrus fruits, corn (field and sweet), cotton, root and tuber vegetables and tops, leafy vegetables and cilantro, peanuts, soybeans, and wild rice, and for previously registered uses including non-cropland (EFED Memo, D260137, T. Nguyen, 11/24/1999, Attachment 5). Tier I surface and ground water EECs were generated using EFED GENEEC and SCI-GROW models, respectively. As the use of azoxystrobin on non-cropland has the highest yearly application rate, this application rate was used in the GENEEC and SCI-GROW models to estimate the concentrations of this chemical in surface water and groundwater, respectively. Should the yearly application rate on non-cropland change, or should a use of azoxystrobin with a higher use rate be added, EFED may have to revise the EECs accordingly.

4.3.1 Environmental Fate Assessment

According to previously submitted data, the primary dissipation pathway of azoxystrobin is by photodegradation in soil (t ½ = 18 to 28 days) and water (t ½ = 11 to 17 days). Azoxystrobin may also be susceptible to runoff and leaching because it is stable to hydrolysis and moderately persistent in aerobic (DT50 = 54 to 164 days) and anaerobic soils (DT50 = 49 to 56 days). However, EFED believes that the magnitude of the azoxystrobin partitioning coefficients (Kd = 1.5 to 23 mL/g) will limit its leaching potential into ground water. Also, because azoxystrobin is mostly foliarly applied to treat fungal diseases, foliar interception and subsequent photodegradation on foliage could substantially reduce the amount of azoxystrobin reaching soil surfaces, and consequently the amount available for leaching and runoff. Azoxystrobin transformation products, Compound 2 (R234886), Compound 28 (R401553), and Compound 30 (R402173), exhibit much lower soil/binding affinity (Kd = 0.35 to 11 mL/g) than the parent compound, and thus possess greater potential to leach through soils. One of the degradates, Compound 2, appears to be the most mobile degradate: it was detected in a majority of laboratory studies, and was also observed to leach through soil in the terrestrial field dissipation (<1% of total applied) and the aquatic soil dissipation studies (<5% of total applied). No persistence and dissipation rates have been reported for this degradate.

4.3.2 EECs/Monitoring Results

Ground Water

Based on the SCI-GROW modeling results, the azoxystrobin EEC in ground water is not expected to exceed **0.064 ppb**. This value can be used for both acute and chronic risk assessments. This value represents upper-bound estimates of the concentrations that might be found in ground water which result from the use of azoxystrobin on turf.

Surface Water

Based on the Tier I GENEEC modeling results, azoxystrobin EECs in surface water are not likely to exceed 141 ppb for the acute (peak) concentration or 127 ppb for the chronic (56- to 60-day) concentration. These values represent upper-bound estimates of the concentrations that might be found in surface water which result from the use of azoxystrobin on turf.

OPP policy allows the 56- to 60-day GENEEC value to be divided by 3 to obtain a value for chronic risk assessment calculations. Therefore, the surface water value to be used in the chronic risk assessment is **42 ppb**.

Use of Results

These EECs for ground and surface water were used qualitatively in conjunction with drinking water levels of comparison (DWLOCs) to evaluate potential risks from azoxystrobin in drinking water. A DWLOC is a theoretical upper limit on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food, drinking water, and through residential uses, if applicable. A DWLOC will vary depending on the toxic endpoint, drinking water consumption, body weights, and pesticide uses. DWLOC values are not regulatory standards for drinking water.

4.4 Residential Exposure/Risk Pathway

4.4.1 Home Uses

Products containing azoxystrobin are registered for application to turf and ornamentals. They may be applied to turf at rates up to 0.95 lb active ingredient (ai) per acre, 5 times per year (i.e., not to exceed 5 lb ai/A/yr), and to ornamentals at rates up to 0.75 lb ai per acre every 7 to 14 days, but not to exceed 5 lb ai/A/yr. The currently registered labels do not prohibit homeowners from mixing/loading/applying either the flowable concentrate or the water-dispersible granule formulations. This residential exposure and risk assessment was conducted using the application rate for turf because it is the highest use rate.

Residential handlers may receive short-term dermal and inhalation exposure to azoxystrobin

when mixing, loading and applying the formulations. Adults and children may be exposed to azoxystrobin residues from dermal contact with foliage during post-application activities. Toddlers may also receive short- and intermediate-term oral exposure from hand-to-mouth ingestion during post-application activities.

As no dermal endpoint was selected by the HIARC, a dermal exposure and risk assessment was not required for residential handlers or post-application activities. NOAELs of 25 mg/kg/day and 20 mg/kg/day were selected by the HIARC for assessing the risk from short- and intermediate-term incidental oral exposures, respectively. These same NOAELs were selected by the HIARC for assessing the risks from short- and intermediate-term inhalation exposures. The HED FQPA Safety Factor Committee met on August 24, 1998 and decided to remove the safety factor (i.e., reduce to 1x) for the U.S. population and all population subgroups and for all exposure scenarios. Thus, the target MOE for risk assessment purposes is 100.

No chemical-specific exposure or residue dissipation data for handler or post-application activities were submitted to HED in support of the registered lawn uses. Therefore, HED's Draft Standard Operating Procedures for Residential Exposure Assessments were used as the basis for all handler exposure calculations. The post-application risk assessment is based on generic assumptions as specified by the newly proposed Residential SOPs and approaches recommended by HED's Exposure Science Advisory Committee (ExpoSAC). Revisions to the Residential SOPs have been proposed that alter the residential post-application scenario assumptions. The proposed assumptions are expected to better represent residential exposure and are still considered to be high-end, screening level assumptions. HED management has authorized the use of the revised residential SOPs that were presented to the FIFRA SAP in September 1999. Therefore, HED has deviated from the current Residential SOP assumptions and used the proposed assumptions to calculate exposure estimates.

4.4.1.1 Residential Handler (Inhalation Exposure)

Inhalation daily doses (mg/kg/day) for non-occupational handlers were calculated with the following equation:

$$\textbf{Inhalation daily dose} = \frac{\text{AR (lb ai/A)} \times \text{UE (mg /lb ai)} \times \text{Acres Treated (A/day)}}{\text{BW (kg)}}$$

Where:

AR (application rate)	=	maximum application rate on product label (lb ai/A)
UE (unit exposure)	=	Exposure value (mg/lb ai handled) derived from August 1998 PHED Surrogate Exposure Table for handlers wearing short sleeves, short pants and no gloves as shown in Appendix B of the 1997 Draft SOPs for Residential Exposure Assessments.
Acres Treated	=	Maximum number of acres treated per day (A/day)
BW	=	body weight (kg)

Inhalation daily doses for handlers were calculated for the flowable concentrate formulation

using data for mixing/loading/applying a liquid; appropriate data are not available for handling the water-dispersible granule formulation for this use, however, based on PHED unit exposure values from other handler scenarios with these formulation types; the exposure is expected to be less than that of handling a liquid. The following handler scenarios were evaluated:

1. mix/load and spot application of liquid formulation (low-pressure hand sprayer), and
2. mix/load and broadcast application of liquid formulation (garden hose-end sprayer)

The following assumptions (which include *current* HED standard values) were used to calculate inhalation exposures.

* The maximum application rate from ABOUND Flowable (EPA Reg No 10182-415) of 1.35 fluid ounces per 1,000 square feet or **0.95 lb ai per acre** was assumed.
* Handlers were assumed to be using a low-pressure hand sprayer for spot treatments to 1,000 ft^2 areas or a garden hose-end sprayer for broadcast to a 0.5 acre lawn.
* The inhalation unit exposures for the low-pressure hand sprayer, and garden hose-end sprayer are 30 μg/lb ai handled, and 9.5 μg/lb ai handled, respectively (from Appendix B of the 1997 Draft SOPs for Residential Exposure Assessments).
* Residential handlers' body weight is 60 kg for calculation of short-term inhalation doses because this endpoint is based on a developmental study (i.e., applicable to females 13+).
* The overall estimate of inhalation exposure represents a central to high-end value.

As shown in Table 5, the inhalation MOEs for residential handlers are well above the target MOE of 100.

Table 5. Handler Exposure and Risk Estimates for Residential Lawn Applicators

Handler Scenario	Rate (lb ai/ acre)	Acres Treated (acres/ day)	PHED Unit Exposure[1] (mg/lb ai)	Short-term Daily Inh. Dose [2] (mg/kg/day)	Short-term Inhalation MOE [3]
1. mix/load and spot application of liquid formulation (low-pressure hand sprayer)	0.95	0.023	0.030	1.1E-05	2.7E+06
2. mix/load and broadcast application of liquid formulation (garden hose-end sprayer)	0.95	0.5	0.0095	7.5E-05	3.9E+05

[1] Data Confidence for inhalation unit exposures:
low-pressure hand sprayer: 80 replicates, ABC grade, medium confidence run
garden hose-end sprayer: 8 replicates, ABC grade, low confidence run due to inadequate replicate

[2] Daily Dose = [Rate (lb.ai/A) x Acres Treated (A/day) x Unit Exposure(mg/lb ai handled)] / Body Weight (60 kg because endpoint based on developmental study)

[3] MOE = NOAEL (25 mg/kg/day) / Daily Inhalation Dose (mg/kg/day)

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4.4.1.2 Residential Post-Application - Incidental Ingestion

As noted previously, a dermal risk assessment for postapplication exposure is not required because no dermal endpoint was selected by the HIARC. Therefore, only the following postapplication exposure scenarios resulting from lawn treatment were assessed:

- Incidental non-dietary ingestion of pesticide residues on lawns from hand-to-mouth transfer,
- Incidental non-dietary ingestion of pesticide-treated turfgrass, and
- Incidental non-dietary ingestion of soil from pesticide-treated residential areas.

The **daily incidental oral doses** (mg/kg/day) were calculated for children's incidental ingestion using the equations below and the results are presented in Table 6:

PDR_t for **hand-to-mouth** $= TTR_t * SA * EX * FQ * ET * CF1$
PDR_t for **eating turfgrass** $= GR_t * IgR1 * CF1$
PDR_t for **soil ingestion** $= SR_t * IgR2 * CF1$

Where:

PDR_t = potential dose rate on day "t" (mg/day)
TTR_t = $AR * F * (1-D)^t * CF2 * CF3$
GR_t = $AR * F * (1-D)^t * CF2 * CF3$
SR_t = $AR * F * (1-D)^t * CF2 * CF3 * CF4$

Where:

TTR_t = turf transferrable residue on day "t" (ug/cm^2 turf)
SA = surface area of the hands (cm^2/event); use palmar surface area of 3 fingers; 20 cm^2
EX = extraction from the hand by saliva = 50%
FQ = frequency of hand-to-mouth activity (events/hr); 20 events/hr
ET = exposure time (hr/day); 2 hrs/day
CF1 = conversion factor (0.001 mg/ug for the TTR or GR equation, or 1E-6 g/ug in the SR equation)
GR_t = grass (and plant matter) residue on day "t" (ug/cm^2)
IgR1 = ingestion rate of grass (cm^2/day); 25 cm^2/day
SR_t = soil residue on day "t" (ug/g)
IgR2 = ingestion rate of soil (mg/day); 100 mg/day
AR = application rate (lb ai/acre); 0.95 lb ai/acre
F = fraction of ai available on turf/grass or in uppermost cm of soil (unitless); 5% on turf/grass, 100% in uppermost 1 cm of soil
D = fraction of residue that dissipates daily (unitless); 10%

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t = postapplication day on which exposure is being assessed
CF2 = conversion factor (4.54E8 ug/lb)
CF3 = conversion factor (2.47E-8 acre/cm^2)
CF4 = conversion factor (0.67 cm^3/g soil)

and

$PDR_{t\text{-}norm} = PDR_t / BW$
$MOE = NOAEL / PDR_{t\text{-}norm}$

Where:

$PDR_{t\text{-}norm}$ = potential dose rate, normalized to body weight, on day "t" (mg/kg/day)
BW = body weight (kg); 15 kg
$NOAEL_{oral}$ = 25 mg/kg/day (short-term), 20 mg/kg/day (intermediate-term)

Table 6. Short- and Intermediate-Term Incidental Ingestion Exposure and Risk

Scenarios	TTR/GR/SR_0 (ug/cm^2 or g)	$PDR_{0\text{-}norm}$ (mg/kg/day)	Short-Term MOE	Intermediate-term MOE
(1) Hand-to-Mouth	0.53	0.014	1,800	1,400
(2) Grass Ingestion	0.53	0.00089	28,000	23,000
(3) Soil Ingestion	7.1	0.000048	530,000	420,000
Total	N/A	0.015	1,700	1,300

Both **short-term and intermediate-term MOEs** for each scenario, and the combined MOE resulting from all three exposures, **are above the target of 100, and therefore, not of concern**.

The exposure estimates generated above are based on some upper-percentile (i.e., maximum application rate, initial amount of transferrable residue and duration of exposure) and some central tendency (i.e., surface area, hand-to-mouth activity, and body weight) assumptions and are considered to be representative of high-end exposures. The uncertainties associated with this assessment stem from the use of an assumed amount of pesticide available from turf, and assumptions regarding transfer of chemical residues and hand-to mouth activity. The estimated exposures are believed to be reasonable high-end estimates based on observations from chemical-specific field studies and professional judgement.

4.4.2 Recreational Exposure

Recreational exposures to turf are expected to be similar to those evaluated in section 4.4.1.2. Residential Postapplication Exposure. Although azoxystrobin may be applied to golf courses, a risk assessment for the golfing scenario is not required because no dermal endpoint was selected by the HIARC.

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4.4.3 Off Target Non-Occupational Exposure

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for azoxystrobin. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

5.1 Acute Aggregate Risk (Food + Drinking Water)

The acute aggregate risk assessment takes into account exposure estimates from dietary consumption of azoxystrobin (food and drinking water). **Acute risk estimates resulting from aggregate exposure to azoxystrobin in food and drinking water are below HED's level of concern.**

The surface and ground water EECs were used to compare against back-calculated DWLOCs for aggregate risk assessments. To calculate the DWLOC for acute exposure relative to an acute toxicity endpoint, the acute dietary food exposure (from DEEM™) was subtracted from the aPAD to obtain the acceptable acute exposure to azoxystrobin in drinking water. The acute DWLOCs are listed in Table 7. For the acute scenario, the DWLOCs are 21,000 ppb for the general U.S. population, 18,000 ppb for females 20+ years old (not pregnant or nursing), and 5,400 ppb for children 1-6 years old. The peak EECs of azoxystrobin in surface and ground water (141 ppm and 0.064 ppm, respectively) are less than HED's DWLOCs for azoxystrobin in drinking water as a contribution to acute aggregate exposure. Therefore, HED concludes with reasonable certainty that residues of azoxystrobin in drinking water do not contribute significantly to the acute aggregate human health risk at the present time, considering the present uses, and uses proposed in this action.

HED bases this determination on a comparison of azoxystrobin EECs in surface and ground waters to DWLOCs for azoxystrobin. The estimated concentrations of azoxystrobin in surface and ground waters are derived from water quality models that use conservative assumptions regarding pesticide transport from the point of application to surface and ground water. Because

HED considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, DWLOCs may vary as those uses change. If new uses are added in the future, HED will reassess the potential impacts of azoxystrobin on drinking water as a part of the aggregate acute risk assessment process.

Table 7. DWLOCs for Acute Dietary Exposure to Azoxystrobin

Population Subgroup [1]	Acute PAD (mg/kg/day)	Food Exposure (mg/kg/day)	Max. Water Exposure (mg/kg/day) [2]	SCI-GROW (μg/L) [3]	GENEEC Peak EEC (μg/L) [3]	DWLOC (μg/L) [4]
U.S. Population (total)	0.67	0.076	0.59	0.064	141	21,000
Females 13+	0.67	0.077	0.59			18,000
Infants/Children	0.67	0.13	0.54			5,400

1 Within each of these subgroups, the subpopulation with the highest (acute) food exposure having an adequately representative number of samples was selected; namely, Females (20+ years old, not pregnant or nursing) and Children (1 to 6 years old). HED default body weights are: General U.S. Population, 70 kg; Females (13+ years old), 60 kg; and, All Infants/Children, 10 kg.

2 Maximum Water Exposure (mg/kg/day) = Acute PAD (mg/kg/day) - Acute Food Exposure.

3 Estimate for the highest use rate was chosen.

4 DWLOC (μg/L) = [Maximum water Exposure (mg/kg/day) x body wt (kg)] ÷ [(10^{-3} mg/μg) x water consumed daily (L/day)]. μg/L = parts per billion. HED default daily drinking rates are 2 L/day for Adults and 1 L/day for Infants Children.

5.2 Short-Term Aggregate Risk (Food + Drinking Water + Residential)

The short-term aggregate risk assessment estimates risks likely to result from 1- to 7-day exposure to azoxystrobin residues from food, drinking water, and residential pesticide uses. High-end estimates of residential exposure are used in the short-term assessment, while average values are used for food and drinking water exposure.

A short-term risk assessment is required for adults because there is a residential handler inhalation exposure scenario. In addition, a short-term risk assessment is required for infants and children because of the residential post-application oral exposure scenario. As no short- or intermediate-term dermal endpoint was established, there is no dermal component to these aggregate risk assessments.

For adults, the daily inhalation dose needs to be aggregated with the average food and water exposure. The average food exposure of the U.S. population (total) is 0.021 mg/kg/day. The maximum daily inhalation dose from the residential inhalation exposure scenarios is 0.000075 mg/kg/day (Table 5, Daily Inhalation Dose). The margin of exposure is equivalent to the NOAEL divided by the sum of the exposures occurring through food, water, and short-term residential inhalation.

$$MOE = \frac{\text{Short-term NOAEL}}{\text{Exposure}_{\text{Food}} + \text{Exposure}_{\text{Water}} + \text{Exposure}_{\text{Inhalation}}} \qquad \text{(Equation 1)}$$

As the water exposure is not known, it is necessary to calculate the MOE for exposures through food and inhalation and then calculate DWLOCs. These DWLOCs can then be compared to the estimated environmental concentrations provided by EFED. The MOE for food and inhalation exposures is given by the following equation.

$$MOE = \frac{25 \text{ mg/kg/day}}{0.021 \text{ mg/kg/day} + 0.000075 \text{ mg/kg/day}} = 1{,}200$$

As the FQPA Safety Factor was removed (i.e., reduced to 1x) for all population subgroups for acute and chronic dietary assessments and residential exposure assessments of all duration, the acceptable MOE is 100. The MOE for exposure through food and inhalation (1,200) is well above 100. As a result, the aggregate short-term food + residential exposure estimate for the U.S. population is below HED's level of concern. The dietary exposure of all adult population subgroups is comparable to that of the U.S. population; therefore, the aggregate food + residential exposure is below HED's level of concern for all adult population subgroups.

In order to calculate the maximum allowable water exposure Equation 1 is used. The exposure through food and inhalation is known so the equation can be solved for the maximum allowable water exposure. From this value the DWLOC can be calculated as it was in Section 5.1 above.

$$100 = \frac{25 \text{ mg/kg/day}}{0.021 \text{ mg/kg/day} + 0.000075 \text{ mg/kg/day} + \text{Max Allowable Water Exposure}}$$

Maximum allowable water exposure = 0.23 mg/kg/day

The DWLOC for the U.S. population is 6,900 ppb (see Table 8, below). This value is considerably higher than the surface water EEC of 42 ppb (i.e., 56- to 60-day EEC of 127 with the 3x adjustment factor) . **The aggregate estimated exposure to azoxystrobin through food, water, and inhalation exposure routes is below HED's level of concern for the U.S. population and all other adult population subgroups.**

For infants and children, the incidental oral exposure from residential post application activities needs to be aggregated with average exposure from food and water. The MOE for exposure through food and incidental oral exposure can be calculated from Equation 1. The estimated dietary exposure for children 1-6 years old is 0.033 mg/kg/day. The incidental oral exposure for this group is 0.015 mg/kg/day. Summing the dietary and incidental oral exposures for this group gives the following value: 0.048 mg/kg/day. The MOE for children for children 1-6 years old is 520.

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In order for the aggregate risk to be below HED's level of concern, the DWLOCs must be greater than the maximum chronic surface water EEC. In Table 8 is given the aggregate dietary and residential estimated exposure for the U.S. population and children (1-6 years old). The chronic surface water EEC is 42 ppb.

