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Evaluation of AZOXYSTROBIN Based on the FQPA of 1996

This is a summary of EPA pending pesticide petitions proposing the establishment of a regulation for residues of azoxystrobin in or on grape, pecan, tomato, peach, banana, peanut and wheat, with anticipated approvals in early 1997, and a petition in or on rice which Zeneca will be submitting in mid 1997. This summary was prepared by Zeneca Ag Products.

SUPPLEMENTARY INFORMATION: The EPA has received pesticide petitions (PP 6F 4762, 6F 6421, 5F 4541) from Zeneca Ag Products, 1800 Concord Pike, P.O. Box 15458, Wilmington, DE 19850-5458, proposing pursuant to section 408(d) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. section 346a(d), to amend 40 CFR part 180 by establishing a tolerance for residues of azoxystrobin (methyl (E)-2-{2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate) and the Z isomer of azoxystrobin, (methyl (Z)-2-{2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate)
in or on the following raw agricultural commodities:

1.0 ppm in/on grapes
0.01 ppm in/on pecans
0.2 ppm in/on tomato
0.6 ppm in/on tomato paste
0.01 ppm in/on peanut
0.03 ppm in/on peanut oil
1.5 ppm in/on peanut hay
0.80 ppm in/on peach
0.5 ppm in/on banana (whole fruit including peel)
0.05 ppm in/on banana pulp
0.04 ppm in/on wheat grain
0.12 ppm in/on wheat bran
13.0 ppm in/on wheat hay
4.0 ppm in/on wheat straw
0.01 ppm in/on Cattle, fat
0.01 ppm in/on Cattle, mbyp
0.01 ppm in/on Cattle, meat
0.01 ppm in/on Goats, fat
0.01 ppm in/on Goats, mbyp
0.01 ppm in/on Goats, meat
0.01 ppm in/on Hogs, fat
0.01 ppm in/on Hogs, mbyp
0.01 ppm in/on Hogs, meat

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0.01 ppm in/on Horses, fat
0.01 ppm in/on Horses, mbyp
0.01 ppm in/on Horses, meat
0.006 ppm in/on Milk
0.01 ppm in/on Poultry, fat
0.01 ppm in/on Poultry, liver
0.01 ppm in/on Poultry, mbyp
0.01 ppm in/on Poultry, meat
0.01 ppm in/on Sheep, fat
0.01 ppm in/on Sheep, mbyp
0.01 ppm in/on Sheep, meat

The proposed analytical methods for non-oily crops are analysis by gas chromatography with nitrogen-phosphorus detection (GC-NPD) or in mobile phase by high performance liquid chromatography with ultra-violet detection (HPLC-UV).

The proposed analytical method for oily crops is analysis by gas chromatography with nitrogen-phosphorus detection (GC-NPD).

A pesticide petition proposing the establishment of a regulation of residues of azoxystrobin in or on rice, with a concurrent application for label registration is targeted for mid 1997. Tolerance levels:

4.0 ppm grain and polished rice
5.0 ppm bran
20.0 ppm hulls

The proposed analytical method for animal tissue and eggs is gas chromatography with nitrogen-phosphorus detection (GC-NPD).

Pursuant to the "section 408 (d) (2) (A) (i) of the FFDCA, as amended, Zeneca Ag Products has submitted the following summary of information, data and arguments in support of their pesticide petition. This summary was prepared by Zeneca and EPA has not fully evaluated the merits of the petition. EPA edited the summary to clarify that the conclusions and arguments were the petitioner's and not necessarily EPA's and to remove certain extraneous material.

PETITION SUMMARY:

1. Residue Chemistry

A. Plant Metabolism

Plant metabolism has been evaluated in three diverse crops, grapes, wheat and peanuts which should serve to define the similar metabolism of azoxystrobin a wide range of crops. Parent azoxystrobin is the major component found in crops. Azoxystrobin does not accumulate in crop seeds or fruits, in fact very low residues are found in wheat grain, banana pulp, pecan nutmeat, and peanut (nuts). Metabolism of azoxystrobin in plants is complex with more than 15 metabolites identified. These metabolites are present at low levels, typically much less than 5% of the TRR.