Table 8. Estimated Short-Term Exposure to Azoxystrobin

Population Subgroup	Short-term NOAEL (mg/kg/day)	Short-Term Target MOE [1]	Target Maximum Exposure [2] (mg/kg/day)	Estimated Food Exposure (mg/kg/day)	Estimated Residential Exposure (mg/kg/day)	Maximum Water Exposure [3] (mg/kg/day)	SCI-GROW (μg/L) [4]	GENEEC 56- to 60-day EEC (μg/L) [4]	Short-Term DWLOC [5] (μg/L)
U.S. Population	25	100	0.25	0.021	0.000075	0.23	0.064	42	6,900
Children (1-6 years old)	25	100	0.25	0.033	0.015	0.20			2,000

[1] The short-term target MOE for azoxystrobin includes the standard intra- and inter-species uncertainty factors as well as the FQPA safety factor of 1x.

[2] Target Max Exposure = NOAEL / Target MOE

[3] Maximum Water Exposure (mg/kg/day) = Target Maximum Exposure (mg/kg/day) - Aggregate Food and Residential Exposure (mg/kg/day).

[4] Estimate for the highest use rate was chosen. 56- to 60-day EEC was adjusted (i.e., reduced) by factor of 3.

[5] DWLOC (μg/L) = Max. water exposure (mg/kg/day) x body wt (kg) ÷ [(10^{-3} mg/μg) * water consumed daily (L/day)]. HED standard body weights are: General U.S. Population, 60 kg (because NOAEL is based on a developmental endpoint) and All Infants/Children, 10 kg. HED standard daily drinking rates are 2 L/day for adults and 1 L/day for children.

The short-term aggregate DWLOC for infants and children is much greater than the maximum EEC for azoxystrobin in surface water (42 ppb); therefore, estimated aggregate (food + water + residential) exposure of infants and children to azoxystrobin residues is below HED's level of concern.

5.3 Intermediate-Term Aggregate Risk (Food + Drinking Water + Residential)

The intermediate-term aggregate risk assessment estimates risks likely to result from more than one week to several months of exposure to azoxystrobin residues from food, drinking water, and residential pesticide uses. High-end estimates of residential exposure are used in the intermediate-term assessment, while average values are used for food and drinking water exposure.

An intermediate-term risk assessment is not required for adults because residential handler scenarios are not expected to occur for longer than a short-term timeframe. However, an intermediate-term risk assessment is required for infants and children because of the residential post-application oral exposure scenario. As no dermal endpoint was established, there is no dermal component to this aggregate risk assessment.

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As was necessary for the short-term aggregate assessment, the incidental oral exposure from residential post application activities for infants and children needs to be aggregated with average exposure from food and water. The MOE for exposure through food and incidental oral exposure can be calculated from Equation 1, presented previously for the short-term aggregate assessment. The estimated dietary exposure for children 1-6 years old is 0.033 mg/kg/day and the incidental oral exposure for this group is 0.015 mg/kg/day. Summing the dietary and incidental oral exposures for this group gives the following value: 0.048 mg/kg/day. The MOE for children for children 1-6 years old is 420.

In order for the aggregate risk to be below HED's level of concern, the DWLOC must be greater than the maximum chronic surface water EEC. In Table 9 is given the aggregate dietary and residential estimated exposure for children (1-6 years old). The chronic surface water EEC is 42 ppb.

Table 9. Estimated Intermediate-Term Exposure to Azoxystrobin

Population Subgroup	Intermed-term NOAEL (mg/kg/day)	Inter-Term Target MOE [1]	Target Maximum Exposure [2] (mg/kg/day)	Estimated Food Exposure (mg/kg/day)	Estimated Residential Exposure (mg/kg/day)	Maximum Water Exposure [3] (mg/kg/day)	SCI-GROW (μg/L) [4]	GENEEC 56- to 60-day EEC (μg/L) [4]	Intermed-Term DWLOC [5] (μg/L)
Children (1-6 years old)	20	100	0.20	0.033	0.015	0.15	0.064	42	1,500

[1] The intermediate-term target MOE for azoxystrobin includes the standard intra- and inter-species uncertainty factors as well as the FQPA safety factor of 1x.

[2] Target Max Exposure = NOAEL / Target MOE

[3] Maximum Water Exposure (mg/kg/day) = Target Maximum Exposure (mg/kg/day) - Aggregate Food and Residential Exposure (mg/kg/day).

[4] Estimate for the highest use rate was chosen. 56- to 60-day EEC was adjusted (i.e., reduced) by factor of 3.

[5] DWLOC (μg/L) = Max. water exposure (mg/kg/day) x body wt (kg) ÷ [(10^{-3} mg/μg) * water consumed daily (L/day)]. HED standard body weight and daily drinking water rate for All Infants/Children are 10 kg and 1 L/day, respectively.

The intermediate-term aggregate DWLOC for infants and children is much greater than the maximum EEC for azoxystrobin in surface water (42 ppb); therefore, estimated aggregate (food + water + residential) exposure of infants and children to azoxystrobin residues is below HED's level of concern.

5.4 Chronic Aggregate Risk (Food + Drinking Water)

The chronic aggregate risk assessment takes into account average exposure estimates from food, drinking water, and residential uses. However, because of the use patterns, no chronic residential exposures are expected. Therefore, the chronic aggregate risk assessment will consider exposure from food and drinking water only. **Chronic risk estimates resulting from aggregate exposure to azoxystrobin in food and water are below HED's level of concern.**

A Tier 1 chronic dietary exposure analysis was performed for the general U.S. population and all population subgroups. The chronic exposure estimates for the general U.S. population and all population subgroups accounted for ≤ 18% of the cPAD. The most highly exposed subgroup was children 1-6 years old (18% of the cPAD). The results of the analysis indicate that the chronic dietary risk estimates for the general U.S. population and all population subgroups associated with the proposed uses of azoxystrobin are below HED's level of concern.

The surface and ground water EECs were used to compare against back-calculated DWLOCs for aggregate risk assessments. To calculate the DWLOC for chronic exposure relative to a chronic toxicity endpoint, the chronic dietary food exposure (from DEEM™) was subtracted from the cPAD to obtain the acceptable chronic exposure to azoxystrobin in drinking water. For the chronic scenario, the DWLOCs are 5,600 ppb for the U.S. population, 4,800 ppb for females 20+ years old (not pregnant or nursing), and 1,500 ppb for children 1-6 years old. The average EECs of azoxystrobin in surface and ground water (42 ppm and 0.064 ppm, respectively) are less than HED's DWLOCs for azoxystrobin in drinking water as a contribution to chronic aggregate exposure (Table 10). Therefore, HED concludes with reasonable certainty that residues of azoxystrobin in drinking water do not contribute significantly to the chronic aggregate human health risk at the present time considering the present uses and uses proposed in this action.

HED bases this determination on a comparison of azoxystrobin EECs in surface and ground waters to DWLOCs for azoxystrobin. The estimates of azoxystrobin concentrations in surface and ground waters are derived from water quality models that use conservative assumptions regarding the pesticide transport from the point of application to surface and ground water. Because HED considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, DWLOCs may vary as those uses change. If new uses are added in the future, HED will reassess the potential impacts of azoxystrobin on drinking water as a part of the aggregate chronic risk assessment process.

Table 10. DWLOCs for Chronic Dietary Exposure to Azoxystrobin

Population Subgroup [1]	Chronic PAD (mg/kg/day)	Food Exposure (mg/kg/day)	Max. Water Exposure (mg/kg/day) [2]	SCI-GROW (μg/L) [3]	GENEEC 56- to 60-day EEC (μg/L) [3]	DWLOC (μg/L) [4]
U.S. Population (total)	0.18	0.021	0.16	0.064	42	5,600
Females 13+	0.18	0.021	0.16			4,800
Infants/Children	0.18	0.033	0.15			1,500

1 Within each of these subgroups, the subpopulation with the highest (chronic) food exposure having an adequately representative number of samples was selected; namely, Females (20+ years old, not pregnant or nursing) and Children (1-6 years old). HED default body weights are: General U.S. Population, 70 kg; Females (13+ years old), 60 kg; and, All Infants/Children, 10 kg.

2 Maximum Water Exposure (mg/kg/day) = Chronic PAD (mg/kg/day) - Chronic Food Exposure.

3 Estimate for the highest use rate was chosen. 56- to 60-day EEC adjusted (i.e., reduced) by factor of 3.

4 DWLOC (μg/L) = [Maximum water Exposure (mg/kg/day) x body wt (kg)] ÷ [(10^{-3} mg/μg) x water consumed daily (L/day)]. μg/L = parts per billion. HED default daily drinking rates are 2 L/day for Adults and 1 L/day for Infants/Children.

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5.5 Cancer Risk

Azoxystrobin was classified by the HED RfD/Peer Review Committee as not likely to be a human carcinogen (11/07/96). Therefore, an aggregate cancer risk assessment was not performed.

6.0 CUMULATIVE RISK

EPA does not have, at this time, available data to determine whether azoxystrobin has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For the purposes of this tolerance action, EPA has not assumed that azoxystrobin has a common mechanism of toxicity with other substances.

On this basis, the petitioner 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 shares a common mechanism of toxicity with any other substance and, if so, whether any tolerances for azoxystrobin need to be modified or revoked.

7.0 OCCUPATIONAL EXPOSURE

Occupational exposure may occur during the handling of azoxystrobin formulated as a flowable concentrate (i.e., Abound® 77.1% ai) or a water-dispersible granule (i.e., Heritage® 50% ai). Scenarios were evaluated for mixing, loading, and applying azoxystrobin via ground and aerial methods. As no dermal endpoint was selected by the HIARC, a dermal exposure and risk assessment was not required for occupational handlers or post-application activities. Inhalation exposure was evaluated for handlers only; postapplication inhalation exposures are considered to be negligible. The duration of exposure for handlers may be short-term (1 to 7 days) or intermediate-term (several months). Chronic occupational exposures are not expected. The activity resulting in the greatest exposure is mixing/loading liquids for aerial application to high acreage crops such as corn or soybeans. The short- and intermediate-term MOEs for this scenario are 4,200 and 3,900, respectively, which are well above the target MOE of 100. Table 11 summarizes the use pattern of azoxystrobin for the proposed uses. An occupational exposure/risk assessment for azoxystrobin is provided in Attachment 6 (Memo, D269111, K. O'Rourke, dated 09/21/2000).

Please note that the previous risk assessments for azoxystrobin did not include a quantitative assessment for occupational exposure because, at the time, there were no inhalation endpoints. The current risk assessment has evaluated only the currently proposed uses. However, based on the use pattern (i.e., application rate and area treated), exposures from the previously registered uses are expected to be similar to, or less than, those evaluated in the current assessment.

Table 11. Summary of Use Patterns/Formulation Information Relevant to Occupational Exposure/Risk Assessment					
Formulation Type (% ai)	**Application Method**	**Use Site**	**Application Rate (lb ai/A)**	**Frequency of Application (interval)**	**Comments**
Flowable Concentrate (77.1 % ai) and Water-Dispersible Granule (50% ai)	Aerial, Chemigation, Groundboom	barley	0.10 - 0.2	2 apps (not specified)	
	Aerial, airblast	citrus	0.20 - 0.25	6 apps (7 - 21 days)	
	Aerial, Chemigation, Groundboom	corn	0.10 - 0.25	8 apps (7 - 14 days)	
	Groundboom	cotton	0.10 - 0.23	1 app (N/A)	in-furrow
	Aerial, Chemigation, Groundboom	leafy vegetables	0.10 - 0.25	6 apps (5 - 14 days)	
	Aerial, Chemigation, Groundboom	onion	0.10 - 0.25	6 apps (5 - 14 days)	
	Aerial, Chemigation, Groundboom	peanuts	0.10 - 0.40	2 apps (30 days)	
	Aerial, Chemigation, Groundboom	root & tuber vegetables	0.10 - 0.33	6 apps (5 - 14 days)	
	Aerial, Chemigation, Groundboom	soybeans	0.15 - 0.25	2 apps (not specified)	

7.1 Occupational Handler

As mentioned previously, no dermal endpoint was selected by the HIARC, therefore, a dermal exposure and risk assessment was not required. NOAELs of 25 mg/kg/day and 20 mg/kg/day were selected by the HIARC for assessing the short- and intermediate-term risk from inhalation exposures, respectively. The target MOE for occupational risk assessment purposes is 100.

No chemical-specific occupational exposure data for handler activities were submitted to HED in support of the proposed uses. Handler exposure estimates were based on surrogate data from the Pesticide Handler Exposure Data Base (Version 1.1).

Ten potential handler exposure scenarios were identified and evaluated. They include mixing, loading, and applying azoxystrobin formulated as a flowable concentrate (i.e., Abound® 77.1% ai) or a water-dispersible granule (i.e., Heritage® 50% ai) via ground and aerial methods. A flagging scenario for aerial operations was also evaluated. Inhalation daily doses (mg/kg/day) were calculated for each of these scenarios. Table 12 presents these doses and the resulting short- and intermediate-term MOEs, all of which are well above the target of 100. The overall estimate of inhalation risk may be considered central to high-end.

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The following assumptions (which include *current* HED standard values) were used to calculate inhalation exposures.

* The maximum application rate of 0.4 lb ai/acre (from peanuts) was used as a screening value, except for: airblast scenarios, which are for citrus only and have a maximum application rate of 0.25 lb ai/A; and higher acreage "sub"-scenarios (i.e., 1,200 acres for aerial and 200 acres for groundboom) which are for corn, soybeans, and cotton only and have a maximum application rate of 0.25 lb ai/A.

* Mixer/loaders will be using an open mixing system (no respirator).

* Applications will be done with open-cab groundboom and airblast sprayers, and enclosed cockpit aircraft (no respirator).

* The maximum number of acres treated per day: 350 to 1,200 acres for aerial applications, 80 to 200 acres for groundboom, and 40 acres for airblast.

* The inhalation unit exposures for mixer/loaders, applicators, and flaggers are from PHED Version 1.1 (8/98). There is high confidence in the values for all of the scenarios except for aerial application with enclosed cockpit, in which there is medium confidence. Data are not available in PHED for water-dispersible granules; therefore, the unit exposure for dry flowable is used, which is considered to be an appropriate surrogate.

• Occupational handlers' body weight is 60 kg for calculation of short-term inhalation doses because this endpoint is based on a developmental study (i.e., applicable to females 13+), while the standard body weight of 70 kg is used for the intermediate-term inhalation dose calculations.

Table 12. Inhalation Exposure and Risk Assessment for Occupational Handlers

PHED Scenario Selected from PSEG (8/98)	PHED Unit Exposure[1] (mg/lb ai)	Application Rate[2] (lb ai/A)	Area Treated[3] (A/day)	Short-term Daily Dose[4] (mg/kg/day)	Int.-term Daily Dose[4] (mg/kg/day)	Short-Term Inhalation MOE[5]	Intermed-Term Inhalation MOE[5]
1. Mixing/Loading Liquids for Aerial/Chemigation Application	0.0012	0.25	1,200	0.0060	0.0051	4,200	3,900
		0.40	350	0.0028	0.0024	8,900	8,300
2. Mixing/Loading Liquids for Groundboom Application		0.25	200	0.0010	0.00086	25,000	23,000
		0.40	80	0.00064	0.00055	39,000	36,000
3. Mixing/Loading Liquids for Airblast Sprayer		0.25	40	0.00020	0.00017	130,000	120,000
4. Mixing/Loading Dry Flowable for Aerial/Chemigation Application	0.00077	0.25	1,200	0.0039	0.0033	6,500	6,100
		0.40	350	0.0018	0.0015	14,000	13,000
5. Mixing/Loading Dry Flowable for Groundboom Application		0.25	200	0.00064	0.00055	39,000	36,000
		0.40	80	0.00041	0.00035	61,000	57,000
6. Mixing/Loading Dry Flowable		0.25	40	0.00013	0.00011	190,000	180,000

Table 12. Inhalation Exposure and Risk Assessment for Occupational Handlers							
PHED Scenario Selected from PSEG (8/98)	PHED Unit Exposure [1] (mg/lb ai)	Application Rate [2] (lb ai/A)	Area Treated [3] (A/day)	Short-term Daily Dose [4] (mg/kg/day)	Int.-term Daily Dose [4] (mg/kg/day)	Short-Term Inhalation MOE [5]	Intermed-Term Inhalation MOE [5]
7. Applying Sprays with Fixed-wing Aircraft (enclosed cockpit)	0.000068	0.25	1,200	0.00034	0.00029	74,000	69,000
		0.40	350	0.00016	0.00014	160,000	150,000
8. Applying Sprays with a Groundboom Sprayer (open cab)	0.00074	0.25	200	0.00062	0.00053	41,000	38,000
		0.40	80	0.00039	0.00034	63,000	59,000
9. Applying Sprays with an Airblast Sprayer (open cab)	0.0045	0.25	40	0.00075	0.00064	33,000	31,000
10. Flagging (Sprays) for Aerial Operations	0.00035	0.40	350	0.00082	0.00070	31,000	29,000

[1] Unit Exposure values are based on exposure without a respirator. There is high confidence in all values except for that of aerial application with an enclosed-cockpit aircraft, for which there is medium confidence.

[2] Maximum application rate of 0.4 lb ai/acre (from peanuts) was used as a screening value, except for: airblast scenarios, which are for citrus only (Max app. rate of 0.25 lb ai/A); and higher acreage scenarios for corn, soybeans, and cotton (i.e., 1,200 acres for aerial and 200 acres for groundboom) which have a max app. rate of 0.25 lb ai/A.

[3] Standard values for acres treated in a day were used. The higher acerages of 1,200 and 200 for aerial and groundboom application, respectively, are for corn, soybeans, and cotton only.

[4] Daily Dose = [Unit Exposure (mg/lb ai handled) x Application Rate (lb ai/A) x Acres Treated (A/day)] / Body Weight (60kg for Short-term; 70 kg for intermediate-term)

[5] MOE = NOAEL/ Daily Inhalation Dose. Short-term Inhalation NOAEL = 25 mg/kg/day. Intermediate-term Inhalation NOAEL = 20 mg/kg/day.

7.2 Occupational Postapplication

The proposed uses for azoxystrobin involve foliar applications. Therefore, there is a potential for postapplication exposure from scouting, harvesting, and other field activities. However, as no dermal endpoints were selected by the HIARC (i.e., no toxicity was observed at the limit dose of 1,000 mg/kg), a dermal risk assessment for post-application exposure is not required. Inhalation exposures are expected to be negligible during postapplication activities associated with the proposed uses.

Azoxystrobin technical has been classified in Toxicity Category III for acute dermal and primary eye irritation, and Toxicity Category IV for primary skin irritation. Per the Worker Protection Standard (WPS), a 12-hr restricted entry interval (REI) is required for chemicals classified under Toxicity Category III or IV, which is the shortest waiting period permitted under the WPS. However, per Pesticide Regulation Notice 95-3 (6/7/95), REIs may be further reduced from 12 hours if certain criteria are met. In a previous risk assessment (Memo, D. Dotson, D248888, 1/28/99), HED determined that the criteria established by Pesticide Regulation Notice 95-3 have been met for azoxystrobin formulated as a water-dispersible granule, and that a 4-hour REI is acceptable on the Heritage® label. However, it is not clear whether the criteria have subsequently been met for the flowable concentrate formulation. This needs to be addressed by the Registration Division (e.g., obtain acute toxicity data for the end-use product) to determine whether the Abound® label may indicate a reduction in REI to 4 hours.

8.0 DATA NEEDS/LABEL REQUIREMENTS

8.1 Toxicology

None

8.2 Product Chemistry

OPPTS GLN 830 Series: Product Properties

No data gaps.

8.3 Residue Chemistry

OPPTS GLN 860.1200: Proposed Uses

A number of revisions are required to the Heritage 50 WDG and Abound Flowable (2.08 lbs ai/A) Fungicide labels. Except for deleting the proposed use on wild rice, the revisions are minor in nature, mostly related to nomenclature. The specifics of the requested revisions are detailed in the Conclusions section of the residue chemistry review of PP#9F06058 (D260134, 9/6/00), which see.

As a condition of registration, if the petitioner wishes to maintain use of the FlC formulation, then separate field trials or bridging data (side-by-side field trials) on representative crops need to be conducted and submitted in support of late season uses.

OPPTS GLN 860.xxxx: Proposed Tolerances

A number of revisions are required to Section F of PP#9F06058 (*op. cit.*). These changes are to nomenclature, proposed tolerance levels, and to delete the proposed tolerances for apple (inadvertent residues), for wild rice, and for sugar beet, dried pulp. The specifics of the requested revisions are incorporated into the Recommendations sections of the residue chemistry review of PP#9F06058 (D260134, 9/6/00), which see.

Note: The listing in this risk assessment review of the proposed tolerances has been revised by the chemistry reviewer to reflect correct nomenclature and appropriate tolerance levels, and to delete the proposed tolerances for wild rice (for which no supporting residue data were provided); for sugar beet, dried pulp (since a separate tolerance was not warranted); and, for apple (inadvertent residues; since it is not OPP policy to establish a tolerance for inadvertent residues based upon concerns about the possibility of spray drift or contaminated equipment).

OPPTS GLN 860.1380: Storage Stability Data

As a condition of registration, additional data depicting the storage stability of residues of azoxystrobin and the Z isomer in/on a representative leafy vegetable, root and tuber vegetable,

and processed commodities of a root and tuber vegetable stored frozen for up to 11 months need to be conducted and submitted.

OPPTS GLN 860.1500: Crop Field Trials

As a condition of registration, two additional spinach field trials, one in Region 2 and one in Region 9, need to be conducted and submitted.

OPPTS GLN 860.1850/1900: Confined/Field Accumulation in Rotational Crops

As a condition of registration, additional limited field rotational crop studies, reflecting 1x the maximum proposed seasonal rate, need to be conducted and submitted.

9.0 ATTACHMENTS

Attachment 1: Report of the FQPA Safety Factor Committee (Memo, HED Doc. No. 012844, 09/03/1998).

Attachment 2: Report of the Hazard Identification Assessment Review Committee - (Memo, HED Doc. No. 014329, 09/25/2000).

Attachment 3: PP#9F06058: Azoxystrobin. Evaluation of Residue Chemistry Data to Support Permanent Tolerances for Use of Azoxystrobin on Barley, Bulb Vegetables, Cilantro, Citrus Fruits, Corn, Cotton, Leafy Vegetables (except *Brassica*), Leaves of Root and Tuber Vegetables, Peanuts, Root and Tuber Vegetables, Soybeans, and Wild Rice; Higher Tolerances for the Fat and Meat Byproducts of Cattle, Goats, Horses, and Sheep; and, Apples (Inadvertent Residues) (Memo, M. Nelson, D260134, 9/06/2000).

Attachment 4: Acute and Chronic Tier 1 Dietary Exposure Analyses for the Proposed Permanent Tolerances for Azoxystrobin on Barley, Citrus, Coriander, Corn, Cotton, Onions, Peanuts, Soybeans, Leafy Vegetables (Except Brassica), Leaves of Root and Tuber Vegetables, Root Vegetables, and Tuberous and Corm Vegetables (Memo, D. Dotson, D267564, 9/06/2000).

Attachment 5: Drinking Water Assessment for Azoxystrobin (128810) in/on Barley, Bulb Vegetables, Citrus Fruits, Corn (Field & Sweet Corn), Cotton, Root & Tuber Vegetables, Tops of Root & Tuber Vegetables, Leafy Vegetables & Cilantro, Peanuts, Soybeans, and Wild Rice. (Memo, D260137, T. Nguyen, 11/24/1999).

Attachment 6: Occupational Risk Assessment to Support Request for a Section 3 Registration of the New Uses of Azoxystrobin for Barley, Bulb Vegetables, Cilantro, Citrus Fruits, Corn, Cotton, Leafy Vegetables (except *Brassica*), Leaves of Root and Tuber Vegetables, Peanuts, Root and Tuber Vegetables, Soybeans, and Wild Rice (Memo, D269111, K. O'Rourke, 09/21/2000).

cc without attachments: PP#9F06058, K. O'Rourke (RAB3), M. Nelson (RAB2), D. Dotson (RAB2), and G. Dannan (RAB3)

Attachment 1

HED Doc. No. 012844

03-SEP-1998

MEMORANDUM

SUBJECT: ***AZOXYSTROBIN*** - Report of the FQPA Safety Factor Committee.

FROM: Brenda Tarplee, Executive Secretary
FQPA Safety Factor Committee
Health Effects Division (7509C)
and
Jess Rowland, Executive Secretary
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

THROUGH: Ed Zager, Chairman
FQPA Safety Factor Committee
Health Effects Division (7509C)

TO: Rick Loranger, Branch Senior Scientist
Registration Action Branch 2
Health Effects Division (7509C)

PC Code: 128810

The Health Effects Division (HED) FQPA Safety Factor Committee FQPA SFC) met on August 24, 1998 to evaluate the hazard and exposure data for Azoxystrobin and recommend application of the FQPA safety factor (as required by Food Quality Protection Act of August 3, 1996), to ensure the protection of infants and children from exposure to this pesticide. The Committee recommended that the 10-fold safety factor for increased susceptibility of infants and children should be removed for this pesticide.

I. HAZARD ASSESSMENT

1. Determination of Susceptibility

On November 7, 1996, the toxicology data base for Fludioxonil was reviewed by the HED RfD/Peer Review Committee. The Toxicology Endpoint Selection (TES) Committee met on November 12, 1996 to establish hazard endpoints for Azoxystrobin. It was determined that the available studies **indicated no increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to Azoxystrobin.** In the prenatal developmental toxicity studies in rats and rabbits and the two-generation reproduction study in rats, any observed toxicity to the offspring occurred at equivalent or higher doses than did toxicity to parental animals (P. Hurley to FQPA SFC, Aug.17, 1998).

2. Adequacy of Toxicity Database

There are **no data gaps** for the assessment of the effects of Azoxystrobin following *in utero* and/or postnatal exposure. Based on the toxicity profile, a developmental neurotoxicity study in rats is not required.

II. EXPOSURE ASSESSMENT AND RISK CHARACTERIZATION

1. Dietary Exposure Considerations

Azoxystrobin is a systemic fungicide classified as a Reduced Risk Pesticide. Permanent tolerances are currently established for residues of Azoxystrobin in/on bananas, grapes, peaches, peanuts, pecans, and tomatoes at levels ranging from 0.01 ppm to 1.0 ppm (40 CFR §180.507). Temporary tolerances have also been granted for several commodities (including meat, milk, poultry, and eggs resulting from use on rice and peanut hay). The parent, Azoxystrobin, and its Z-isomer are regulated. There are no established or proposed Codex MRLs.

Azoxystrobin is used on foods which are highly consumed by infants and children, including bananas and peaches (1993 NAS report, Pesticides in the Diets of Infants and Children). No monitoring data or percent crop treated (%CT) information are currently available for Azoxystrobin. Field trial studies, however, have been conducted in several commodities. The maximum residue value found in banana field studies was 0.27 ppm. The maximum residue value found in peach field studies was 0.74 ppm.

The HED Dietary Exposure Evaluation Model (DEEM) will be used to assess the risk from chronic dietary exposure to Azoxystrobin in food. The analysis will most likely be unrefined (using no %CT information or anticipated residues), making the conservative assumption that all commodities contain residues of Azoxystrobin at the level of the established or proposed tolerance. This results in an overestimate of dietary

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exposure. No acute dietary risk assessment is required since an appropriate endpoint for this exposure was not identified.

2. Drinking Water Exposure Considerations

The environmental fate data base for Azoxystrobin is complete. The environmental fate data indicate that Azoxystrobin is moderately persistent in aerobic and anaerobic soils. However the magnitude of its partitioning coefficients should limit its leaching potential into ground water. Also, since Azoxystrobin is mostly foliar applied (to treat fungus on leaves) foliar interception and subsequent photodegradation on foliage could substantially reduce the amount of this chemical reaching the soil and therefore available for leaching and runoff. Transformation products of Azoxystrobin exhibit a much lower soil/binding affinity than the parent compound, and thus possess greater potential to leach through soils.

No targeted monitoring data are available for Azoxystrobin. Therefore, the drinking water exposure assessment uses modeling estimates for both surface and ground water. Estimated Environmental Concentrations (EECs) have been calculated for ground and surface water based on the current EFED first level screening models, SCI-GROW and PRZM/EXAMS respectively.

3. Residential Exposure Considerations

There are currently no registered residential uses for Azoxystrobin.

III. SAFETY FACTOR RECOMMENDATION AND RATIONALE

1. Recommendation of the Factor

The Committee recommended that the **10x factor** for increased susceptibility of infants and children (as required by FQPA) should be **removed.**

2. Rationale for Selection of the FQPA Factor

The Committee recommended that the10x Safety Factor should be removed. since: 1) the toxicology data base is complete; 2) the developmental and reproductive toxicity data did not indicate increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure; 3) unrefined chronic dietary exposure estimates (assuming all commodities contain tolerance level residues) will overestimate dietary exposure; 4) modeling data are used for ground and surface source drinking water exposure assessments resulting in estimates considered to be upper-bound concentrations; and 5) there are currently no registered residential uses for Azoxystrobin.

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Attachment 2

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

014329

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: September 25, 2000

MEMORANDUM

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

FROM: Ghazi A. Dannan, Pharmacologist Ghazi A. Dannan 10/3/00
Registration Action Branch 3
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair 10/3/00
and
Elizabeth Doyle, Co-Chair E. A. Doyle 10/3/00
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

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

PC Code: 128810

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

Committee Members in Attendance

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

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

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

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

Data Evaluation / Report Presentation

Ghazi A. Dannan

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1. INTRODUCTION

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

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

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

2. HAZARD IDENTIFICATION

2.1 Acute Reference Dose (RfD)

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

MRID No.: 43678134, 44182013, 44182015

Executive Summary:

In an acute neurotoxicity study (MRID 43678134, 44182013, 44182015), ICIA5504 (Azoxystrobin, 96.2% a.i.) was administered once in corn oil (10 mL/kg body wt) by gavage to 3 groups of 10 Alpk:ApfSD rats/sex/dose at doses of 0, 200, 600 or 2000 mg/kg. All animals were evaluated in functional observational battery (FOB) and motor activity (MA) testing on days -7 (7 days prior to dosing), 1 (2 hr post-dosing), 8, and 15. Five control and high dose animals/sex perfused in situ were evaluated for microscopic neuropathology. At 200 mg/kg and higher, diarrhea/signs of diarrhea were observed at 2 hr post-dosing in both sexes (males, 1, 4, 5 and 10; females, 0, 9, 9 and 6). Tip-toe gait and upwardly curved spine at 2 hr were also observed in treated but not control animals (no dose-response observed). No treatment-related effects on survival, food consumption, motor activity, brain weight/dimensions, or gross/ microscopic pathology were observed. Body weights of males at 2000 mg/kg were slightly decreased (2.9% and 2.6% at day 8 and 15). Statistically significant increases in landing foot splay on day 8 in females at 600 and 2000 mg/kg are noted (23.7% and 20.5% higher than controls, respectively; on day 1, females at 600 and 2000 mg/kg had nonstatistically significantly increased values of

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11.8 and 12.5%, respectively). These were not considered indicative of neurotoxicity because of a 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 LOAEL is 200 mg/kg, based on occurrence of transient diarrhea in both sexes. The systemic toxicity NOAEL 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 acceptable and satisfies the guideline requirement for an acute oral neurotoxicity study (81-8).

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

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

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

Acute RfD =	$\frac{\text{200 mg/kg (LOAEL)}}{\text{300 (UF)}}$	=	0.7	**mg/kg**

2.2 Chronic Reference Dose (RfD)

Study Selected: Combined Chronic Toxicity/Carcinogenicity Rat Feeding study §870.4300

MRID No.: 43678139

Executive Summary:

In a combined chronic/oncogenicity study (MRID 43678139) ICIA5504 (azoxystrobin, 96.2% w/w a.i., Lot# P49) was administered to 52 Alpk:APfSD rats/sex/dose in the feed at dose levels of 0, 60, 300, and 750 ppm/1500 ppm (males/females) (males: 0, 3.6, 18.2, and 34.0 mg/kg/day; females: 0, 4.5, 22.3, and 117.1 mg/kg/day) for 104 weeks. An additional 12 rats/sex/dose were designated for interim sacrifice at week 52. Due to excessive mortality the high dose was reduced to 750 ppm in males beginning at week 52 and the animals of this group designated for interim sacrifice were retained with the main study.

Distended abdomens were observed in males beginning at week 17 with 5, 0, 5, and 15 animals

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

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

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

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

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

There was no evidence of carcinogenic activity in this study. Among female rats, there was a significant dose-related decrease in the incidence of benign fibroadenomas of the mammary gland with 10/52, 3/52, 2/52 ($p \leq 0.05$), and 1/52 ($p \leq 0.01$) affected in the control, 60, 300, and 1500 ppm groups, respectively.

This combined chronic/oncogenicity toxicity study in the rat is acceptable and satisfies the

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guideline requirement for a combined chronic/oncogenicity feeding study (83-5a) in rats.

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

Uncertainty Factor(s): 100

Comments about Study/Endpoint/Uncertainty Factor:

Chronic RfD = $\frac{\text{18.2 mg/kg/day (NOAEL)}}{\text{100 (UF)}}$ = **0.18 mg/kg/day**

2.3 Occupational/Residential Exposure

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

Study Selected: Prenatal Rat Oral Developmental Toxicity Study §870.3700

MRID No.: 43678142

Executive Summary:

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

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

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

Due to maternal toxicity at the high dose level, this study must be considered a two dose study, which makes it deficient. However, since valid NOEL and LOEL were obtained from the data, the developmental toxicity study in the rat is classified acceptable and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; §83-3 a) in the rat.

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

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

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

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

MRID No.: 43678135

Executive Summary:

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

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

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significant. All of these findings were less marked in the groups receiving 2000 ppm and were absent in the groups receiving 200 ppm. Increases in liver and kidney weights adjusted for body weight in the 2000 and 4000 ppm treatment groups were attributable to treatment. Changes in organ weights were accompanied by histopathological findings in two males in the 4000 ppm treatment group. Treatment-related effects in these males included marked elevations in total bilirubin, cholesterol, triglycerides, and plasma enzyme activities. The effect on the liver of these two animals was observed microscopically as proliferation of the intrahepatic bile duct/ductiles and oval cells. Hepatocellular hyperplasia and an enlarged hepatic lymph node was observed in one of the two males. **The LOEL is 2000 ppm (211.0 and 223.0 mg/kg/day for males and females) based on decreased weight gain in both sexes, clinical observations of distended abdomens and reduced body size, and clinical pathology findings attributable to reduced nutritional status. The NOEL is 200 ppm (20.4 and 22.4 mg/kg/day for males and females).**

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

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

Comments about Study/Endpoint: The study is appropriate for this exposure scenario and the population of concern (toddlers).

2.3.3 Dermal Absorption

Dermal Absorption Factor: 2 - 4 %

MRID No.: 43678155

Executive Summary:

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

No animals died as a result of the treatment. Percutaneous absorption was minimal (≤ 4.2%) and did not appear to exhibit a dose-response relationship. Limited absorption precluded accurate assessment of distribution and metabolite characterization. Both fecal and urinary excretion were quantified, the former representing ≈6% or less of total absorption and the latter accounting for <0.1% of the absorbed dose over a 24-hr period. Overall recovery of administered radioactivity was 95-105%.

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

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

Study Selected: None §

MRID No.: None

Executive Summary: None

Dose and Endpoint for Risk Assessment: Not Applicable

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

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

Study Selected: None §

MRID No.: None

Executive Summary: None

Dose/Endpoint for Risk Assessment: Not Applicable

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

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

Study Selected: None §

MRID No.: None

Executive Summary: None

Dose and Endpoint for Risk Assessment: Not Applicable

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

2.3.7 Inhalation Exposure (All Durations)

a) Short-Term

Study Selected: Prenatal Rat Oral Developmental Toxicity Study §870.3700

MRID No.: 43678142

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

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

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

> Convert the inhalation exposure component (i.e., µg a.i./day) using a 100% absorption rate (default value) and an application rate to an **equivalent oral dose** (mg/kg/day) and compare the oral equivalent dose to the oral NOAEL of 25 mg/kg/day to calculate the MOE for the Short-term exposure scenario.

b) Intermediate-Term

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

MRID No.: 43678135

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

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

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

> Convert the inhalation exposure component (i.e., µg a.i./day) using a 100% absorption rate (default value) and an application rate to an **equivalent oral dose** (mg/kg/day) and compare the oral equivalent dose to the oral NOAEL of 21 mg/kg/day to calculate the MOE for the Intermediate-term exposure scenario.

c) Long-Term

The long-term inhalation exposure is not applicable to the use scenario. Nonetheless, the HIARC selected the Combined Chronic Toxicity/Carcinogenicity Rat Feeding study (MRID 43678139, under above item 2.2) if this risk assessment becomes necessary in the future. The HIARC also recommended using a route-to-route extrapolation, a 100% absorption rate (default value), and the oral NOAEL of 18.2 mg/kg/day.

2.3.8 Margins of Exposure for Occupational/Residential Risk Assessments

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

2.4 Recommendation for Aggregate Exposure Risk Assessments

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

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

For **short- and intermediate-term** aggregate exposure risk assessment, the short-term and intermediate-term inhalation exposures should be converted to oral equivalent doses (using 4%

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dermal absorption rate and 100% inhalation absorption rate), and should be added to the oral exposures (from food + water) and compared to the respective oral NOAELs.

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

3 CLASSIFICATION OF CARCINOGENIC POTENTIAL

3.1 Combined Chronic Toxicity/Carcinogenicity Study in Rats

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

Discussion of Tumor Data There was no evidence of carcinogenicity.

Adequacy of the Dose Levels Tested The tested dose levels were 0, 60, 300, and 750 ppm/1500 ppm (males/females) (males: 0, 3.6, 18.2, and 34.0 mg/kg/day; females: 0, 4.5, 22.3, and 117.1 mg/kg/day). The highest dose levels tested were adequate for assessing carcinogenicity based on body weight reduction in both sexes, bile duct lesions in males, and excessive mortality among males before they were switched from the 1500 ppm to the 750 ppm dietary level at week 52. The NOAEL/ LOAEL for the chronic toxicity phase were considered to be 18.2/34.0 mg/kg/day in males and 22.3/117.1 mg/kg/day in females based on reduced body weights in both sexes and bile duct lesions in males. The HED-RfD/Peer Review Committee also considered the study and doses adequate for testing carcinogenicity (RfD/Peer Review Report dated 1/14/97).

3.2 Carcinogenicity Study in Mice § 870.4200

MRID No. 43678141

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

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

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(272.4 and 363.3 mg/kg/day, respectively). The systemic toxicity NOEL is 300 ppm (37.5 and 51.3 mg/kg/day).

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

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

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

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

3.3 Classification of Carcinogenic Potential

In accordance with the 1996 Cancer Risk Assessment Guidelines, the HED-RfD/Peer Review Committee classified azoxystrobin as "**not likely**" to be carcinogenic to humans via relevant routes of exposure based on the lack of evidence of carcinogenicity in mice or rats (RfD/Peer Review Report dated 1/14/97, HED Doc. No. 012133).

4 MUTAGENICITY

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

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

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

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

3) In vitro chromosome aberrations in human lymphocytes assay (MRID No. 43678147, HED Doc. No. 012115): The test was positive for the induction of chromosomal aberrations in both the

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presence and absence of S9 activation at doses (5-50 µg/mL -S9; 100-200 µg/mL +S9) that were moderately to severely cytotoxic (i.e., ≥16-70% reductions in mitotic cells, respectively).

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

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

The [RfD/Peer Review] Committee overall concluded that Azoxystrobin in the presence and absence of exogenous metabolic activation induced a weak mutagenic response in the mouse lymphoma assay. Although colony sizing was not performed in the mouse lymphoma assay, it is likely that the increased MFs seen in this study were associated with a chromosomal rather than point mutational event. This interpretation is based on the similarity of the response uncovered in the mouse lymphoma assay to the clastogenic response seen with and without S9 activation in human lymphocytes. However, the negative genotoxicity associated with bone marrow cytotoxicity in the micronucleus assay provides confidence that Azoxystrobin is not an in vivo genotoxicant. This assumption is further supported by the negative findings of the UDS assay, the lack of an oncogenic effect in rat or mouse long-term feeding studies and the absence of significant reproductive or developmental toxicity attributable to a mutagenic mode of action (i.e., decreased total implants, increased resorptions). Hence, it can be concluded that Azoxystrobin is active in vitro but this genotoxicity is not expressed in whole animals.