Grapes

In grapes parent azoxystrobin was the major component representing between 34.6% and 64.6% TRR. The metabolism of azoxystrobin was complex, involving at least six distinct metabolic pathways, yielding a large number of minor metabolites. In total fifteen metabolites have been identified. Metabolite azoxystrobin/28 (4-hydroxy-6-(2-cyanophenoxy)pyrimidine) was present at levels up to 5.2% TRR, azoxystrobin/13 (2-cyanophenol) was present at levels of up to 5.7%, with no other metabolites present at levels greater than 4.0% TRR.

Wheat

In wheat the total radioactive residues in the grain were very low ranging from 0.075 to 0.077 ppm azoxystrobin equivalents. As expected residues in forage and straw were higher (1.02 to 2.79 ppm and 3.06 to 9.41 ppm, respectively).

The only significant residue in the grain was parent azoxystrobin (17.1 - 22.0% TRR, 0.013 - 0.017 ppm). No metabolite was present at > 3.3% TRR.

In wheat straw, the major component of the residue was parent azoxystrobin (22.1 - 43.3% TRR, 0.676 - 4.07 ppm). In total 14 metabolites were identified, the most significant of which was Compound 28 (8.2 - 10.4% TRR, 0.319 - 0.731 ppm - sum of free conjugated and bound forms). Z isomer was present at 2.1 - 3.5% TRR (0.064 - 0.329 ppm). No other metabolite was present at > 3.5% TRR.

In wheat forage azoxystrobin was the major component of the residue (54.9 - 64-7% TRR, 0.56 - 1.81 ppm). The two most significant metabolites were compound 28 (3.2 - 3.7% TRR, 0.038 - 0.090 ppm - total) and Z isomer (1.9 - 2.9% TRR, 0.019 - 0.081 ppm). No other metabolite was present at > 1.1% TRR.

Peanuts

In peanuts the total radioactive residues in the nuts and hulls were low compared to the foliage.

The majority of the residue in the nuts was identified as radiolabeled natural products, resulting from the mineralization of azoxystrobin in soil and subsequent incorporation of the evolved $^{14}CO_2$ via photosynthesis. The major radiolabeled natural products identified were fatty acids and these accounted for 42.1 - 49.1% TRR (0.101 - 0.319 ppm). Incorporation of radioactivity into simple sugars was also, confirmed, accounting for 5.8 - 8.5% TRR (0.014 - 0.042 ppm). The presence of radiolabeled glutamic acid, an amino acid was also confirmed. azoxystrobin was not detected in the nut (0.001 ppm) and no individual metabolite was present at a level greater than 0.002 ppm.

In the hay the major component or the residue was parent azoxystrobin (33.0 - 43.8% TRR, 13.3 - 20.4 ppm). In total 10 metabolites were identified, the most significant of which were Compound 28 in both the free and conjugated forms (7.0 - 9.0% TRR, 2.74 - 3.62 ppm). The next most significant metabolites were Compound 13 in both the free and conjugated forms (6.3% TRR, 2.53 ppm) and Z isomer (2.4 - 2.8% TRR, 0.965 - 1.30 ppm).

B. Analytical Method

Non-oily Crops

Azoxystrobin and Z isomer residues in grape and grain samples are extracted in 90:10/acetonitrile:water. An aliquot of the extract is cleaned up by adsorption chromatography on a silica sorbent. The eluate is evaporated to dryness and taken up in a known volume of acetone for analysis by GC-NPD or in mobile phase for analysis by high performance liquid chromatography with ultra-violet detection (HPLC-UV). The limit of quantitation of the method is typically 0.02 to 0.05 ppm.

Oily Crops

Azoxystrobin and Z isomer residues in oily crop samples are extracted in 90:10/acetonitrile:water. An aliquot of the extract is cleaned up by passing through a C^{18} sep-pak. All extracts were cleaned up by gel permeation chromatography eluting through

alumina and Florisil solid phase extraction cartridges. The eluate was evaporated to dryness and redissolved in a known volume of acetone for analysis by GC-NPD. The limit of quantitation of the method is typically 0.01 ppm.

Analytical Method in Animal Tissues (liver), Milk and Eggs

Residue of azoxystrobin in tissue and egg samples are extracted in acetonitrile . An aliquot of the extract is cleaned up by gel permeation chromatography (GPC) eluting through alumina-n and Florisil solid phase extraction cartridges. The eluate is evaporated to dryness and taken up in a known volume of acetone for analysis by gas chromatography with nitrogen-phosphorus detection (GC-NPD). The limit of quantitation is typically 0.01 ppm.