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

5 FQPA CONSIDERATIONS

5.1 Adequacy of the Data Base

The data base is adequate for the assessment of increased susceptibility of infants and children.

5.2 Neurotoxicity

-- *Acute Neurotoxicity* - § 870.6200 (81-8), MRID 43678134, 44182013, 44182015

EXECUTIVE SUMMARY: In an acute neurotoxicity study (MRID 43678134, 44182013, 44182015), ICIA5504 (Azoxystrobin, 96.2% a.i.) was administered once in corn oil (10 mL/kg body

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wt) by gavage to 3 groups of 10 Alpk:ApfSD rats/sex/dose at doses of 0, 200, 600 or 2000 mg/kg. All animals were evaluated in functional observational battery (FOB) and motor activity (MA) testing on days -7 (7 days prior to dosing), 1 (2 hr post-dosing), 8, and 15. Five control and high dose animals/sex perfused in situ were evaluated for microscopic neuropathology. At 200 mg/kg and higher, diarrhea/signs of diarrhea were observed at 2 hr post-dosing in both sexes (males, 1, 4, 5 and 10; females, 0, 9, 9 and 6). Tip-toe gait and upwardly curved spine at 2 hr were also observed in treated but not control animals (no dose-response observed). No treatment-related effects on survival, food consumption, motor activity, brain weight/dimensions, or gross/ microscopic pathology were observed. Body weights of males at 2000 mg/kg were slightly decreased (2.9% and 2.6% at day 8 and 15). Statistically significant increases in landing foot splay on day 8 in females at 600 and 2000 mg/kg are noted (23.7% and 20.5% higher than controls, respectively; on day 1, females at 600 and 2000 mg/kg had nonstatistically significantly increased values of 11.8 and 12.5%, respectively). These were not considered indicative of neurotoxicity because of a 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 LOAEL is 200 mg/kg, based on occurrence of transient diarrhea in both sexes. The systemic toxicity NOAEL 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 acceptable and satisfies the guideline requirement for an acute oral neurotoxicity study (81-8).

-- *Subchronic Neurotoxicity* - § 870.6200 (82-7), MRID 43678138, 44182014

EXECUTIVE SUMMARY: In a subchronic neurotoxicity study (MRID 43678138, 44182014), ICIA5504 (96.2% a.i.) was administered to 12 Alpk:Apfsd rats/sex/dose in the diet at 0, 100, 500 or 2000 ppm for 13 weeks (average daily consumption of 0, 8.0, 38.5 or 161 mg/kg/day, males and 0, 9.1, 47.9 or 201.5 mg/kg/day, females). All animals were used for functional observational battery (FOB) and motor activity (MA) testing and 6 control and high dose animals/sex were perfused in situ and evaluated for microscopic neuropathology. At 2000 ppm, mean body weights of males were statistically significantly decreased throughout the study (at week 13, 12.6% less than controls). Mean body weights of females were slightly decreased (at week 13, 5.1% less than controls; significant only at week 2). Cumulative body weight gains were 18% lower (males) and 10% lower (females). Food consumption was statistically significantly lower in males (5.4% to 15.4%) but not females. Food utilization in males at 2000 ppm was statistically significantly decreased during weeks 1-4 (9.7%) and 1-13 (11.7%) and was non-significantly less in females during the same periods (11.8% and 14.4%, respectively). There were no consistent indications of treatment-related neurotoxicity (clinical signs, qualitative or quantitative neurobehavioral effects, brain weight/dimensions, or gross/microscopic pathology). [Statistically significant decreases in landing foot splay in males (week 5, 19%, 16.4% and 24.1%, low to high dose; week 9, 18% at high dose), forelimb grip strength (males week 5, 14.3%, 14.3% and 19%, low to high dose and females week 14, 12.9%, high dose), hindlimb grip strength in males (week 5, 13.3%, 15.3% and 12.9%, low to high dose) and motor activity in females (21%, week 9) are noted but are not considered treatment-related because of a lack of dose-response, inconsistency of observations at different time points, variability of pretreatment values and/or small magnitude of response; see review for details]. The

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systemic toxicity LOAEL is 161 mg/kg/day, based on decreased body weight/weight gain and food utilization in both sexes (marginal in females). The NOAEL is 38.5 mg/kg/day. This study is classified as acceptable and satisfies the guideline requirement for a subchronic oral neurotoxicity study (82-7) in rats.

5.3 Developmental Toxicity

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

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

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

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

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

The RfD/Peer Review Committee considered the first developmental toxicity study in rabbits (MRID 43678143) to be unacceptable and provided the following excerpted comments (RfD/Peer Review Report dated 1/14/97, HED Doc. No. 012133). The chemical was administered by gavage at dose levels of 7.5, 20, or 50 mg/kg/day on gestation days 8-20. The study, although performed in accordance with the USEPA guidelines, failed to accurately provide an overall NOEL. The Registrant submitted several supplementary nonguideline studies (MRID Nos. 44058702, 44058703, 44058705, 44073202 and 44073201) supporting their claim that the stress resulting from the dosing volume used (2 ml corn oil/kg) and maternal diarrhea caused by corn oil might have contributed to the effects seen in this study. In that particular testing facility, doses of corn oil at 2 mL/kg body weight and above may enhance the toxicity of Azoxystrobin. Because of all the uncertainties regarding the effects and the lack of definite etiology, the Committee considered the first rabbit

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developmental toxicity study (MRID No. 43678143) unacceptable and concluded that it should not be used for regulatory or risk assessment purposes and NOEL/LOELs should not be set (RfD/Peer Review Report dated 1/14/97, HED Doc. No. 012133). The RfD Report added that the second study (MRID 44058701) demonstrated a completely different toxicity pattern with respect to maternal and fetal toxicity to Azoxystrobin; therefore, it was judged to be acceptable for regulatory or risk assessment purposes and should supersede the previous developmental toxicity study in rabbits (MRID 43678143).

5.4 Reproductive Toxicity

In the 2-generation reproductive toxicity study in rats (83-4, MRID No. 43678144), azoxystrobin was tested at dietary levels of 60, 300, or 1500 ppm (approx. 6.4, 32.3 or 165.4 mg/kg/day for males and 6.8, 33.8 or 175.0 mg/kg/day for females). The systemic toxicity NOEL/LOEL were considered to be 32.3 and 165.4 mg/kg/day, respectively, based on reduced body weight, reduced food consumption, and increased adjusted liver weights in both sexes in addition to histopathologic lesions of the bile duct and liver in males. The reproductive toxicity NOEL/LOEL were considered to be 32.3 and 165.4 mg/kg/day, respectively, based on decreased body weights for male and female pups of both generations (DER signed by M. Ottley and M. Copley and dated 10/28/96). However, since none of the reproductive parameters were affected at any of the dose levels tested, the actual reproductive toxicity NOAEL/LOAEL should be 165.4/>165.4 mg/kg/day, respectively. This conclusion is also supported by the comments of the RfD/Peer Review report which noted that "the body weight decrements in pups were not apparent on Day 1 of lactation, but appeared by Day 5 or 11, indicating an early postnatal origin." The RfD/Peer Review Committee "further noted that liver weight increases in the weanling pups are probably more indicative of systemic, rather than reproductive, toxicity." Henceforth, the offspring or developmental NOAEL/LOAEL are 32 and 165 mg/kg/day, respectively based on reduced pup body weight and increased liver weights.

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

N/A

5.6 Determination of Susceptibility

The HIARC reaffirmed the FQPA SF Committee's conclusions that the available studies **indicated no increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to azoxystrobin.** In the prenatal developmental toxicity studies in rats and rabbits and the two-generation reproduction study in rats, any observed toxicity to the offspring occurred at equivalent or higher doses than did toxicity to parental animals. The FQPA SF Committee considered the available toxicology data base adequate for an FQPA assessment and recommended that the 10-fold safety factor for increased susceptibility of infants and children should be removed for azoxystrobin (FQPA Report dated 9/3/98, HED Doc. No. 012844). The following rationale was provided in the FQPA Report. "The Committee recommended that the 10x Safety Factor should be removed. since: 1) the toxicology data base is complete; 2) the developmental and reproductive toxicity data did not

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indicate increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure; 3) unrefined chronic dietary exposure estimates (assuming all commodities contain tolerance level residues) will overestimate dietary exposure; 4) modeling data are used for ground and surface source drinking water exposure assessments resulting in estimates considered to be upper-bound concentrations; and 5) there are currently no registered residential uses for Azoxystrobin."

5.7 Recommendation for a Developmental Neurotoxicity Study

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

According to a recent health risk assessment for some food tolerances, the HIARC had also previously addressed this issue and decided not to recommend a developmental neurotoxicity study (see memorandum dated 1/28/99, t:\hed\reviews\128810\risk\d248888.mem). The following is a quotation from that memorandum. "Azoxystrobin was brought to the Hazard Identification Assessment Review Committee (HIARC) on 10/13/98, specifically to address the requirement for a developmental neurotoxicity study. The HIARC did not recommend a requirement for a developmental neurotoxicity study at this time. Neither the acute nor the subchronic mammalian neurotoxicity study gave a clear, consistent indication of neurotoxicity. There was no microscopic evidence of neuropathology in either of these two studies or in any of the other studies conducted with azoxystrobin. In addition, there were no behavioral effects in pups in the 2-generation reproduction study and there were no alterations in the development of the central nervous system in the developmental studies."

5.7.1 Evidence that suggest requiring a Developmental Neurotoxicity study:

N/A

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

N/A

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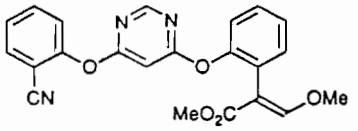
6 HAZARD CHARACTERIZATION

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



The most common toxicity findings from administration of azoxystrobin to rats, via the oral route, were decreased body weight, decreased food intake/utilization, increased diarrhea, and other clinical toxicity observations such as, increased urinary incontinence, hunched postures and distended abdomens. One or more of these effects were reported in most rat studies including subchronic, combined chronic toxicity/oncogenicity, prenatal developmental toxicity, 2-generation reproduction, acute neurotoxicity, and subchronic neurotoxicity. In the repeated dosing rat studies, these effects were not seen at the NOAEL values that ranged from 18 mg/kg/day in the chronic rat dietary feeding study to nearly 32 mg/kg/day (300 ppm) in the 2-generation rat reproduction study. In one instance (rat subchronic neurotoxicity study), the NOAEL was 38.5 mg/kg/day (500 ppm) based on decreased body weight/weight gain and food utilization.

In addition, increased lethality was seen after repeated oral administration at relatively high doses. For instance, in the combined chronic toxicity/oncogenicity study, the high dose male group was switched from dietary feeding at 1500 ppm to 750 ppm (34.0 mg/kg/day) due to excessive mortality beginning at week 52. Also, in the prenatal developmental toxicity study, three of the first 12 pregnant rats (25%) died after two days of treatment at the high dose (300 mg/kg/day in 10 ml corn oil/kg); henceforth, the study authors discontinued dosing at this level. It is interesting to note that these results do not appear to be consistent with the rat oral LD_{50} reported to be > 5000 mg/kg. In this acute toxicity study, five rats of each sex were gavaged a single dose of azoxystrobin at 5000 mg/kg (in 10 ml/kg corn oil); all rats survived the 14 day follow up with no reported clinical toxicity effects or changes in body weight. It is not clear why the chemical is more lethal in the developmental toxicity study than in the acute toxicity study; however, it is possible that there is enhanced toxicity due to pregnancy. Alternatively, chance variations among the studies and/or the small number of animals per group in the rat oral LD_{50} study might have contributed to these inconsistencies.

In the two-generation rat reproduction study and the subchronic and chronic toxicity studies in rat and dog, the liver and bile duct are the major target organs for azoxystrobin as evidenced by clinical chemistry, increased weight, gross pathology and/or microscopic changes in the liver and biliary tracts.

Minor hematological effects were also reported in the rat and dog subchronic toxicity studies including decreased hemoglobin, MCV, and MCH in both species, increased white blood cells and decreased platelets in rats, and increased platelets in dogs; however, the changes were not considered toxicologically relevant because the magnitude was small (<10%) and there were no dose-response relationship.

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

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

Based on pharmacokinetics and metabolism studies in rats, azoxystrobin was widely distributed following oral administration as single gavage doses of 1 or 100 mg/kg or 14-day repeated doses of 1 mg/kg. The greatest amounts of absorbed azoxystrobin were detected in organs associated with excretory function, especially the liver and kidneys. However, less than 0.5% of the administered dose was detected in the tissues at seven days postdosing and there was no apparent sex-related differences in distribution and no evidence of potential for bioaccumulation. Excretion via expired air was minimal. The primary route of excretion was via the feces (≈73-89%), although ≈9-18% was detected in the urine of the various dose groups. The fecal vs. urinary route of excretion did not vary considerably with dose or sex. However, a definitive quantitative assessment of absorption was difficult because of fecal sample extraction difficulties. Biliary metabolites were assessed using rats with cannulated bile ducts given a single 100 mg/kg gavage dose of azoxystrobin. For the single high-dose group, assessment of biliary excretion suggested approximately 70% absorption with approximately 32% of administered

radioactivity remaining as parent compound in the gastrointestinal tract. Absorbed azoxystrobin appeared to be extensively metabolized with minor sex-related qualitative and quantitative differences in biliary metabolites. With the exception of metabolite V (a glucuronide conjugate) which represented 29.3% (males) and 27.4% (females) of the administered dose, individual biliary metabolites represented less than 10% of the administered dose. A metabolic pathway was proposed showing hydrolysis and subsequent glucuronide conjugation as the major biotransformation process.

7 · DATA GAPS

The HIARC determined that a 28-day inhalation toxicity study (nose-only) is required due to concern for occupational/residential exposure via this route based on the current use pattern; the 90-day protocol should be followed with an exposure duration of 28-days.

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8 ACUTE TOXICITY

Acute Toxicity of Azoxystrobin

Guideline No.	Study Type	MRID #	Results	Toxicity Category
81-1	Acute Oral - Rat	43678122	LD_{50} > 5000 mg/kg (Limit Test) in Males & Females	IV
81-2	Acute Dermal - Rat	43678124	LD_{50} > 2000 mg/kg (Limit Test) in Males & Females	III
81-3	Acute Inhalation - Rat	43678126	LC_{50} **Males = 0.962 mg/L (95% C.I. = 0.674, *)** **Females = 0.698 mg/L (95% C.I. = 0.509, 2.425)** **The combined LC50 was not calculated** * Not calculated due to mortality pattern	III
81-4	Primary Eye Irritation - Rabbit	43678128	Slight to moderate erythema and slight chemosis in all rabbits within one hour, but effects resolved within 48 hours of treatment.	III
81-5	Primary Skin Irritation - Rabbit	43678130	Very slight erythema and edema that persisted for three days on one rabbit and for one hour on another.	IV
81-6	Dermal Sensitization - Guinea Pig	43678132	No erythema or edema were found 38 or 48 hrs after challenge with test material.	Not a dermal sensitizer
81-8	Acute Neurotoxicity	43678134, 44182013, 44182015	No indication of neurotoxicity at any dose level tested. NOAEL/LOAEL based on transient diarrhea in both sexes. NOAEL = < 200 mg/kg LOAEL = 200 mg/kg	

9 SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

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

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	NOAEL < 200 mg/kg UF = 300	Diarrhea at two-hours post dose at all dose levels up to and including the lowest tested dose of 200 mg/kg (LOAEL).	Acute Neurotoxicity - Rat (MRID 43678134, 44182013, 44182015)
	Acute RfD = 0.7 mg/kg		
Chronic Dietary	NOAEL = 18.2 UF = 100	NOAEL = 300 ppm (males 18.2, females 22.3 mg/kg/day) based on reduced body weights in both sexes and bile duct lesions in males. The LOAEL in males/females = 750/1500 ppm (34/117 mg/kg/day).	Combined Chronic Toxicity/Carcinogenicity Feeding study - Rat (MRID 43678139)
		Chronic RfD = 0.18 mg/kg/day	
Incidental Oral, Short-Term	NOAEL = 25	Increased maternal diarrhea, urinary incontinence, and salivation at 100 mg/kg/day (LOAEL).	Prenatal Developmental Oral Toxicity - Rat (MRID 43678142)
Incidental Oral, Intermediate-Term	NOAEL = 21	NOAEL = 200 ppm (20.4/22.4 mg/kg/day in males/females) based on decreased body weight gain in both sexes and clinical signs indicative of reduced nutrition at the LOAEL of 2000 ppm (211/223 mg/kg/day in males/females).	90-Day Feeding - Rat (MRID 43678135)
Dermal, Short-Term	NOAEL = N/A	This risk assessment is not required since no dermal or systemic effects were seen at the limit dermal dose (1000 mg/kg/day).	21-Day Repeated Dose Dermal - Rat (MRID 43678137)
Dermal, Intermediate-Term	NOAEL = N/A	This risk assessment is not required since no dermal or systemic effects were seen at the limit dermal dose (1000 mg/kg/day).	21-Day Repeated Dose Dermal - Rat (MRID 43678137)
Dermal, Long-Term	NOAEL = N/A	This risk assessment is not required based on the use pattern.	
Inhalation, Short-Term	NOAEL = 25	Increased maternal diarrhea, urinary incontinence, and salivation at 100 mg/kg/day (LOAEL). Use route-to-route extrapolation and 100% absorption rate (default value).	Prenatal Developmental Oral Toxicity - Rat (MRID 43678142)

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Inhalation, Intermediate-Term	NOAEL = 21	NOAEL = 200 ppm (20.4/22.4 mg/kg/day in males/females) based on decreased body weight gain in both sexes and clinical signs indicative of reduced nutrition at 2000 ppm (211/223 mg/kg/day in males/females). Use route-to-route extrapolation and 100% absorption rate (default value).	90-Day Feeding - Rat (MRID 43678135)
Inhalation, Long-Term	NOAEL = N/A	This risk assessment is not applicable to the use scenario of azoxystrobin.	

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Attachment 3
Available Electronically

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Attachment 4

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: 9/6/2000

SUBJECT: Acute and Chronic Tier 1 Dietary Exposure Analyses for the Proposed Permanent Tolerances for Azoxystrobin on Barley, Citrus, Coriander, Corn, Cotton, Onions, Peanuts, Soybeans, Leafy Vegetables (Except Brassica), Leaves of Root and Tuber Vegetables, Root Vegetables, and Tuberous and Corm Vegetables

PP#:	9F6058
DP Barcode #:	D267564
Chemical No.:	128810
40 CFR:	180.507

TO: K. O'Rourke, Chemist
RAB3/HED

FROM: Douglas Dotson, Chemist
RAB2/HED

THROUGH: W. Cutchin and C. Swartz, Dietary Exposure SAC Reviewers
Richard A. Loranger, Branch Senior Scientist
RAB2/HED (7509C)

Action Requested

Provide acute and chronic dietary exposure analyses for the proposed Section 3 uses of azoxystrobin on barley, citrus, coriander, corn (sweet, pop, and field), cotton, onions, peanuts, soybeans, leafy vegetables (except brassica), leaves of root and tuber vegetables, root vegetables, and tuberous and corm vegetables. The most recent DEEM analysis for azoxystrobin was performed on 9/1/2000 when time-limited (Section 18) tolerances were recommended for azoxystrobin residues on carrots, citrus, cottonseed, garden beets, and ginseng (Memo, D267517, D. Dotson, 9/1/2000).

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Executive Summary

Tier 1 acute and chronic dietary exposure analyses were performed for azoxystrobin. Tier 1 analyses are the most conservative estimates of dietary exposure which HED performs. Tolerance level residues were used in the analyses, and it was assumed that 100% of all crops with azoxystrobin tolerances will be treated. The acute and chronic dietary exposure to azoxystrobin reported in this assessment, as represented by the percent population adjusted dose (PAD), is below HED's level of concern for the U.S. population and all population subgroups.