Residue of azoxystrobin in milk samples are extracted in acetonitrile and partitioned in dichloromethane. The extract is again cleaned up by GPC eluting through alumina-n and Florisil solid phase cartridges. The eluate is evaporated to dryness and taken up in a known volume of acetone for analysis by GC-NPD. The limit of quantitation is typically 0.006 ppm.

C. Magnitude of residues

Grapes

Trials were carried out in 1994 in five different states, California, New York, Arkansas, Michigan, and Washington. And an additional nine trials were conducted in 1995 in New York, California (6) and Oregon and Washington.

Azoxystrobin 80WG was applied at a rate of 0.25 lb ai/A. A total of 6 applications was made. The first application was at 1 to 5 inch shoot growth, the second at 8 to 12 inch shoot growth. The third application was at bloom plus or minus 2 days. The last three applications were made at 46 (± 3), 35 (± 3), and 12-14 days prior to normal harvest.

Residues ranged between 0.20 and 0.84 ppm supporting the proposed tolerance of 1 ppm. No concentration of residues were seen in grape juice or raisins.

Pecans

Trials were carried out between June and November 1994 in four different states, Alabama, Georgia, Mississippi and Texas.

Azoxystrobin 80WG was applied at a rate of 0.2 lb ai/A. A total of 6 applications was made. Applications were made from bud break up to 42 days of harvest on a three week application schedule.

Azoxystrobin and Z isomer residues on pecans after the final spray, were <0.01 ppm supporting the proposed tolerance of 0.01 ppm.

Banana

A total of 6 residue trials were conducted in Hawaii, Florida, and Puerto Rico during 1995-1996. Azoxystrobin was applied eight times at a rate of 0.135 lb ai/A. Applications were made every 12-14 days with the last application just prior to harvest. Immediately following the second application, bags were placed over several bunches of bananas in both the treated an untreated plots. The bags were left in place until harvest. Samples of bagged and unbagged bananas were collected immediately after the last application, after the spray deposit had dried. Samples of whole bananas and banana pulp were analyzed for residues of azoxystrobin and the Z isomer.

Azoxystrobin residues on bagged whole bananas sampled immediately after the last application ranged from <0.01 to 0.15 ppm. Azoxystrobin residues on unbagged whole bananas sampled immediately after the last application ranged from 0.08 to 0.26 ppm. Residues of azoxystrobin in banana pulp were low in both bagged and unbagged bananas ranging from <0.01 to 0.03 ppm. Residues of Z isomer were <0.01 ppm in all samples of whole bananas and banana pulp, both bagged and unbagged. These data support the proposed tolerances of 0.5 ppm in whole bananas and 0.05 ppm in banana pulp.

Peaches

Fourteen trials were carried out in North Carolina (2), California (4), Michigan (2), Texas Arkansas, Pennsylvania (2), Georgia and South Carolina on peaches during 1995. Azoxystrobin was applied at 0.15 lb ai/A starting at pink bud to 5% blossom and repeating at 5-10 day intervals. All the samples were analyzed for azoxystrobin and the Z isomer.

Azoxystrobin residues on peaches, sampled 11-14 days after the final spray, ranged from 0.07-0.70 ppm. Residues of the Z isomer were low and ranged from <0.01-0.05 ppm. These data support the proposed tolerance of 0.8 ppm.

Peanuts

Twelve residue trials were carried out in Georgia (2), North Carolina (3), Oklahoma, Texas (2), Virginia (2), Florida, and Alabama on peanuts during 1994 and in 1995. Azoxystrobin was applied as a foliar broadcast spray at 0.4 lb ai/A at two spray intervals, 8 to 9 weeks after planting and 12 to 13 weeks after planting.

Azoxystrobin residues on peanut hay, sampled about 50 days after the final spray, ranged from 0.25-0.91 ppm. Residues of the Z isomer, were low and ranged from <0.02-0.38 mg ppm in the hay.

A trace residue of azoxystrobin (0.01 ppm), was found in one nutmeat sample only, all the remainder were <0.01 ppm. These data support the proposed tolerances of 0.01 ppm in the peanut, 1.5 ppm in peanut hay. Processing data indicate a possible 3X concentration in peanut oil supporting a proposed tolerance of 0.03 ppm.

Tomato

Sixteen residue trials were carried out in California (10), Florida (2), New Jersey, North Carolina and Indiana on tomatoes during 1994 and 1995 . Azoxystrobin was applied at 0.1 lb ai/A starting at early fruiting and repeating on a 6-8 day interval until eight applications had been made. Samples of mature fruits were taken 1 day after the final spray and analyzed for azoxystrobin and the Z isomer.

Azoxystrobin residues, one day after the final spray, ranged from 0.01-0.16 ppm. Only traces of the Z isomer ranging from <0.01-0.02 ppm were found. These data support the proposed tolerances of 0.2 ppm in tomato, processing data show a possible 3X concentration in tomato paste support a proposed tolerance of 0.6 ppm.

Wheat

Six magnitude of the residue trials were carried in Georgia, Tennessee, Montana, Nebraska, Virginia and Oregon on wheat during 1994. Azoxystrobin was applied twice at growth stages Zadoks 43-45 and 55-59 at 0.2 lb ai/A Samples of hay, straw and grain were analyzed for azoxystrobin and the Z isomer.

Azoxystrobin residues on hay, sampled two weeks after the final spray, ranged from 0.19 - 6.5 ppm. At harvest, 33-74 days after treatment residues in wheat grain were low and ranged from <0.01-0.03 ppm. Residues on straw ranged from 0.03-3.4 ppm.

A total of 16 residues trials were conducted in Mississippi, Illinois, Ohio, Wisconsin,Texas (2), Nebraska, Montana (2), North Dakota, Colorado, Kansas (2), Oklahoma, New Mexico and California during 1995. Azoxystrobin was applied two times at a rate of 0.2 lb ai/A. Application timings were at Zadoks 43 to 45 (boot) and 30-45 days prior to grain harvest (no later than Zadoks *58*, head emergence).

Azoxystrobin residues on hay sampled 13 to 33 days after the last application ranged from 0.09 to 11.1 ppm. Residues of azoxystrobin on straw sampled 36 to 52 days after the last application ranged from 0.03 to 1.31 ppm. Residues of azoxystrobin on grain sampled 36 to 52 days after the last application were low, ranging from <0.01 to 0.06 ppm.
Residues of z isomer on hay ranged from <0.01 to 0.8 ppm. Residues of Z isomer on straw were low, ranging from <0.01 to 0.13 ppm. Residues of the Z isomer on grain were <0.01 ppm on all samples. These data support proposed tolerances of 0.04 ppm on grain, 4.0 ppm on straw and 13 ppm on hay. Processing data indicate a possible 3X concentration in wheat bran supporting a proposed tolerance of 0.12 ppm.

Rice

Sixteen residue trials conducted in Arizona, California, Louisiana, Mississippi, Missouri, and Texas during 1995. Two applications of azoxystrobin were made at 0.2 lb a.i. acre^{-1}, followed by a third application at 0.3 lb a.i. acre^{-1}. Duplicate samples of grain and straw were taken for analysis at harvest 26-28 days after the final spray.

Mean azoxystrobin residues on grain sampled 26-28 days after the last application ranged from 0.07 - 3.2 mg/kg (0.01-0.38 mg/kg of the Z isomer, R230310). Mean azoxystrobin residue levels in the straw ranged from 0.56-8.8 mg/kg (0.04-0.42 mg/kg of the Z isomer).

A processing study was conducted in Mississippi in 1995. Azoxystrobin was applied twice at 0.2 lb a.i. acre^{-1} followed by a third application at 0.3 lb a.i. acre^{-1} at full heading. Samples of grain were taken at harvest 28 days after the last spray.

Whole grain sampled 28 days after the final spray contained azoxystrobin residues of 0.28 mg/kg (0.05 mg/kg of the Z isomer, R230310). A sample taken from the bulk sample prior to processing contained a similar residue of 0.33 mg/kg. After processing, white milled rice contained a much lower residue of 0.03 mg/kg. The majority of the residue was contained in the hulls (1.6 mg/kg), with some in the bran (0.39 mg/kg). These data support the proposed tolerances of 4.0 ppm on grain and polished rice. Processing data show a possible 1.2x concentration in bran, supporting a proposed tolerance of 5 ppm.