Toxicological Information

The HIARC established doses and endpoints for azoxystrobin (Memo, HIARC, G. Dannan, In Preparation). The FQPA Safety Factor Committee met to determine whether or not the Safety Factor should be retained (Memo, FQPA Safety Factor Committee, HED Document Number 012844, 9/3/98). The doses and endpoints are summarized in Table 1.

Table 1. Summary of Toxicological Doses and Endpoints for Azoxystrobin

Endpoint	Dose (mg/kg/day)	Endpoint	Study
Acute Dietary	NOAEL < 200 mg/kg UF = 300	Diarrhea at two-hours post dose at all dose levels up to, and including, the lowest tested dose of 200 mg/kg (LOAEL).	Acute Neurotoxicity: Rat (MRID 43678134)
	Acute RfD = 0.67 mg/kg **Acute PAD = 0.67 mg/kg**		
Chronic Dietary	NOAEL = 18.2 UF = 100	NOAEL=300 ppm (males 18.2, females 22.3 mg/kg/day) based on reduced body weights in both sexes and bile duct lesions in males. The LOAEL in males/females = 750/1500 ppm (34/117 mg/kg/day).	Combined Chronic Toxicity/Carcinogenicity feeding study - Rat (MRID 42678135)
	Chronic RfD = 0.18 mg/kg/day **Chronic PAD = 0.18 mg/kg/day**		
FQPA Safety Factor	FQPA SF = 1x	The FQPA Safety Factor Committee recommended that the 10x Safety Factor for increased susceptibility of infants and children be removed. (FQPA document No. 012844, 9/3/98).	Rat neurotoxicity, developmental, and reproductive studies. Rabbit developmental study.

Carcinogenicity		In accordance with the 1996 Cancer Risk Assessment Guidelines, the HED-RfD/Peer Review Committee classified azoxystrobin as **"not likely"** to be carcinogenic to humans via relevant routes of exposure based on the lack of evidence of carcinogenicity in mice and rats (RfD/Peer Review Report dated 1/14/97, HED Doc. No. 012133).	Rat and mice carcinogenicity studies.

Residue Information

Tolerances for azoxystrobin (including time-limited tolerances) are published in 40 CFR §180.507. The tree nuts tolerance of 0.01 ppm which is listed in the 40 CFR was amended to 0.02 ppm (Memo, D256308, D. Dotson, 5/27/99). 40CFR gives an expiration date of 6/30/2000 for soybeans and sugar beets and an expiration date of 7/30/2000 for strawberries. The Registration Division has extended these tolerances until 12/30/2001. The time-limited tolerance for sugar beets is greater than the permanent tolerance being established by the current action. Therefore, the time-limited tolerance of 0.7 ppm has been used in these dietary exposure analyses. The permanent tolerance being established for soybeans is greater than the time-limited tolerance currently in effect. Therefore, the permanent tolerance of 0.5 ppm has been used in these analyses. For soybean oil, however, the time limited tolerance of 2.0 ppm has been used because this tolerance will be in effect until 12/30/2001. The following additional time-limited tolerances have been established in conjunction with Section 18 exemptions: lima beans (0.2 ppm, 99DE0009, D258937, W. Wassell, 9/14/99), Brassica leafy vegetables (25 ppm, 99GA0009, D255311, 5/7/99, D. Dotson), and parsley (20 ppm, 99CA0019, D255830, D. Dotson, 5/17/99). HED recently recommended in favor of the following time-limited tolerances: carrots, roots (0.50 ppm), citrus fruit (3.0 ppm), cottonseed (0.10 ppm), garden beet, roots (0.50 ppm), garden beet, tops (50 ppm), and ginseng (0.50 ppm). The time-limited tolerances recommended for carrots, garden beets (roots and tops), and ginseng are the same as the permanent tolerances being recommended for these commodities. The RD did not grant the citrus fruit tolerance (Jackie Gwalney, personal communication). Therefore, the tolerance of 1.0 ppm being established in this action was used in the dietary exposure analysis. A time-limited tolerance of 0.1 ppm was established for cottonseed (expiration date 12/30/2001). As this tolerance is higher than the permanent tolerance of 0.02 ppm which is being established, a value of 0.1 ppm was used in the dietary exposure analysis. Table 2 gives the recommended tolerances which are included in this action.

Tolerances have been proposed for onion, dry bulb (1.0 ppm) and onion, green (7.5 ppm). 40CFR §180.1(h) directs that tolerances also be established for the following commodities: garlic (1.0 ppm), leeks (7.5 ppm), shallots (7.5 ppm). DEEM does not specify whether the shallots are dried or green, therefore the higher tolerance (7.5 ppm) was used.

Table 2. Proposed Tolerances	
Crop	**Proposed Tolerance (ppm)**
Barley, grain	0.1
Coriander Leaves	30
Corn, Sweet	0.05
Corn Grain, Oil	0.3
Cottonseed	0.02
Citrus Fruit	1.0
Onion, Dry Bulb	1.0
Onion, Green	7.5
Peanuts	0.2
Peanuts, Oil	0.6
Soybeans, Seed	0.5
Leafy Vegetables (Except Brassica) Group	30
Leaves of Root and Tuber Vegs. Group	50
Root Vegetable Subgroup	0.5
Tuberous and Root Vegs. Subgroup	0.03

The recommended tolerances given in Table 2 were used in these analyses with the exception of those for cottonseed, soybean oil, and sugar beets. As stated above, the Section 18 tolerances were used for these commodities. These time-limited tolerances all expire on 12/30/2001. After that date the permanent tolerances should be used in dietary exposure analyses.

For this analysis, tolerance level residues and 100 percent crop treated assumptions were made for all commodities. Processing studies show that residues do not concentrate in the following foods: citrus juice, grapes-raisins, plums-prunes (dried), potatoes-white (dry), grape juice, tomato juice, and tomatoes-puree. As a result, DEEM™ default processing factors (adjustment factors #1) were set to 1.0 for these commodities. The concentration factors for the following juice concentrates were changed to preserve the concentration ratio from juice to concentrate: grapes (3.6 to 3.0), grapefruit (8.3 to 3.9), lemons (11.4 to 5.7), limes (6 to 3), oranges (6.7 to 3.7), and tangerines (7.4 to 3.2).

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Consumption Information

HED conducts dietary risk assessments using DEEM™, which incorporates consumption data generated in USDA's Continuing Surveys of Food Intake by Individuals (CSFII), 1989-1992. For acute dietary risk assessments, one-day consumption data are summed and a food consumption distribution is calculated for each population subgroup of interest. The consumption distribution can be multiplied by a residue point estimate for a deterministic (Tier I/II type) exposure/risk assessment, or used with a residue distribution in a probabilistic (Monte Carlo) type risk assessment. Acute exposure estimates are expressed in mg/kg bw/day and as a percent of the acute PAD (aPAD). For chronic risk assessments, residue estimates for foods (e.g., apples) or food-forms (e.g., apple juice) of interest are multiplied by the averaged consumption estimate of each food/food-form of each population subgroup. Chronic exposure estimates are expressed in mg/kg bw/day and as a percent of the chronic PAD (cPAD).

Results

The FQPA Safety Factor was removed (i.e., reduced to 1x) for the U.S. population and all population subgroups. As a result, the aPAD (acute PAD) and cPAD (chronic PAD) are equivalent to the acute RfD and chronic RfD, respectively. HED's level of concern is 100% of the PAD. That is, estimated exposures above this level are of concern, while estimated exposures at or below this level are not of concern. The DEEM analyses estimate the dietary exposure of the U.S. population and 26 population subgroups. The results reported in Tables 3 and 4 are for the U.S. Population (total), all infants (<1 year old), the 2 subgroups comprised of children only, the female subgroup with the highest exposure of the female subgroups, and the male subgroup with the highest exposure of the male subgroups. The subgroups which had few respondents in the 1989-1992 CSFII are not included. The subgroups which are broken down by region, season, and ethnicity are also not included. HED notes that there is a degree of uncertainty in extrapolating exposures for certain population subgroups which may not be sufficiently represented in the consumption surveys, (e.g., nursing infants, non-nursing infants, females 13+(preg/not nursing)). Therefore, risks estimated for these subpopulations were included in representative populations having sufficient numbers of survey respondents (e.g., all infants or females, 13-50 years).

Table 3. Results of Acute Dietary Exposure Analysis at the 95th Percentile of Exposure

Subgroup	Exposure (mg/kg)	% aPAD
U.S. Population (total)	0.075860	11
All Infants (< 1 year)	0.046999	7.0
Children 1-6 years	0.130133	19

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Children 7-12 years	0.091091	14
Females 20+ (not preg or nsg)	0.077027	12
Males 20+ years	0.063933	9.5

Table 4. Chronic Dietary Exposure Summary

Subgroup	Exposure (mg/kg/day)	% cPAD
U.S. Population (total)	0.021140	12
All Infants (< 1 year)	0.017058	9.5
Children 1-6 years	0.033105	18
Children 7-12 years	0.023923	13
Females 20+ (not preg or nsg)	0.021408	12
Males 20+ years	0.018109	10

Discussion

The Tier 1 acute and chronic dietary exposure analyses for azoxystrobin are conservative estimates of dietary exposure with tolerance level residues and 100% crop treated. The estimated risk from acute and chronic dietary exposure to azoxystrobin as represented by the %cPAD is below HED's level of concern for the U.S. population and all population subgroups.

Attachments: 1. Commodity Residue List
2. Acute Dietary Exposure Analysis Results
3. Chronic Dietary Exposure Analysis Results

cc: D. Dotson, L. Richardson (CEB1)

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Attachment 1: Commodity Residue List

Chemical: AZOXYSTROBIN Filename: C:\doug\resdata\azoxy14.RS7
RfD(Chronic): 0.18 mg/kg bw/day NOEL(Chronic): 18.2 mg/kg bw/day
RfD(Acute): 0.67 mg/kg bw/day NOEL(Acute): 200 mg/kg bw/day
Date created/last modified: 09-05-2000/14:45:44/8 Program ver. 7.075

Food Code	Crop Grp	Food Name	Def Res (ppm)	Adj.Factors #1	#2	Comment
40	14	Almonds	0.020000	1.000	1.000	7F4864
498	4A	Amaranth	30.000000	1.000	1.000	New: 9F6058
410	12	Apricot juice	1.500000	1.000	1.000	8F4995
59	12	Apricots	1.500000	1.000	1.000	8F4995
60	12	Apricots-dried	1.500000	6.000	1.000	8F4995
203	1CD	Artichokes-jerusalem	0.030000	1.000	1.000	New: 9F6058
497	9B	Balsam pear	0.300000	1.000	1.000	7F4864
72	0	Bananas	0.100000	1.000	1.000	8F4995
73	0	Bananas-dried	0.100000	3.900	1.000	8F4995
378	0	Bananas-juice	0.100000	1.000	1.000	8F4995
265	15	Barley	0.100000	1.000	1.000	New: 9F6058
229	6C	Beans-dry-lima	0.200000	1.000	1.000	99DE0009
233	6B	Beans-succulent-lima	0.200000	1.000	1.000	99DE0009
51	14	Beech-nuts	0.020000	1.000	1.000	7F4864
323	M	Beef-dried	0.010000	1.920	1.000	7F4864
324	M	Beef-fat w/o bones	0.030000	1.000	1.000	7F4864
325	M	Beef-kidney	0.070000	1.000	1.000	7F4864
327	M	Beef-lean (fat/free) w/o bones	0.010000	1.000	1.000	7F4864
326	M	Beef-liver	0.070000	1.000	1.000	7F4864
321	M	Beef-meat byproducts	0.070000	1.000	1.000	7F4864
322	M	Beef-other organ meats	0.070000	1.000	1.000	7F4864
197	1AB	Beets-garden-roots	0.500000	1.000	1.000	New: 9F6058
165	2	Beets-garden-tops(greens)	50.000000	1.000	1.000	New: 9F6058
152	9B	Bitter melon	0.300000	1.000	1.000	7F4864
452	5B	Bok choy	25.000000	1.000	1.000	99GA0009
41	14	Brazil nuts	0.020000	1.000	1.000	7F4864
168	5A	Broccoli	25.000000	1.000	1.000	99GA0009
451	5A	Broccoli-chinese	25.000000	1.000	1.000	99GA0009
169	5A	Brussels sprouts	25.000000	1.000	1.000	99GA0009
382	1AB	Burdock	0.500000	1.000	1.000	New: 9F6058
49	14	Butter nuts	0.020000	1.000	1.000	7F4864
170	5A	Cabbage-green and red	25.000000	1.000	1.000	99GA0009
383	5B	Cabbage-savoy	25.000000	1.000	1.000	99GA0009
301	0	Canola oil (rape seed oil)	1.000000	1.000	1.000	8F4995
198	1AB	Carrots	0.500000	1.000	1.000	New: 9F6058
143	9A	Casabas	0.300000	1.000	1.000	7F4864
42	14	Cashews	0.020000	1.000	1.000	7F4864
222	1CD	Cassava (yuca blanca)	0.030000	1.000	1.000	New: 9F6058
171	5A	Cauliflower	25.000000	1.000	1.000	99GA0009
199	1AB	Celeriac	0.500000	1.000	1.000	New: 9F6058
166	4B	Celery	30.000000	1.000	1.000	New: 9F6058
384	4B	Celery juice	30.000000	1.000	1.000	New: 9F6058
61	12	Cherries	1.500000	1.000	1.000	7F4864
62	12	Cherries-dried	1.500000	4.000	1.000	7F4864
63	12	Cherries-juice	1.500000	1.500	1.000	7F4864
447	4A	Chervil	30.000000	1.000	1.000	New: 9F6058
43	14	Chestnuts	0.020000	1.000	1.000	7F4864
114	1AB	Chicory	0.500000	1.000	1.000	New: 9F6058
167	4A	Chicory(french/belgian endive)	30.000000	1.000	1.000	New: 9F6058
386	9B	Christophine	0.300000	1.000	1.000	7F4864
20	10	Citrus citron	1.000000	1.000	1.000	New: 9F6058
172	5B	Collards	25.000000	1.000	1.000	99GA0009
121	19B	Coriander	30.000000	1.000	1.000	New: 9F6058
267	15	Corn grain-bran	0.050000	1.000	1.000	New: 9F6058

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266	15	Corn grain-endosperm	0.050000	1.000	1.000	New: 9F6058
289	15	Corn grain-oil	0.300000	1.000	1.000	New: 9F6058
268	15	Corn grain/sugar/hfcs	0.050000	1.500	1.000	New: 9F6058
388	15	Corn grain/sugar-molasses	0.050000	1.500	1.000	New: 9F6058
237	15	Corn/pop	0.050000	1.000	1.000	New: 9F6058
238	15	Corn/sweet	0.050000	1.000	1.000	New: 9F6058
291	O	Cottonseed-meal	0.100000	1.000	1.000	00LA0009 (0.02 after 12/31/01: 9F6058)
290	O	Cottonseed-oil	0.100000	1.000	1.000	00LA0009 (0.02 after 12/31/01: 9F6058)
144	9A	Crenshaws	0.300000	1.000	1.000	7F4864
180	4A	Cress-garden/field	30.000000	1.000	1.000	New: 9F6058
191	4A	Cress-upland	30.000000	1.000	1.000	New: 9F6058
148	9B	Cucumbers	0.300000	1.000	1.000	7F4864
177	4A	Dandelion-greens	30.000000	1.000	1.000	New: 9F6058
178	4A	Endive-curley and escarole	30.000000	1.000	1.000	New: 9F6058
44	14	Filberts (hazelnuts)	0.020000	1.000	1.000	7F4864
202	3	Garlic	1.000000	1.000	1.000	New: 9F6058
124	1CD	Ginger	0.030000	1.000	1.000	New: 9F6058
450	1AB	Ginseng	0.500000	1.000	1.000	New: 9F6058
330	M	Goat-fat w/o bone	0.030000	1.000	1.000	7F4864
331	M	Goat-kidney	0.070000	1.000	1.000	7F4864
333	M	Goat-lean (fat/free) w/o bone	0.010000	1.000	1.000	7F4864
332	M	Goat-liver	0.070000	1.000	1.000	7F4864
328	M	Goat-meat byproducts	0.070000	1.000	1.000	7F4864
329	M	Goat-other organ meats	0.070000	1.000	1.000	7F4864
23	10	Grapefruit-juice	1.000000	1.000	1.000	New: 9F6058
441	10	Grapefruit-juice-concentrate	1.000000	3.900	1.000	New: 9F6058
448	10	Grapefruit peel	1.000000	1.000	1.000	New: 9F6058
22	10	Grapefruit-peeled fruit	1.000000	1.000	1.000	New: 9F6058
13	O	Grapes	1.000000	1.000	1.000	5F4541
15	O	Grapes-juice	1.000000	1.000	1.000	5F4541
392	O	Grapes-juice-concentrate	1.000000	3.000	1.000	5F4541
195	O	Grapes-leaves	1.000000	1.000	1.000	5F4541
14	O	Grapes-raisins	1.000000	1.000	1.000	5F4541
315	O	Grapes-wine and sherry	1.000000	1.000	1.000	5F4541
45	14	Hickory nuts	0.020000	1.000	1.000	7F4864
334	M	Horsemeat	0.010000	1.000	1.000	7F4864
126	1AB	Horseradish	0.500000	1.000	1.000	New: 9F6058
174	5B	Kale	25.000000	1.000	1.000	99GA0009
175	5A	Kohlrabi	25.000000	1.000	1.000	99GA0009
24	10	Kumquats	1.000000	1.000	1.000	New: 9F6058
204	3	Leeks	7.500000	1.000	1.000	New: 9F6058
28	10	Lemons-juice	1.000000	1.000	1.000	New: 9F6058
442	10	Lemons-juice-concentrate	1.000000	5.700	1.000	New: 9F6058
27	10	Lemons-peel	1.000000	1.000	1.000	New: 9F6058
26	10	Lemons-peeled fruit	1.000000	1.000	1.000	New: 9F6058
182	4A	Lettuce-unspecified	30.000000	1.000	1.000	New: 9F6058
176	4A	Lettuce-leafy varieties	30.000000	1.000	1.000	New: 9F6058
192	4A	Lettuce-head varieties	30.000000	1.000	1.000	New: 9F6058
32	10	Limes-juice	1.000000	1.000	1.000	New: 9F6058
443	10	Limes-juice-concentrate	1.000000	3.000	1.000	New: 9F6058
31	10	Limes-peel	1.000000	1.000	1.000	New: 9F6058
30	10	Limes-peeled fruit	1.000000	1.000	1.000	New: 9F6058
46	14	Macadamia nuts (bush nuts)	0.020000	1.000	1.000	7F4864
141	9A	Melons-cantaloupes-juice	0.300000	1.000	1.000	7F4864
142	9A	Melons-cantaloupes-pulp	0.300000	1.000	1.000	7F4864
145	9A	Melons-honeydew	0.300000	1.000	1.000	7F4864
146	9A	Melons-persian	0.300000	1.000	1.000	7F4864
398	D	Milk-based water	0.006000	1.000	1.000	7F4864
319	D	Milk-fat solids	0.006000	1.000	1.000	7F4864
318	D	Milk-nonfat solids	0.006000	1.000	1.000	7F4864
320	D	Milk sugar (lactose)	0.006000	1.000	1.000	7F4864
183	5B	Mustard greens	25.000000	1.000	1.000	99GA0009
64	12	Nectarines	1.500000	1.000	1.000	8F4995
397	9B	Okra/chinese (luffa)	0.300000	1.000	1.000	7F4864
206	3	Onions-dehydrated or dried	1.000000	9.000	1.000	New: 9F6058
205	3	Onions-dry-bulb (cipollini)	1.000000	1.000	1.000	New: 9F6058
262	3	Onions-green	7.500000	1.000	1.000	New: 9F6058
36	10	Oranges-juice	1.000000	1.000	1.000	New: 9F6058