2. Toxicological Profile

A Acute toxicity

Azoxystrobin technical

Acute Oral Rat	LD_{50} > 5000 mg/kg	IV
Acute Dermal Rat	LD_{50} > 2000 mg/kg	III
Acute Inhalation Rat	LC_{50} = 698µg/l for females LC_{50} = 962 µg/l for males	III
Eye Irritation Rabbit	Slight irritant, no corneal effects	III
Skin Irritation Rabbit	Slight irritant	IV
Skin Sensitization Guinea Pig	Not a skin sensitizer	

B. Genotoxicity

Azoxystrobin gave a weak clastogenic response in mammalian cells *in vitro* at cytotoxic doses. In the whole animal azoxystrobin was negative in established assays for chromosomal damage (clastogenicity) and general DNA damage, at high dose levels (≥ 2000 mg/kg). The weak clastogenic effects seen *in vitro* are not expressed in the whole animal and azoxystrobin is considered to have no genotoxicity *in vivo*.

Assay	Type	Result
In vitro	Ames L5178Y IVC	negative weakly positive weakly positive
In vivo	Micronucleus UDS	negative negative

C. Reproductive and Developmental Toxicity

Reproductive Toxicity

Azoxystrobin showed no evidence of reproductive toxicity.

The No Observed Effect Level for toxicity was judged to be 300 ppm azoxystrobin, which for the premating period, translates into a daily dose of 32 mg azoxystrobin/kg body weight/day based on body weight reductions relative to control and liver toxicity in adult males.

The liver toxicity observed in the reproductive toxicity study was manifest as gross distension of the common bile duct accompanied by histological change. The histological changes in the intraduodenal bile duct were characterized by an increase (a hyperplasia) in the number of lining (epithelial) cells and bile duct inflammation (cholangitis). In the liver, there was an increased severity of hepatic proliferative cholangitis. The increased severity of the microscopic liver effects were confined to those animals showing gross bile duct changes, suggesting that these effects were secondary to biliary toxicity.

These observations were confined to male F0 and F1 adult rats and were not detected in female animals or in pups.

Reproductive Toxicity Doses

Azoxystrobin in Diet (ppm)	Dose (mg/kg/day)
60	6.5
300	32
1500	162

Developmental Toxicity

There were no adverse effects , in the rat or the rabbit, on the number, survival and growth of the fetuses in utero. Azoxystrobin caused no developmental toxicity in the rat or in the rabbit up to and including dose levels shown to be maternally toxic.

Study Type : Developmental Toxicity	NOEL/LEL (mg/kg/day)	Effect Description
Rabbit (by gavage)	No developmental effects. NOEL for developmental toxicity > 500 mg/kg/day. NOAEL for maternal toxicity = 50 mg/kg/day.	No developmental effects. NOAEL for maternal toxicity = 50 mg/kg/day. LEL for maternal toxicity = 150 mg/kg/day; reduced body weight, clinical effects.
Rat (by gavage)	No developmental effects, NOEL = 25 mg/kg/day for maternal and fetotoxicity	LEL for fetotoxicity is 100 mg/kg/day. Effect 'delayed ossification', LEL for maternal toxicity 100 mg/kg/day, effect reduced body weight.

D. Subchronic Toxicity

Azoxystrobin is of low subchronic toxicity in 21-day dermal testing.

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E. Chronic Toxicity

Azoxystrobin is non-oncogenic in the rat.

Azoxystrobin in Diet (ppm)	Male rat (mg/kg/day)	Female rat (mg/kg/day)
60	3.6	4.5
300	18.2	22.3
1500/750	82.4	117.6

The NOEL/NOAEL for azoxystrobin in the rat is 18 mg/kg wt/day.

We suggest that this chronic rat study has the lowest NOAEL of the chronic studies conducted with azoxystrobin. The RfD for azoxystrobin should be based upon the NOAEL of 18 mg/kg bw/day with an uncertainty factor of 100, RfD = 0.18 mg/kg/day .

A dietary inclusion level of 1500ppm was established as a maximum tolerated dose in female rats where decrements in body weight gain relative to control of approx. 19% at week 53 and 11% at week 105 were observed. The maximum reduction relative to control was seen at week 73 (approx. 20%). In male rats this dose level was in excess of an MTD (biliary toxicity), resulting in a reduction in the top dose level from 1500ppm to 750ppm for the second year of the study. Reductions in male body weight gain relative to control animals were seen throughout the duration of the study with a maximum reduction of approx. 11% in the first year (at week 45), continuing into the second year (maximum reduction of approx. 13% at week 99).