33	10	Oranges-juice-concentrate	1.000000	3.700	1.000	New: 9F6058
35	10	Oranges-peel	1.000000	1.000	1.000	New: 9F6058
34	10	Oranges-peeled fruit	1.000000	1.000	1.000	New: 9F6058
184	4A	Parsley	30.000000	1.000	1.000	New: 9F6058
225	1AB	Parsley roots	0.500000	1.000	1.000	New: 9F6058
220	1AB	Parsnips	0.500000	1.000	1.000	New: 9F6058
65	12	Peaches	1.500000	1.000	1.000	8F4995
66	12	Peaches-dried	1.500000	7.000	1.000	8F4995
402	12	Peaches-juice	1.500000	1.000	1.000	8F4995
403	0	Peanuts-butter	0.200000	1.890	1.000	6F4762
940	0	Peanuts-hulled	0.200000	1.000	1.000	6F4762
293	0	Peanuts-oil	0.600000	1.000	1.000	6F4762
47	14	Pecans	0.020000	1.000	1.000	6F4642
50	0	Pistachio nuts	0.020000	1.000	1.000	7F4864
480	0	Plantains-green	0.100000	1.000	1.000	8F4995
94	0	Plantains-ripe	0.100000	1.000	1.000	8F4995
481	0	Plantains-dried	0.100000	3.900	1.000	8F4995
67	12	Plums (damsons)	1.500000	1.000	1.000	8F4995
68	12	Plums-prunes (dried)	1.500000	1.000	1.000	8F4995
69	12	Plums/prune-juice	1.500000	1.400	1.000	8F4995
344	M	Pork-fat w/o bone	0.010000	1.000	1.000	7F4864
345	M	Pork-kidney	0.010000	1.000	1.000	7F4864
347	M	Pork-lean (fat free) w/o bone	0.010000	1.000	1.000	7F4864
346	M	Pork-liver	0.010000	1.000	1.000	7F4864
342	M	Pork-meat byproducts	0.010000	1.000	1.000	7F4864
343	M	Pork-other organ meats	0.010000	1.000	1.000	7F4864
210	1C	Potatoes/white-dry	0.030000	1.000	1.000	New: 9F6058
209	1C	Potatoes/white-peeled	0.030000	1.000	1.000	New: 9F6058
211	1C	Potatoes/white-peel only	0.030000	1.000	1.000	New: 9F6058
208	1C	Potatoes/white-unspecified	0.030000	1.000	1.000	New: 9F6058
207	1C	Potatoes/white-whole	0.030000	1.000	1.000	New: 9F6058
149	9B	Pumpkin	0.300000	1.000	1.000	7F4864
407	1AB	Radishes-japanese (daiken)	0.500000	1.000	1.000	New: 9F6058
212	1AB	Radishes-roots	0.500000	1.000	1.000	New: 9F6058
213	2	Radishes-tops	50.000000	1.000	1.000	New: 9F6058
185	4B	Rhubarb	30.000000	1.000	1.000	New: 9F6058
408	15	Rice-bran	5.000000	1.000	1.000	7F4864
271	15	Rice-milled (white)	5.000000	1.000	1.000	7F4864
270	15	Rice-rough (brown)	5.000000	1.000	1.000	7F4864
214	1AB	Rutabagas-roots	0.500000	1.000	1.000	New: 9F6058
215	2	Rutabagas-tops	50.000000	1.000	1.000	New: 9F6058
216	1AB	Salsify(oyster plant)	0.500000	1.000	1.000	New: 9F6058
217	3	Shallots	7.500000	1.000	1.000	New: 9F6058
338	M	Sheep-fat w/o bone	0.030000	1.000	1.000	7F4864
339	M	Sheep-kidney	0.070000	1.000	1.000	7F4864
341	M	Sheep-lean (fat free) w/o bone	0.010000	1.000	1.000	7F4864
340	M	Sheep-liver	0.070000	1.000	1.000	7F4864
336	M	Sheep-meat byproducts	0.070000	1.000	1.000	7F4864
337	M	Sheep-other organ meats	0.070000	1.000	1.000	7F4864
303	6A	Soybean-other	0.500000	1.000	1.000	New: 9F6058
307	6A	Soybeans-flour (defatted)	0.500000	1.000	1.000	New: 9F6058
306	6A	Soybeans-flour (low fat)	0.500000	1.000	1.000	New: 9F6058
305	6A	Soybeans-flour (full fat)	0.500000	1.000	1.000	New: 9F6058
304	6A	Soybeans-mature seeds dry	0.500000	1.000	1.000	New: 9F6058
297	6A	Soybeans-oil	2.000000	1.000	1.000	98AR0012 (0.5 after 12/30/01: 9F6058)
482	0	Soybeans-protein isolate	0.500000	1.000	1.000	New: 9F6058
255	6A	Soybeans-sprouted seeds	0.500000	0.330	1.000	New: 9F6058
186	4A	Spinach	30.000000	1.000	1.000	New: 9F6058
150	9B	Squash-summer	0.300000	1.000	1.000	7F4864
415	9B	Squash-spaghetti	0.300000	1.000	1.000	7F4864
151	9B	Squash-winter	0.300000	1.000	1.000	7F4864
17	0	Strawberries	10.000000	1.000	1.000	98FL0022
416	0	Strawberries-juice	10.000000	1.000	1.000	98FL0022
282	1A	Sugar-beet	0.700000	1.000	1.000	98MN0020 (0.5 after 12/30/01: 9F6058)
379	1A	Sugar-beet-molasses	0.700000	1.000	1.000	98MN0020 (0.5 after 12/30/01: 9F6058)
218	1CD	Sweet potatoes (incl yams)	0.030000	1.000	1.000	New: 9F6058
418	2	Sweet potatos-leaves	50.000000	1.000	1.000	New: 9F6058
187	4B	Swiss chard	30.000000	1.000	1.000	New: 9F6058

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37	10	Tangelos	1.000000	1.000	1.000	New: 9F6058
38	10	Tangerines	1.000000	1.000	1.000	New: 9F6058
39	10	Tangerines-juice	1.000000	1.000	1.000	New: 9F6058
420	10	Tangerines-juice-concentrate	1.000000	3.200	1.000	New: 9F6058
201	1CD	Taro-root	0.030000	1.000	1.000	New: 9F6058
190	2	Taro-greens	50.000000	1.000	1.000	New: 9F6058
163	8	Tomatoes-catsup	0.600000	1.000	1.000	6F4762
423	8	Tomatoes-dried	0.200000	14.300	1.000	6F4762
160	8	Tomatoes-juice	0.200000	1.000	1.000	6F4762
162	8	Tomatoes-paste	0.600000	1.000	1.000	6F4762
161	8	Tomatoes-puree	0.200000	1.000	1.000	6F4762
159	8	Tomatoes-whole	0.200000	1.000	1.000	6F4762
153	O	Towelgourd	0.300000	1.000	1.000	7F4864
137	1CD	Turmeric	0.030000	1.000	1.000	New: 9F6058
219	1AB	Turnips-roots	0.500000	1.000	1.000	New: 9F6058
188	2	Turnips-tops	50.000000	1.000	1.000	New: 9F6058
429	M	Veal-dried	0.010000	1.920	1.000	7F4864
424	M	Veal-fat w/o bones	0.030000	1.000	1.000	7F4864
426	M	Veal-kidney	0.070000	1.000	1.000	7F4864
425	M	Veal-lean (fat free) w/o bones	0.010000	1.000	1.000	7F4864
427	M	Veal-liver	0.070000	1.000	1.000	7F4864
430	M	Veal-meat byproducts	0.070000	1.000	1.000	7F4864
428	M	Veal-other organ meats	0.070000	1.000	1.000	7F4864
431	14	Walnut oil	0.020000	1.000	1.000	7F4864
48	14	Walnuts	0.020000	1.000	1.000	7F4864
189	O	Watercress	1.000000	1.000	1.000	98AL0005 (Expires 10/30/2000)
147	9A	Watermelon	0.300000	1.000	1.000	7F4864
436	9A	Watermelon-juice	0.300000	1.000	1.000	7F4864
278	15	Wheat-bran	0.200000	1.000	1.000	7F4864
279	15	Wheat-flour	0.100000	1.000	1.000	7F4864
277	15	Wheat-germ	0.100000	1.000	1.000	7F4864
437	15	Wheat-germ oil	0.100000	1.000	1.000	7F4864
276	15	Wheat-rough	0.100000	1.000	1.000	7F4864
439	9B	Wintermelon	0.300000	1.000	1.000	7F4864
221	1CD	Yam-bean tuber (jicama)	0.030000	1.000	1.000	New: 9F6058
224	1CD	Yautia (tanier)	0.030000	1.000	1.000	New: 9F6058

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Attachment 2: Acute Dietary Exposure Analysis Results

U.S. Environmental Protection Agency Ver. 7.075
DEEM ACUTE analysis for AZOXYSTROBIN (1989-92 data)
Residue file: azoxy14.RS7 Adjustment factor #2 NOT used.
Analysis Date: 09-06-2000/10:49:39 Residue file dated: 09-06-2000/10:31:45/8
NOEL (Acute) = 200.000000 mg/kg body-wt/day
RfD (Acute) = 0.67 mg/kg
PAD (Acute) = 0.67 mg/kg
Daily totals for food and foodform consumption used.

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Summary calculations (per capita):

	95th Percentile			99th Percentile			99.9th Percentile	
	Exposure	% aRfD	MOE	Exposure	% aRfD	MOE	Exposure	% aRfD	MOE
U.S. Population:	0.075860	11.32	2636	0.146413	21.85	1366	0.318726	47.57	627
U.S. Population (spring season):	0.080555	12.02	2482	0.149316	22.29	1339	0.294004	43.88	680
U.S. Population (summer season):	0.074244	11.08	2693	0.146457	21.86	1365	0.397519	59.33	503
U.S. Population (autumn season):	0.070989	10.60	2817	0.149379	22.30	1338	0.318895	47.60	627
U.S. Population (winter season):	0.077654	11.59	2575	0.136707	20.40	1462	0.278826	41.62	717
Northeast region:	0.078422	11.70	2550	0.158026	23.59	1265	0.284571	42.47	702
Midwest region:	0.064697	9.66	3091	0.127023	18.96	1574	0.318396	47.52	628
Southern region:	0.078447	11.71	2549	0.148491	22.16	1346	0.321870	48.04	621
Western region:	0.080246	11.98	2492	0.146584	21.88	1364	0.368215	54.96	543
Hispanics:	0.062524	9.33	3198	0.111375	16.62	1795	0.260484	38.88	767
Non-hispanic whites:	0.073954	11.04	2704	0.131557	19.64	1520	0.323663	48.31	617
Non-hispanic blacks:	0.098042	14.63	2039	0.195339	29.16	1023	0.320951	47.90	623
Non-hisp/non-white/non-black:	0.111701	16.67	1790	0.261131	38.97	765	0.332096	49.57	602
All infants:	0.046999	7.01	4255	0.130625	19.50	1531	0.302769	45.19	660
Nursing infants (<1 yr old):	0.030868	4.61	6479	0.046436	6.93	4307	0.189229	28.24	1056
Non-nursing infants (<1 yr old):	0.058642	8.75	3410	0.131049	19.56	1526	0.301251	44.96	663
Children 1-6 yrs:	0.130133	19.42	1536	0.288558	43.07	693	0.430644	64.28	464
Children 7-12 yrs:	0.091091	13.60	2195	0.155064	23.14	1289	0.367179	54.80	544

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U.S. Environmental Protection Agency Ver. 7.075
DEEM ACUTE analysis for AZOXYSTROBIN (1989-92 data)
Residue file: azoxy14.RS7 Adjustment factor #2 NOT used.
Analysis Date: 09-06-2000/10:49:39 Residue file dated: 09-06-2000/10:31:45/8
NOEL (Acute) = 200.000000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: ""

Summary calculations:

	95th Percentile			99th Percentile			99.9th Percentile	
Exposure	aRfD	MOE	Exposure	aRfD	MOE	Exposure	aRfD	MOE
Females 13+ (preg/not nursing):								
0.061744	9.22	3239	0.127338	19.01	1570	0.240488	35.89	831
Females 13+ (nursing):								
0.082883	12.37	2413	0.194184	28.98	1029	0.194636	29.05	1027
Females 13-19 (not preg or nursing):								
0.065651	9.80	3046	0.132378	19.76	1510	0.236282	35.27	846
Females 20+ (not preg or nursing):								
0.077027	11.50	2596	0.130141	19.42	1536	0.222289	33.18	899
Females 13-50 yrs:								
0.072199	10.78	2770	0.125523	18.73	1593	0.221221	33.02	904
Males 13-19 yrs:								
0.056565	8.44	3535	0.097367	14.53	2054	0.168634	25.17	1186
Males 20+ yrs:								
0.063933	9.54	3128	0.108199	16.15	1848	0.202019	30.15	990
Seniors 55+:								
0.080497	12.01	2484	0.132638	19.80	1507	0.242014	36.12	826
Pacific:								
0.085188	12.71	2347	0.156544	23.36	1277	0.395431	59.02	505

Attachment 3: Chronic Dietary Exposure Analysis Results

U.S. Environmental Protection Agency Ver. 7.075
DEEM Chronic analysis for AZOXYSTROBIN (1989-92 data)
Residue file name: C:\doug\resdata\azoxy14.RS7 Adjustment factor #2 NOT used.
Analysis Date 09-06-2000/10:44:57 Residue file dated: 09-06-2000/10:31:45/8
Reference dose (RfD, Chronic) = 0.18 mg/kg bw/day
Population Adjusted Dose (PAD, Chronic) = 0.18 mg/kg bw/day

Total exposure by population subgroup

Population Subgroup	Total Exposure mg/kg body wt/day	Total Exposure Percent of PAD
U.S. Population (total)	0.021140	11.7%
U.S. Population (spring season)	0.022585	12.5%
U.S. Population (summer season)	0.021033	11.7%
U.S. Population (autumn season)	0.019713	11.0%
U.S. Population (winter season)	0.021372	11.9%
Northeast region	0.022540	12.5%
Midwest region	0.018048	10.0%
Southern region	0.021018	11.7%
Western region	0.023626	13.1%
Hispanics	0.019976	11.1%
Non-hispanic whites	0.020592	11.4%
Non-hispanic blacks	0.023517	13.1%
Non-hisp/non-white/non-black	0.030368	16.9%
All infants (< 1 year)	0.017058	9.5%
Nursing infants	0.005521	3.1%
Non-nursing infants	0.021913	12.2%
Children 1-6 yrs	0.033105	18.4%
Children 7-12 yrs	0.023923	13.3%
Females 13-19 (not preg or nursing)	0.017526	9.7%
Females 20+ (not preg or nursing)	0.021408	11.9%
Females 13-50 yrs	0.019617	10.9%
Females 13+ (preg/not nursing)	0.017196	9.6%
Females 13+ (nursing)	0.025948	14.4%
Males 13-19 yrs	0.015526	8.6%
Males 20+ yrs	0.018109	10.1%
Seniors 55+	0.022427	12.5%
Pacific Region	0.024799	13.8%

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Attachment 5

Risk Assessment of New Uses:

DATE: November 24, 1999

SUBJECT: Azoxystrobin (128810) in/on Barley, Bulb Vegetables, Citrus Fruits, Corn (Field & Sweet Corn), Cotton, Root & Tuber Vegetables, Tops of Root & Tuber Vegetables, Leafy Vegetables & Cilantro, Peanuts, Soybeans, and Wild Rice.
DP: D260137

FROM: Thuy L. Nguyen, MS, Chemist
William Erickson, Ph D, Biologist
Environmental Risk Branch III/EFED (7507C)

THRU: Daniel Rieder, Branch Chief
Environmental Risk Branch III/EFED (7507C)

TO: Cynthia Giles-Parker, Product Manager
John Bazuin, PM Team Reviewer
Registration Division (7505C)

The Environmental Risk Branch III of EFED has completed the environmental fate and effects risk assessment for the proposed new uses of azoxystrobin. This report uses the information provided in the June 23, 1998 review of azoxystrobin use on Muscadines, Plantains, Almonds, Tree Nuts, Pistachios, Rice, Cucurbits, and Wheat, and was developed by comparing the risk of the new uses against the previous uses. The comparison was made on application rates, crop types, and agricultural conditions of the uses (temperature, rainfall, and soil series).

Application information for the proposed new uses is tabulated below.

Crop	Application Rate (lb ai/A)	Interval (days between application)	Maximum lb ai/A/year
Barley	0.1 - 0.2		0.4
Bulb Vegetables	0.1 - 0.25	5 - 7	1.5
Citrus Fruit	0.2 - 0.25	7 - 21	1.5
Corn	0.1 - 0.25	7 - 14	2
Cotton	0.1 - 0.2 oz ai per 1000ft of row	0	0.2 oz ai per 1000ft of row (0.172 lb ai/A/year)
Tuber Vegetables	0.1 - 0.33	7 - 14	2
Leafy Vegetables	0.1 - 0.25	5 - 7	1.5
Peanut	0.1 - 0.4	10 -14	0.8
Soybean	0.15 - 0.25		1.5
Wild Rice	0.1 - 0.3	7 - 14	0.7

Risk Overview

Although moderately persistent in soils and stable to hydrolysis, the likelihood of azoxystrobin moving into ground and surface water is low due to high soil/water partitioning coefficients and low single application rates. However, with multiple applications and repeated usage, azoxystrobin and especially its degradate (compound 2) may eventually build up in environmental compartments and move into drinking water resources. Compound 2 has greater potential to leach into ground water than the parent as indicated in the terrestrial field studies. In these studies, the parent azoxystrobin remained on the soil surface whereas compound 2 was detected in deeper soil profiles.

Based on the information provided in the June 23, 1998 report and the new use patterns, the following risks are presumed for the new uses:

	Acute High Risk	Acute Restricted Use	Acute Endangered Species	Chronic Risk
Birds & Mammals				
Freshwater Fish		Wild Rice, Tuber Vegetables, and Citrus Fruits	Wild Rice, Tuber Vegetables, and Citrus Fruits	
Freshwater Invertebrates		Wild Rice, Tuber Vegetables, and Citrus Fruits	Wild Rice, Barley, Tuber Vegetables, and Citrus Fruits	Wild Rice
Estuarine/Marine Fish				
Estuarine/Marine Invertebrates	Citrus Fruit and Tuber Vegetables	Citrus Fruit, Corn, Tuber Vegetables, Bulb Vegetables, Leafy Vegetables, Peanut, and Soybean	* Citrus Fruit, Corn, Tuber Vegetables, Bulb Vegetables, Leafy Vegetables, Peanut, and Soybean	Citrus Fruit, Corn, Tuber Vegetables, Bulb Vegetables, Leafy Vegetables, Peanut, and Soybean
Terrestrial plants				
Aquatic Plants	Wild Rice			

* - Note that there are no federally listed threatened or endangered estuarine/marine invertebrate species.

Minimal risk is presumed for Barley and Cotton.

Environmental Fate

According to previously submitted data, the primary dissipation pathway of azoxystrobin is by photodegradation in soil (t ½ = 18 to 28 days) and water (t ½ = 11 to 17 days). Azoxystrobin may also be susceptible to runoff and leaching since it is stable to hydrolysis and moderately persistent in aerobic (DT_{50} = 54 to 164 days) and anaerobic soils (DT_{50} = 49 to 56 days). However, EFED believes that the magnitude of the azoxystrobin partitioning coefficients

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(K_d = 1.5 to 23 mL/g) will limit its leaching potential into ground water. Also, since azoxystrobin is mostly foliarly applied to treat fungal diseases, foliar interception and subsequent photodegradation on foliage could substantially reduce the amount of azoxystrobin reaching soil surfaces, and consequently the amount available for leaching and runoff. Azoxystrobin transformation products, Compound 2 (R234886), Compound 28 (R401553), and Compound 30 (R402173), exhibit much lower soil/binding affinity (K_d = 0.35 to 11 mL/g) than the parent compound, and thus possess greater potential to leach through soils. One of the degradates, Compound 2, appears to be the most mobile degradate: it was detected in a majority of laboratory studies, and was also observed to leach through soil in the terrestrial field dissipation (<1% of total applied) and the aquatic soil dissipation studies (<5% of total applied). No persistence and dissipation rates have been reported for this degradate.

Ground and Surface Water Concerns

Although azoxystrobin is moderately persistent in laboratory studies, EFED believes that significant concentrations of azoxystrobin in ground water as a result of the proposed new uses are unlikely since the leaching potential of this chemical is be limited by high soil/water partitioning. Compound 2 has greater potential for moving into ground water than parent azoxystrobin, but it is also not predicted to pose a major ground water concern due to the low single application rate. However, with multiple applications, azoxystrobin and its degradate may build up in environmental compartments and eventually enter ground water resources. Therefore, if azoxystrobin use increases significantly, additional information of persistence and dissipation of Compound 2 may be required to accurately determine its potential for accumulating in the environment.