In the rat, there was no statistical increase in the number of tumor-bearing animals, animals with malignant tumors, benign tumors, multiple tumors, single tumors or metastic tumors in animals treated with azoxystrobin at dose levels of up to 1500ppm (up to 117.1 mg azoxystrobin/kg/day) for 2 years.

Oncogenicity - Mouse

Azoxystrobin in Diet (ppm)	Male mouse (mg/kg/day)	Female mouse (mg/kg/day)
50	6.2	8.5
300	37.5	51.3
2000	272.4	363.3

Azoxystrobin is non-oncogenic in the mouse. There was no increased tumor incidence or early onset of tumors in mice receiving up to 2000ppm azoxystrobin for up to 2 years. Dietary administration of 2000ppm Azoxystrobin was associated with reduced growth and food utilization.

A maximum Tolerated Dose (MTD) was established in the mouse oncogenicity study based on body weight gain depression and decreased food utilization seen at the highest dose tests, 2000 ppm. At this dose level body weight gain was depressed 20% at week 13 and 28% at week 53 in males, and 11% at week 13 and 19% at week 53 in females.

There was no statistically significant change or alteration in tumor incidence in the mouse attributable to treatment with azoxystrobin at dose levels of up to 2000ppm (up to 363.3mg azoxystrobin/kg/day) for 2 years.

One-year Feeding Study - Dog

Azoxystrobin was administered to groups of 4 beagle dogs at dose levels of 0, 3, 25 and 200 mg/kg/day, as a daily oral dose.

Adaptive liver responses were observed at 25 and 200 mg/kg/day which were not considered to be toxicologically significant. The adaptive liver responses were increased liver weights and increased serum liver enzyme activities in the absence of any liver histopathology. Liver weights were increased in both sexes at 200 mg/kg/day, and in females at 25 mg/kg/day. Plasma alkaline phosphatase, cholesterol and triglyceride levels were elevated at the top dose in both sexes, with plasma albumin elevated at 200 mg/kg/day in males only. Plasma triglycerides were also elevated at 25 mg/kg/day in males only. No such effects were observed at 3 mg/kg/day.

These changes were not accompanied by any histopathological change in the liver. Such changes in the absence of signs of a toxic lesion are generally considered to reflect the liver compensating for the increased work it must perform in metabolizing the test compound. While they can be considered to be effects of azoxystrobin treatment, these changes are of no toxicological significance.

The No Observed Adverse Effect level in this study was 200 mg/kg/day.

F. Animal Metabolism

Azoxystrobin is well absorbed and completely metabolized in the rat. Excretion is rapid and there is no accumulation of azoxystrobin or metabolites. There are no significant plant metabolites that are not animal metabolites.

G. Metabolite Toxicology

Toxicity testing results on the azoxystrobin parent compound are indicative of the toxicity of all significant metabolites seen in either plants or mammals

3. Aggregate Exposure

A. Dietary Exposure

1) Food

For the purpose of assessing the potential dietary exposure from these proposed tolerances, EPA generally estimates aggregate exposure based on the TMRC from the tolerances proposed for azoxystrobin as listed above. The TMRC is obtained by multiplying the tolerance level residue for each food by the consumption data which estimate the amount of food and food products eaten by various population subgroups. Animal feeds (such as wheat forage) are fed to animals; thus exposure of humans to residue in the animal feeds might result if such residues are transferred to meat, milk or poultry. Animal metabolism and feeding studies indicate that low residues may occur in meat and milk when azoxystrobin is used as proposed. The TMRC for each animal product is obtained by multiplying the tolerance (worst-case) level of residues possible in meat and milk by the food consumption data which estimate the amount of food and food products eaten by various population subgroups. Very conservative assumptions -- 100% of foods, meat and milk products will contain azoxystrobin residues and those residues would be at the level of the tolerance -- which result in an overestimate of human exposure. This is a very conservative approach to exposure assessment. Zeneca used the food consumption data from the years 1989-1992 combined. The potential exposure for the U.S. population is 0.0019 mg/kg bwt/day. Potential exposure for children's population subgroups ranged from 0.0027 mg/kg bwt/day for Children 7-12 to 0.0050 mg/kg bwt/day for Children 1-6. This chronic dietary exposure analysis is based on the combined years 1989 - 1992 U. S. Department of Agriculture's Nationwide Food Consumption Survey using the Technical Assessment Systems, Inc. "EXPOSURE 1" Software

2) Drinking water

Azoxystrobin does not leach. It is unlikely that azoxystrobin could be present in drinking water or groundwater. Therefore it is not appropriate to assess aggregate exposure from drinking water.