Drinking Water Resource Assessment

Presented below is a summary of the Drinking Water Assessment reported in the June 23, 1998 review. Tier I drinking water EECs were estimated using GENEEC (Generic Expected Environmental Concentration) and SCI-GROW (Screening Concentration in Ground Water) models. Refined Tier II estimated environmental surface water concentrations were also presented based on PRZM (Pesticide Root Zone Model version 3.1) and EXAMS (Exposure Analysis Modeling Systems version 2.97.5) models. Since azoxystrobin is a new chemical, monitoring data are not available to confirm surface and ground water Estimated Environmental Concentrations (EECs).

Ground Water Modeling

The SCI-GROW screening model developed in EFED estimates potential ground water concentrations under hydrologically vulnerable conditions. Based on the highest use rate (turf use, 9 applications per year, 10-day interval, and 0.55 lb ai/A/application), the upper-bound concentration of azoxystrobin was estimated at 0.06 ppb.

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Surface Water Modeling

Tier I Modeling: The GENEEC model indicates that the maximum surface water concentration of azoxystrobin on a variety of crops ranges from 13 ppb for wheat to 141 for turf.

Crops	Application Rate (lb ai/A)	No. of Appl.	Application Interval	Initial EEC (ppb)	21-day EEC (ppb)	56-60-day EEC (ppb)
Wheat	0.20	2	10	13	13	12
Bananas	0.10-0.135	8	5-12	31	29	28
Pecans	0.15-0.20	6-8	7	37	36	33
Peanuts	0.40	2	30	26	25	24
Grapes	0.25	6	7-10	46	44	42
Turf	0.55	9	10	141	135	127
Rice *	0.25	3	7	117	108	95

* Modified GENEEC (GENEECX) for aquatic use.

It is not expected that the proposed new uses will result in drinking water EECs higher that those reported for the previous uses.

Refined EECs for Aquatic Exposure

Since PRZM/EXAMS scenarios are not available for every crop, the refined surface water concentrations reported in the June 23, 1998 review were based on cucurbit, peanut, grape, and almond scenarios.

Crop	Application method	Application rate #appl/interv	Peak Initial (ppb)	4-day average (ppb)	21-day average (ppb)	60-day average (ppb)	90-day average (ppb)	yearly (ppb)
Almond	Airblast/ Aerial	0.25 lb ai/A 6/10 days	4.1	4.1	3.8	3.5	3.2	2.1
Cucurbits	Aerial	0.25 lb ai/A 6/7 days	32	31	30	28	26	14
Grapes	Airblast/ Aerial	0.25 lb ai/A 6/14	5	4.9	4.6	4.2	3.9	2.7
Peanuts	Aerial	0.4 lb ai/A 2/30	11.3	11.1	10.3	9.5	8.8	4.1

EFED did not perform additional surface water modeling for the proposed new uses. The risks associated with the new uses are assessed by comparing the application rates, the crop types, and the agricultural conditions of the proposed new crops versus the above listed crops.

1. The new proposed use on wild rice should not result in surface water

concentrations higher than rice (Tier I model).

2. The application rates suggest that the EECs of barley and cotton should not exceed those of wheat (Tier I model).

3. Corn has a higher use rate than cucurbits. However, EFED believes that the EECs for corn will be much lower than cucurbits, since runoff is more favorable on cucurbit than on corn crop: corn is simulated on moderately well drained soils (Central Ohio), while the cucurbit analysis was simulated on poorly drained soils. In addition, the mean annual precipitation for cucurbits is 62 inches, while only 36 inches was recorded for corn (Tier II model)

4. Citrus fruit has similar rates and modeling scenarios (weather and soil) as cucurbits. However, since the foliar interception of azoxystrobin by citrus trees is greater than cucurbits, EFED expects the EECs for citrus fruit to be lower than cucurbits (Tier II model).

5. Bulb vegetables, leafy vegetables, and soybean have similar use rate to cucurbits. However, based on the PRZM/EXAMS scenarios (soil type, slope of land, location, and rainfall), EFED believes that the EECs resulting from these uses will be lower than those for cucurbits (Tier II model).

6. Tuber vegetables have a relatively high use rate and are planted on poorly drained soils (South Central Panhandle) which are also subject to flooding and runoff. Therefore, the use of azoxystrobin on this crop may lead to higher surface water concentration than on cucurbits. Based on a linear extrapolation of the EEC values for cucurbits, 6 applications of 0.33 lb ai/A/each will yield average EEC of 42 ppb for peak, 40 ppb for 21-day, and 37 ppb for 60-day average. EFED expects the EECs for tuber vegetables to be comparable to or slightly higher than these extrapolated values (Tier II model).

Ecological Risks

According to the above aquatic exposure assessment and the RQ values from the June 23, 1998 report, the following ecological risks are presumed for the proposed new uses. Table I summarizes the risk conclusions from the previous uses and how those conclusions relate to the proposed new patterns.

1. Terrestrial animals: Minimal acute and chronic risks are presumed for birds and mammals.

2. Freshwater animals:

- Based the RQ for rice, wild rice RQ exceeds the LOCs for restricted use and endangered species, and for chronic risk to aquatic invertebrates. Note that the wild rice aquatic exposure assessment was based on a modified GENEEC model for aquatic use sites (i.e. rice), and the estimate should be considered conservative.

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- Based on the RQ for cucurbit. tuber vegetables and citrus fruit uses pose acute risks for restricted use and endangered species for freshwater animals.

- Based on the RQ for wheat, acute risk for endangered species is presumed for barley use

Acute high risk is not presumed for any of the new proposed uses. Except for wild rice, chronic risk is minimal for all uses.

3. Estuarine/marine animals: Azoxystrobin residues from all new proposed crops, except for barley, bulb vegetables, and wild rice, may enter estuarine/marine environments when used in coastal counties.

- Based on peanut EECs, the RQs of all new proposed crops grown in coastal counties exceeds the LOCs for estuarine/marine invertebrates endangered species. However, currently there are no federally listed threatened or endangered estuarine / marine invertebrate species.

- Based on peanut EECs, acute restricted use and chronic risk to invertebrates are presumed for all new proposed uses in coastal counties, with the exception of cotton due to its low use pattern.

- Based on cucurbit EECs, acute high risk to estuarine/marine invertebrates is presumed for citrus fruit and tuber vegetables.

- No risk is presumed to estuarine/marine fish for the above mentioned crops.

4. Plants: High risk to aquatic plants is expected for non-vascular species exposed to azoxystrobin from treated wild rice. Risks to terrestrial plants (non-endangered and endangered), and endangered aquatic plants is minimal for all other uses.

Endangered Species Concerns

Endangered species LOCs are exceeded for freshwater fish, freshwater invertebrates, and aquatic plants. Zeneca should address these concerns via the Endangered Species Task Force.

Labeling

The labeling recommended in the June 23, 1998 review is applicable to these new proposed uses.

Acknowledgment

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The review team for azoxystrobin thanks Ron Bloom for performing the secondary review of this report.

If you have questions concerning this review, please contact Thuy Nguyen at 605-0562

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Table I - **Risk Conclusions from previous assessme .nd how those conclusions relate to prop d use patterns**

Uses previously reviewed		Risk conclusions from previous review				Proposed Use patterns to which this risk applies	
Site Appl. Rate (lbs ai/A), (No Appl.) and Max appl (ai / acre /yr)	Peak EEC and long-term EEC	Freshwater Fish acute toxicity: LC50=470 ppb chronic toxicity: MATC=468 ppb	Freshwater Inverts acute toxicity: EC50=259 ppb chronic toxicity: NOAEC=44 ppb	Estuarine Fish acute toxicity: LC50=670 ppb no chronic tox data	Estuarine Invertebrates acute toxicity: EC50=56 ppb chronic toxicity: NOAEC=9.5 ppb	Use Site	Use Rate and total applied per season
			PRZM2/EXAM II				
Cucurbits 0.25 lb (6) 1.5 lb	32 ppb 28 ppb	Exceeds Endangered Species LOC	Exceeds Restricted Use and Endangered Species LOCs	No LOC exceedance[1]	Exceeds High Acute, Restricted Use, Chronic Risk LOCs[1]	Tuber vegetables Citrus	0.1-0.33 lb ai/acre Max 2 lb ai/acre/year 0.2 - 0.25 lb ai/acre Max 1.5 lb ai/acre/year
Peanuts 0.4 lb (2) 0.8 lb	11 ppb 10 ppb	No LOC exceedance	No LOC exceedance	No LOC exceedance	Exceeds Restricted Use Chronic Risk LOCs	---------- Bulb vegetables Leafy vegetables Corn Soybeans	---------- 0.1 - 0.25 lb ai/acre Max 1.5 lb ai/acre/year 0.1 - 0.25 lb ai/acre Max 1.5 lb ai/acre/year 0.1 - 0.25 lb ai/acre Max 2 lb ai/acre/year 0.15 - 0.25 lb ai/acre Max 1.5 lb ai/acre/year
			GENEEC				
Wheat 0.2 lb (2) 0.4 lb	13 ppb	No LOC exceedance	Exceeded Endangered Species LOC's	No LOC exceedance	Exceeds Restricted Use Chronic Risk LOCs	---------- Barley and cotton [2]	---------- 0.1 - 0.2 lb ai/acre Max 0.4 lb ai/acre/year 0.1-0.2 oz ai/ 1000ft Max 0.2 oz /acre/year or 0.172 lb ai/acre/year
Rice 0.25 lb (3) 0.7 lb	117 ppb 108 ppb	Exceeds Restricted Use and Endangered Species LOCs	Exceeds Restricted Use and Endangered Species LOCs	Exceeds Restricted Use and Endangered Species LOCs	Exceeds High Acute, Restricted Use, Chronic Risk LOCs	Wild Rice. The original modeling in the previous review, for rice, was with a modified GENEEC, designed for aquatic use sites like rice.	0.1-0.3 lb ai/acre Max 0.7 lb ai/acre/year

[1]In the original review, no assessment was made with estuarine species for these crops because those uses were not considered to result in significant estuarine or marine exposure. The risk conclusions presented here are based on screening level EECs compared to the toxicity of the appropriate estuarine organism. The results can be applied to new proposed use patterns that are similar to these crops and that are grown near estuaries.

[2]Use on cotton is not expected to exceed any LOCs.

Attachment 6

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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: September 21, 2000

Subject: Occupational and Residential Risk Assessment to Support Request for a Section 3 Registration of Azoxystrobin on Barley, Bulb Vegetables, Cilantro, Citrus Fruits, Corn, Cotton, Leafy Vegetables, Root and Tuber Vegetables, Peanuts, and Soybeans

DP Barcode:	PC Code:	Trade Name:	EPA Reg#	MRID#	PRAT Case	Class	Caswell#	40 CFR
D269111	128810	Heritage®	10182-408	N/A	292287	Fungicide	N/A	N/A
		Abound®	10182-415					

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

From: Kelly O'Rourke, Biologist — Kelly M. O'Rourke 21 Sept 2000
Health Effects Division
Registration Action Branch 3 (7509C)

Peer Review: Jack Arthur, Environmental Scientist — Jack Arthur 9/21/2000
Health Effects Division
Registration Action Branch 3 (7509C)

Thru: Stephen Dapson, Branch Senior Scientist — Stephen C. Dapson 09/21/2000
Health Effects Division
Registration Action Branch 3 (7509C)

Introduction

The registrant, Zeneca Ag Products, requests the establishment of tolerances for residues of the fungicide azoxystrobin on barley, bulb vegetables, citrus fruits, field corn, sweet corn, cotton, root and tuber vegetables and tops, leafy vegetables and cilantro, peanuts, soybeans, and

wild rice. Wild rice will not be included in this assessment because residue chemistry data were not adequate to support the proposed tolerance. This memorandum addresses risk from occupational and residential exposure only. An aggregate human risk assessment for azoxystrobin will be included as a separate HED memorandum.

1.0 Executive Summary

Azoxystrobin is currently registered on bananas, canola, cucurbits, stone fruits, grapes, various nuts, peanuts, potatoes, rice, tomatoes, wheat, and turfgrass/ornamentals. The formulated end use products evaluated in this assessment are labeled under the trade names Heritage® and Abound®. In this memorandum, the name azoxystrobin will be used for the active ingredient(ai) in these products.

Azoxystrobin is a broad spectrum fungicide for the control of plant diseases on agricultural crops, turf, and ornamentals. The formulations of azoxystrobin evaluated in this assessment are the flowable concentrate (i.e., Abound® 77.1% ai) and water-dispersible granule (i.e., Heritage® 50% ai). The registrant proposes multiple foliar sprays, banded, or in-furrow applications using ground, aerial, or chemigation equipment. Applications are proposed to begin prior to, or in the early stages of, disease development and continue throughout the season up to, and often including, the day of harvest. Proposed use rates are in the range of 0.1-0.4 lb ai/A/application, with a seasonal maximum of 1.5-2.0 lbs ai/A Many of the target crops may receive up to 6-8 applications during a season, at intervals of 7 to 14 days. For cotton, the use is limited to a single, soil-directed spray at-planting. There are no non-agricultural use sites associated with the proposed uses. However, there are registered non-agricultural uses; e.g., outdoor residential (lawns and ornamentals) and recreational (e.g., golf courses, parks, and athletic fields) sites.

There is a potential for occupational exposure to azoxystrobin during mixing, loading, application, and post-application activities. The HIARC did not select any dermal endpoints for azoxystrobin, because no toxicity was observed at the limit dose of 1,000 mg/kg/day. Therefore, the occupational risk assessment was based on inhalation exposure only. For handlers, daily inhalation doses were converted to oral equivalent doses, assuming an absorption factor of 100%, and compared to the oral NOAELs of 25 mg/kg/day (prenatal developmental oral study in the rat) and 20 mg/kg/day (90-day feeding study in the rat) to estimate the risk from short- and intermediate-term inhalation exposures, respectively. Chronic exposures are not expected for handlers of azoxystrobin for the proposed use patterns.

No chemical-specific handler exposure data were submitted in support of this Section 3 registration. It is the policy of the HED to use data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 as presented in PHED Surrogate Exposure Guide (8/98) to assess handler exposures for regulatory actions when chemical-specific monitoring data are not available (HED Science Advisory Council for Exposure Draft Policy # 7, dated 1/28/99).

Occupational **handlers' inhalation MOEs range from 3,900** for intermediate-term mixing loading liquids for aerial application **to 190,000** for short-term mixing/loading dry flowables for airblast application. These MOEs are greater than HED's target MOE of 100, and therefore, are not of concern.

Occupational **postapplication dermal exposure** is possible following treatment of crops with azoxystrobin. However, because no appropriate dermal endpoints were identified for this exposure potential, a **risk assessment is not required**. Postapplication inhalation exposure is expected to be negligible; therefore, a risk assessment for this route is also not required.

The azoxystrobin technical material has been classified in Toxicity Category III for acute dermal and primary eye irritation, and Toxicity Category IV for primary skin irritation. Per the Worker Protection Standard (WPS), a 12-hr restricted entry interval (REI) is required for chemicals classified under Toxicity Category III or IV, which is the shortest waiting period permitted under the WPS. However, per Pesticide Regulation Notice 95-3 (6/7/95), REIs may be further reduced from 12 hours if certain criteria are met. In a previous risk assessment (Memo, D. Dotson, D248888, 1/28/99), HED determined that the criteria established by Pesticide Regulation Notice 95-3 have been met for azoxystrobin formulated as a water-dispersible granule, and that a 4-hour REI is acceptable on the Heritage® label. However, it is not clear whether the criteria have subsequently been met for the flowable concentrate formulation. This needs to be addressed by the Registration Division (e.g., obtain acute toxicity data for the end-use product) to determine whether the Abound® label may indicate a reduction in REI to 4 hours.

Azoxystrobin is currently registered for use on residential turfgrass and ornamentals. Short-term exposures may occur during adult residential handling activities. Short- and intermediate-term exposures may occur during postapplication activities for adults and children. Because the HIARC did not select applicable dermal endpoints, **a risk assessment for dermal exposure during handling and postapplication activities is not required**. Inhalation exposure and risk estimates for adult residential handlers were assessed using the same short-term inhalation endpoint described previously for occupational exposure. HED's Draft Standard Operating Procedures (SOPs) for Residential Exposure Assessments were used as the basis for all residential handler exposure calculations.

Toddlers may receive short- and intermediate-term exposure from incidental non-dietary ingestion (i.e., hand-to-mouth, turfgrass transfer, and soil ingestion) during post-application activities on treated turf. The post-application risk assessment is based on generic assumptions as specified by the newly proposed Residential SOPs and recommended approaches by HED's Exposure Science Advisory Committee (ExpoSAC). Revisions to the Residential SOPs have been proposed that alter the residential post-application scenario assumptions. The proposed assumptions are expected to better represent residential exposure and are still considered to be high-end, screening level assumptions. HED management has authorized the use of the revised residential SOPs that were presented to the FIFRA SAP in September 1999. Therefore, HED has deviated from the current Residential SOP assumptions and uses the proposed assumptions to

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calculate exposure estimates. **All calculated non-occupational postapplication MOEs are greater than the target of 100.**

2.0 Hazard Profile

On August 15, 2000, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base on azoxystrobin, established Reference Doses (RfDs) and selected the toxicological endpoints for occupational/residential exposure and risk assessments. The Committee's conclusions are summarized in Tables 1 and 2. The potential enhanced sensitivity of infants and children from exposure to azoxystrobin as required by the Food Quality Protection Act of 1996 was previously addressed by HED's FQPA Safety Factor Committee (08/24/98).

Table 1. Acute Toxicity Data on Azoxystrobin Technical

Guideline No.	Study Type	MRID #	Results	Toxicity Category
870.1100	Acute Oral - Rat	43678122	LD_{50} > 5000 mg/kg (Limit Test) in Males & Females	IV
870.1200	Acute Dermal - Rat	43678124	LD_{50} > 2000 mg/kg (Limit Test) in Males & Females	III
870.1300	Acute Inhalation - Rat	43678126	LC_{50} Males = 0.962 mg/L (95% C.I. = 0.674, *) Females = 0.698 mg/L (95% C.I. = 0.509, 2.425) The combined LC50 was not calculated due to mortality pattern	III
870.2400	Primary Eye Irritation - Rabbit	43678128	Slight to moderate erythema and slight chemosis in all rabbits within one hour, but effects resolved within 48 hours of treatment.	III
870.2500	Primary Skin Irritation - Rabbit	43678130	Very slight erythema and edema that persisted for three days on one rabbit and for one hour on another.	IV
870.2600	Dermal Sensitization - Guinea Pig	43678132	No erythema or edema were found 38 or 48 hrs after challenge with test material.	Not a dermal sensitizer

Table 2. Summary of Toxicological Doses and Endpoints for Azoxystrobin for Use in Human Risk Assessment			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**FQPA SF and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary general population including infants and children	NOAEL < 200 mg/kg/day UF = 300 **Acute RfD** = 0.67 mg/kg/day	FQPA SF = 1X **aPAD** = acute RfD / FQPA SF = 0.67 mg/kg/day	Acute Neurotoxicity - Rat (MRID 43678134) LOAEL = 200 mg/kg based on diarrhea at two-hours post dose at all dose levels up to and including the LOAEL.
Chronic Dietary all populations	NOAEL= 18 mg//kg/day UF = 100 **Chronic RfD** = 0.18 mg/kg/day	FQPA SF = 1X **cPAD** = chronic RfD / FQPA SF = 0.18 mg/kg/day	Combined Chronic Toxicity/Carcinogenicity Feeding study - Rat (MRID 43678139) LOAEL in males/females = 34/117 mg/kg/day based on reduced body weights in both sexes and bile duct lesions in males.
Short-Term (1-7 days) Incidental Oral (Residential)	NOAEL= 25 mg//kg/day UF = 100	FQPA SF = 1X	Prenatal Developmental Oral Toxicity - Rat (MRID 43678142) LOAEL = 100 mg/kg/day based on increased maternal diarrhea, urinary incontinence, and salivation.
Intermediate-Term (1 week to several months) Incidental Oral (Residential)	NOAEL= 20 mg//kg/day UF = 100	FQPA SF = 1X	90-Day Feeding - Rat (MRID 43678135) LOAEL = 211/223 mg/kg/day in males/females based on decreased body weight gain in both sexes and clinical signs indicative of reduced nutrition.
Short-, Intermediate-, and Long-Term Dermal (Occupational/ Residential)	none	No dermal or systemic toxicity was seen at the limit dose (1000 mg/kg/day). This risk assessment is not required.	21-Day Repeated Dose Dermal - Rat (MRID 43678137)
Short-Term (1-7 days) Inhalation (Occupational/ Residential)	oral NOAEL= 25 mg/kg/day Use route-to-route extrapolation (inhalation absorption rate = 100%)	**LOC for MOE** = 100 (Occupational/ Residential)	Prenatal Developmental Oral Toxicity - Rat (MRID 43678142) LOAEL = 100 mg/kg/day based on increased maternal diarrhea, urinary incontinence, and salivation.
Intermediate-Term (1 week to several months) Inhalation (Occupational Residential)	oral NOAEL= 20 mg/kg/day Use route-to-route extrapolation (inhalation absorption rate = 100%)	**LOC for MOE** = 100 (Occupational/ Residential)	90-Day Feeding - Rat (MRID 43678135) LOAEL = 211/223 mg/kg/day in males/females based on decreased body weight gain in both sexes and clinical signs indicative of reduced nutrition.
Long-Term (> 180 days) Inhalation	NOAEL N/A	This risk assessment is not applicable to the use scenario.	

UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern.

3.0 Use Profile

Currently, azoxystrobin is registered on bananas, canola, cucurbits, stone fruits, grapes, various nuts, peanuts, potatoes, rice, tomatoes, wheat, and turfgrass/ornamentals. The proposed uses for this Section 3 petition are summarized in Table 3.

Table 3. Summary of Use Patterns/Formulation Information Relevant to Occupational Exposure/Risk Assessment

Formulation Type (% ai)	Application Method	Use Site	Application Rate (lb ai/A)	Frequency of Application (interval)	Comments
Flowable Concentrate (77.1 % ai) and Water-Dispersible Granule (50% ai)	Aerial, Chemigation, Groundboom	barley	0.10 - 0.2	2 apps (not specified)	
	Aerial, airblast	citrus	0.20 - 0.25	6 apps (7 - 21 days)	
	Aerial, Chemigation, Groundboom	corn	0.10 - 0.25	8 apps (7 - 14 days)	
	Groundboom	cotton	0.10 - 0.23	1 app (N/A)	in-furrow
	Aerial, Chemigation, Groundboom	leafy vegetables	0.10 - 0.25	6 apps (5 - 14 days)	
	Aerial, Chemigation, Groundboom	onion	0.10 - 0.25	6 apps (5 - 14 days)	
	Aerial, Chemigation, Groundboom	peanuts	0.10 - 0.40	2 apps (30 days)	
	Aerial, Chemigation, Groundboom	root & tuber vegetables	0.10 - 0.33	6 apps (5 - 14 days)	
	Aerial, Chemigation, Groundboom	soybeans	0.15 - 0.25	2 apps (not specified)	

4.0 Occupational Exposure

4.1 Handler Exposure and Risk

There is a potential for exposure to azoxystrobin during mixing, loading, and application activities. An exposure/risk assessment using applicable endpoints selected by the HIARC was performed. Handler's exposure and risk were estimated for the following scenarios: (1) mixing/loading liquids for aerial/chemigation application, (2) mixing/loading liquids for groundboom application, (3) mixing/loading liquids for airblast sprayer, (4) mixing/loading dry flowable for aerial/chemigation application, (5) mixing/loading dry flowable for groundboom application, (6) mixing/loading dry flowable for airblast sprayer, (7) applying sprays with fixed-wing aircraft, (8) applying sprays with a groundboom sprayer, (9) applying sprays with an

airblast sprayer, and (10) flagging sprays for aerial operations. Flaggers for aerial application are assessed for 350 acres per day application, because a larger number of acres treated would likely require pilot-activated mechanical flagging or Global Positioning Systems, and not human flaggers.

The minimum level of PPE for handlers is based on acute toxicity for the end-use products. The Registration Division (RD) is responsible for ensuring that PPE listed on the label is in compliance with the Worker Protection Standard (WPS).

No chemical-specific handler exposure data were submitted in support of this Section 3 registration. In accordance with HED's Exposure Science Advisory Council (SAC) policy, exposure data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 as presented in PHED Surrogate Exposure Guide (8/98) were used with other HED default values for acres treated per day, body weight, and the level of personal protective equipment to assess handler exposures. The water-dispersible granular formulation is also known as a dry flowable formulation. The flowable concentrate is considered the same as an emulsifiable concentrate (i.e., liquid) for exposure assessment purposes.

As mentioned previously, no dermal endpoint was selected for azoxystrobin by the HIARC, because no toxicity was observed at the limit dose of 1,000 mg/kg/day. Therefore, the occupational risk assessment was based on inhalation exposure only. The daily inhalation doses were converted to oral equivalent doses, assuming an absorption factor of 100%, and compared to the oral NOAELs of 25 mg/kg/day (prenatal developmental oral study in the rat) and 20 mg/kg/day (90-day feeding study in the rat) to estimate the risk from short- and intermediate-term inhalation exposures, respectively.

The MOEs range from 3,900 for intermediate-term mixing/loading liquids for aerial application to 190,000 for short-term mixing/loading dry flowables for airblast application. **These MOEs exceed HED's target of 100, and therefore, are not of concern.** Exposure assumptions and estimates for occupational handlers are summarized in Table 4.

4.2 Post-Application Exposure and Risk

This Section 3 action on azoxystrobin involves foliar applications. Therefore, there is a potential for postapplication exposure to scouts, harvesters and other field workers. However, because no appropriate dermal endpoints were identified for this exposure potential, a **risk assessment is not required**. Postapplication inhalation exposure is expected to be negligible; therefore, a risk assessment for this route is also not required. Non-occupational postapplication risk in residential settings is covered in Section 5.2

The azoxystrobin technical material has been classified in Toxicity Category III for acute dermal and primary eye irritation, and Toxicity Category IV for primary skin irritation. Per the Worker Protection Standard (WPS), a 12-hr restricted entry interval (REI) is required for

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chemicals classified under Toxicity Category III or IV, which is the shortest waiting period permitted under the WPS. However, per Pesticide Regulation Notice 95-3 (6/7/95), REIs may be further reduced from 12 hours if certain criteria are met. In a previous risk assessment (Memo, D. Dotson, D248888, 1/28/99), HED determined that the criteria established by Pesticide Regulation Notice 95-3 have been met for azoxystrobin formulated as a water-dispersible granule, and that a 4-hour REI is acceptable on the Heritage® label. However, it is not clear whether the criteria have subsequently been met for the flowable concentrate formulation. This needs to be addressed by the Registration Division (e.g., obtain acute toxicity data for the end-use product) to determine whether the Abound® label may indicate a reduction in REI to 4 hours.

Table 4. Inhalation Exposure and Risk Assessment for Occupational Handlers

PHED Scenario Selected from PSEG (8/98)	PHED Unit Exposure [1] (mg/lb ai)	Application Rate [2] (lb ai/A)	Area Treated [3] (A/day)	Short-term Daily Dose [4] (mg/kg/day)	Int.-term Daily Dose [4] (mg/kg/day)	Short-Term Inhalation MOE [5]	Intermed-Term Inhalation MOE [5]
1. Mixing/Loading Liquids for Aerial/Chemigation Application	0.0012	0.25	1,200	0.0060	0.0051	4,200	3,900
		0.40	350	0.0028	0.0024	8,900	8,300
2. Mixing/Loading Liquids for Groundboom Application		0.25	200	0.0010	0.00086	25,000	23,000
		0.40	80	0.00064	0.00055	39,000	36,000
3. Mixing/Loading Liquids for Airblast Sprayer		0.25	40	0.00020	0.00017	130,000	120,000
4. Mixing/Loading Dry Flowable for Aerial/Chemigation Application	0.00077	0.25	1,200	0.0039	0.0033	6,500	6,100
		0.40	350	0.0018	0.0015	14,000	13,000
5. Mixing/Loading Dry Flowable for Groundboom Application		0.25	200	0.00064	0.00055	39,000	36,000
		0.40	80	0.00041	0.00035	61,000	57,000
6. Mixing/Loading Dry Flowable for Airblast Sprayer		0.25	40	0.00013	0.00011	190,000	180,000
7. Applying Sprays with Fixed-wing Aircraft (enclosed cockpit)	0.000068	0.25	1,200	0.00034	0.00029	74,000	69,000
		0.40	350	0.00016	0.00014	160,000	150,000
8. Applying Sprays with a Groundboom Sprayer (open cab)	0.00074	0.25	200	0.00062	0.00053	41,000	38,000
		0.40	80	0.00039	0.00034	63,000	59,000
9. Applying Sprays with an Airblast Sprayer (open cab)	0.0045	0.25	40	0.00075	0.00064	33,000	31,000
10. Flagging (Sprays) for Aerial Operations	0.00035	0.40	350	0.00082	0.00070	31,000	29,000

[1] Unit Exposure values are based on exposure without a respirator. There is high confidence in all values except for that of aerial application with an enclosed-cockpit aircraft, for which there is medium confidence.

[2] Maximum application rate of 0.4 lb ai/acre (from peanuts) was used as a screening value, except for: airblast scenarios, which are for citrus only (Max app. rate of 0.25 lb ai/A); and higher acreage scenarios for corn, soybeans, and cotton (i.e., 1,200 acres for aerial and 200 acres for groundboom) which have a max app. rate of 0.25 lb ai/A.

[3] Standard values for acres treated in a day were used. The higher acreage of 1,200 and 200 for aerial and groundboom application, respectively, are for corn, soybeans, and cotton only.

[4] Daily Dose = [Unit Exposure (mg/lb ai handled) x Application Rate (lb ai/A) x Acres Treated (A/day)] / Body Weight (60kg for Short-term; 70 kg for intermediate-term)

[5] MOE = NOAEL/ Daily Inhalation Dose. Short-term Inhalation NOAEL = 25 mg/kg/day. Intermediate-term Inhalation NOAEL = 20 mg/kg/day.

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5.0 Non-Occupational/Residential Exposure

Products containing azoxystrobin are registered for application to turf and ornamentals. They may be applied to turf at rates up to 0.95 lb active ingredient (ai) per acre 5 times per year (i.e., not to exceed 5 lb ai/A yr) and to ornamentals at rates up to 0.75 lb ai per acre every 7 to 14 days, but not to exceed 5 lb ai/A/yr. The currently registered labels do not prohibit homeowners from mixing/loading/applying either the flowable concentrate or the water-dispersible granule formulations. This residential exposure and risk assessment was conducted using the application rate for turf because it is the highest use rate.

Residential handlers may receive short-term dermal and inhalation exposure to azoxystrobin when mixing, loading and applying the formulations. Adults and children may be exposed to azoxystrobin residues from dermal contact with foliage during post-application activities. Toddlers may receive short- and intermediate-term oral exposure from hand-to-mouth ingestion during post-application activities.

As no dermal endpoint was selected by the HIARC, a dermal exposure and risk assessment was not required for residential handlers or post-application activities. NOAELs of 25 mg/kg/day and 20 mg/kg day were selected by the HIARC for assessing the risk from short- and intermediate-term incidental oral exposures, respectively. These same NOAELs were selected by the HIARC for assessing the risks from short- and intermediate-term inhalation exposures. The HED FQPA Safety Factor Committee met on August 24, 1998 and decided to remove the safety factor (i.e., reduce to 1x) for the U.S. population and all population subgroups and for all exposure scenarios. Thus, the target MOE for risk assessment purposes is 100.

No chemical-specific exposure or residue dissipation data for handler or post-application activities were submitted to HED in support of the registered lawn uses. Therefore, HED's Draft Standard Operating Procedures for Residential Exposure Assessments were used as the basis for all handler exposure calculations. The post-application risk assessment is based on generic assumptions as specified by the newly proposed Residential SOPs and approaches recommended by HED's Exposure Science Advisory Committee (ExpoSAC). Changes to the Residential SOPs have been proposed that alter the residential post-application scenario assumptions. The proposed assumptions are expected to better represent residential exposure and are still considered to be high-end, screening level assumptions. HED management has authorized the use of the revised residential SOPs that were presented to the FIFRA SAP in September 1999. Therefore, HED has deviated from the current Residential SOP assumptions and used the proposed assumptions to calculate exposure estimates.

5.1 Residential Handler Exposure and Risk

Inhalation daily doses for residential handlers were calculated for the flowable concentrate formulation using data for mixing/loading/applying a liquid; appropriate data are not available for handling the water-dispersible granule formulation for this use, however, based on PHED unit exposure values from other handler scenarios with these formulation types, the

exposure is expected to be less than that of handling a liquid. The following handler scenarios were evaluated:

1. mix/load and spot application of liquid formulation (low-pressure hand sprayer), and
2. mix/load and broadcast application of liquid formulation (garden hose-end sprayer)

The following assumptions (which include *current* HED standard values) were used to calculate inhalation exposures.

* The maximum application rate from ABOUND Flowable (EPA Reg No 10182-415) of 1.35 fluid ounces per 1,000 square feet or **0.95 lb ai per acre** was assumed.
* Handlers were assumed to be using a low-pressure hand sprayer for spot treatments to 1,000 ft^2 areas or a garden hose-end sprayer for broadcast to a 0.5 acre lawn.
* The inhalation unit exposures for the low-pressure hand sprayer, and garden hose-end sprayer are 30 μg/lb ai handled, and 9.5 μg/lb ai handled, respectively (from Appendix B of the 1997 Draft SOPs for Residential Exposure Assessments).
* Residential handlers' body weight is 60 kg for calculation of short-term inhalation doses because this endpoint is based on a developmental study (i.e., applicable to females 13+).
* The overall estimate of inhalation exposure represents a central to high-end value.

As shown in Table 5, the inhalation MOEs for residential handlers are well above the target MOE of 100.

Table 5. Handler Exposure and Risk Estimates for Residential Lawn Applicators

Handler Scenario	Rate (lb ai/ acre)	Acres Treated (acres/ day)	PHED Unit Exposure[1] (mg/lb ai)	Short-term Daily Inh. Dose [2] (mg/kg/day)	Short-term Inhalation MOE [3]
1. mix/load and spot application of liquid formulation (low-pressure hand sprayer)	0.95	0.023	0.030	1.1E-05	2.7E+06
2. mix/load and broadcast application of liquid formulation (garden hose-end sprayer)	0.95	0.5	0.0095	7.5E-05	3.9E+05

[1] Data Confidence for inhalation unit exposures:
low-pressure hand sprayer: 80 replicates, ABC grade, medium confidence run
garden hose-end sprayer: 8 replicates, ABC grade, low confidence run due to inadequate replicate

[2] Daily Dose = [Rate (lb ai/A) x Acres Treated (A/day) x Unit Exposure(mg/lb ai handled)] Body Weight (60 kg for Short-term because endpoint based on a developmental study)

[3] MOE = NOAEL (25 mg/kg/day) / Daily Inhalation Dose (mg/kg/day)

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5.2 Residential Postapplication Exposure and Risk

As noted previously, a dermal risk assessment for postapplication exposure is not required because no dermal endpoint was selected by the HIARC. Therefore, only the following postapplication exposure scenarios resulting from lawn treatment were assessed: (1) incidental non-dietary ingestion of pesticide residues on lawns from hand-to-mouth transfer, (2) incidental non-dietary ingestion of pesticide-treated turfgrass, and (3) incidental non-dietary ingestion of soil from pesticide-treated residential areas. Postapplication exposures from various activities following lawn treatment are considered to be the most common and significant in residential settings. The exposure via incidental non-dietary ingestion of other plant material may occur but is considered negligible.

The exposure and risk estimates for the residential exposure scenarios are assessed for the day of application (day "0") because it is assumed that toddlers could contact the lawn immediately after application. On the day of application, it was assumed that 5 percent of the application rate is available from the turfgrass as transferrable residue. Both short- and intermediate-term exposure is expected. Risk from short-and intermediate-term incidental ingestion by toddlers is assessed by comparing these exposures to the NOAELs of 25 mg/kg/day and 20 mg/kg/day, respectively. The equations used for the exposure calculations are presented below and the results are presented in Table 6.

PDR_t for **hand-to-mouth** $= TTR_t * SA * EX * FQ * ET * CF1$
PDR_t for **eating turfgrass** $= GR_t * IgR1 * CF1$
PDR_t for **soil ingestion** $= SR_t * IgR2 * CF1$

Where:

PDR_t = potential dose rate on day "t" (mg/day)
TTR_t = $AR * F * (1-D)^t * CF2 * CF3$
GR_t = $AR * F * (1-D)^t * CF2 * CF3$
SR_t = $AR * F * (1-D)^t * CF2 * CF3 * CF4$

Where:

TTR_t = turf transferrable residue on day "t" (ug/cm^2 turf)
SA = surface area of the hands (cm^2/event); use palmar surface area of 3 fingers; 20 cm^2
EX = extraction from the hand by saliva = 50%
FQ = frequency of hand-to-mouth activity (events/hr); 20 events/hr
ET = exposure time (hr/day); 2 hrs/day
CF1 = conversion factor (0.001 mg/ug for the TTR or GR equation, or 1E-6 g/ug in the SR equation)
GR_t = grass (and plant matter) residue on day "t" (ug/cm^2)
IgR1 = ingestion rate of grass (cm^2/day); 25 cm^2/day

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SR_t = soil residue on day "t" (ug/g)
IgR2 = ingestion rate of soil (mg/day); 100 mg/day
AR = application rate (lb ai/acre); 0.95 lb ai/acre
F = fraction of ai available on turf/grass or in uppermost cm of soil (unitless); 5% on turf/grass, 100% in uppermost 1 cm of soil
D = fraction of residue that dissipates daily (unitless); 10%
t = postapplication day on which exposure is being assessed
CF2 = conversion factor (4.54E8 ug/lb)
CF3 = conversion factor (2.47E-8 acre/cm^2)
CF4 = conversion factor (0.67 cm^3/g soil)

and

$PDR_{t\text{-}norm} = PDR_t / BW$
$MOE = NOAEL / PDR_{t\text{-}norm}$

Where:

$PDR_{t\text{-}norm}$ = potential dose rate, normalized to body weight, on day "t" (mg/kg/day)
BW = body weight (kg); 15 kg
$NOAEL_{oral}$ = 25 mg/kg/day (short-term), 20 mg/kg/day (intermediate-term)

Table 6. Short- and Intermediate-Term Incidental Ingestion Exposure and Risk

Scenarios	TTR/GR/SR_0 (ug/cm^2 or g)	$PDR_{0\text{-}norm}$ (mg/kg/day)	Short-Term MOE	Intermediate-term MOE
(1) Hand-to-Mouth	0.53	0.014	1,800	1,400
(2) Grass Ingestion	0.53	0.00089	28,000	23,000
(3) Soil Ingestion	7.1	0.000048	530,000	420,000
Total	N/A	0.015	1,700	1,300

Both short-term and intermediate-term MOEs for each scenario, and the combined MOE resulting from all three exposures, are above the target of 100, and therefore, are not of concern.

The exposure estimates generated above are based on some upper-percentile (i.e., maximum application rate, initial amount of transferrable residue and duration of exposure) and some central tendency (i.e., surface area, hand-to-mouth activity, and body weight) assumptions and are considered to be representative of high-end exposures. The uncertainties associated with this assessment stem from the use of an assumed amount of pesticide available from turf, and assumptions regarding transfer of chemical residues and hand-to mouth activity. The estimated exposures are believed to be reasonable high-end estimates based on observations from chemical-specific field studies and professional judgement.

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5.3 Recreational Postapplication Exposure and Risk

Recreational exposures to turf are expected to be similar to those evaluated in section 5.2 Residential Postapplication Exposure and Risk. Although azoxystrobin may be applied to golf courses, a risk assessment for the golfing scenario is not required because no dermal endpoint was selected by the HIARC.

5.4 Off Target Non-Occupational Exposure

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for azoxystrobin. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

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