Azoxystrobin is an analogue of naturally occurring strobilurins which are sensitive to sunlight (photolysis). Azoxystrobin, although more stable than the strobilurins, has a favorable environmental profile. Azoxystrobin is degraded rapidly under agricultural field conditions with a soil half-life of less than 2 weeks. The compound is non-volatile and does not leach, but it is very susceptible to photolysis. Photolysis accounts for the majority of the initial loss of the compound, the remainder being degraded microbially.

Based on laboratory data the predicted mobility of azoxystrobin in soil is relatively low. The soil adsorption coefficient corrected for soil organic matter (K_{oc}) ranges from 300 to 1690. Consequently, the potential mobility is low to medium. As a measure of possible mobility the standard GUS index value is 1.0; which equates to a non-leacher.

Results from field trials support these laboratory data. After using ^{14}C-labeled azoxystrobin as a 'worst case' field application - bare surface, irrigated and poorly retentive soil (light texture and low organic matter content), the compound was retained in the upper 2 inches or so of the soil throughout its lifetime.

As azoxystrobin does not leach it is very unlikely to enter into water bodies except by accidental, direct over-spray. However, the compound in laboratory tests degrades with a half-life of approximately 7 weeks in flooded anaerobic soils. There is also potential for photolytic degradation in natural aqueous environments; the aqueous photolysis half-life is 11 -17 days.

B. Non-Dietary Exposure

Other potential sources of exposure of the general population to residues of pesticides is non-occupation exposure. Since the proposed registrations for azoxystrobin are limited to commercial crop production, turf farms and golf courses; the potential for non-occupational exposure to the general population is not expected to be significant.

4. Cumulative Effects

Azoxystrobin is a new class of chemistry for pesticides, β- methoxyacrylate fungicide. Azoxystrobin has the same biochemical mode of action as the naturally occurring strobilurins, inhibition of electron transport. Since there are no other registered pesticides in this chemical class or this mode of action or mechanism of action, cumulative exposure assessment is not appropriate at this time.

No evidence or information exists to suggest that toxic effects produced by azoxystrobin would be cumulative with those of any other chemical compounds.

5. Safety Determination

A. U.S. population in general

Using the conservative assumptions described above, based on the completeness and reliability of the toxicity data the aggregate exposure to azoxystrobin will utilize 1.1% of the RfD for the U.S. populations. This chronic dietary exposure analysis is based on the combined years 1989 - 1992 U. S. Department of Agriculture's Nationwide Food Consumption Survey using the Technical Assessment Systems, Inc. "EXPOSURE 1" Software. Generally there are no concerns for exposures below 100 percent of the RfD. The EPA defines the RfD to represent the level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risk to human health.

B. Infants and children

In assessing the potential for additional sensitivity of infants and children to residues of azoxystrobin we have considered the 2- generation reproduction study in the rat and the developmental toxicity studies in the rat and rabbit. Azoxystrobin showed no evidence of reproductive toxicity. Azoxystrobin caused no developmental toxicity in the rat or in the rabbit up to and including dose levels shown to be maternally toxic. There were no adverse effects, in the rat or the rabbit, on the number, survival and growth of the fetuses in utero.

Based on the current toxicological data requirements, the database relative to pre- and post- natal effects for children is complete. Further azoxystrobin shows no evidence of reproductive or developmental toxicity, therefore we suggest that use of an additional uncertainty factor is not warranted and that the RfD of 0.18 mg/kg/day is appropriate for assessing aggregate risk to infants and children.

Using the conservative exposure assumption describe above, we conclude that the percent of the RfD that will be utilized by aggregate exposure to residues of azoxystrobin ranges from 1.2% for nursing infants up to 3.9% for non-nursing infants (<1 year old). In conclusion there is reasonable certainty that no harm will result to infants and children from aggregate exposure to azoxystrobin residues.

6. International Tolerances

There are no Codex Maximum Residue Level's established for azoxystrobin.