US Environmental Protection Agency
Office of Pesticide Programs

Petition for Etoxazole - Tab E - Reduced Risk Petition/ OP Replacement Petition MRID 45630502 - Environmental Fate and Effects

August 11 , 2010

C. ENVIRONMENTAL FATE AND EFFECTS

A comparison of the ecological effects data, estimated environmental concentrations, and risk quotients for etoxazole and seven of the most widely used competing products for pome fruit, cotton, and strawberry are summarized in Appendix III. These analyses consistently found favorable estimates of risk for etoxazole when compared to currently available competitor products. Specifically:

Etoxazole poses minimal acute risk to fresh and saltwater fish with Risk Quotients (RQ's) ranging from 0.001 to 0.017. The etoxazole RQ's are, in each case, lower (by at least a factor of 3) than the respective RQ's from the competitive products used on pome fruit, cotton, and strawberry crops.

Etoxazole poses potential to high acute risk to fresh and saltwater invertebrates with RQ's ranging from 0.13 to 2.23. But RQ values for etoxazole are lower than most of the competitive products (by as much as 458 times) used on pome fruit, cotton, and strawberry.

Etoxazole poses minimal to potential chronic risk to fish but RQ values for etoxazole (0.054 to 0.147) are lower than most of the competitive products (by as much as 285 times) used on pome fruit, cotton, and strawberry.

Etoxazole poses a high chronic risk to both fresh and saltwater invertebrates with RQ values ranging from 2.78 to 12.9. Most of the competitive products are similarly toxic to these organisms with RQ values that are generally higher than those calculated for etoxazole. For the cotton products, the RQ value for etoxazole is lower than all of the competitive products used on cotton for which RQ's could be calculated. For the strawberry products, however, etoxazole's RQ's are significantly greater than those of its competitors.

Etoxazole poses a minimal acute risk to avian species tested (2 species) via oral and dietary administrations. The RQ values for etoxazole are the lowest in all categories as compared to RQs of all competitive products evaluated. Based on worst case, peak (short rangegrass) estimated residues, etoxazole presents a minimal chronic risk to birds. RQ values range from 1.3 to over 16,000 times lower than values for all competitive products evaluated.

The potential of etoxazole to bioconcentrate is moderate (rainbow trout BCF=1500) but rapid clearance (i.e., depuration) of ^{14}C demonstrates that neither etoxazole nor any of its metabolites accumulate irreversibly.

Etoxazole poses a reduced risk of surface water contamination compared to the competitive products, as evidenced by the estimated environmental concentration (EEC) values calculated for products using GENEEC. Only two products used in the pome fruit market show EEC's that are consistently lower than etoxazole's.

1. Acute and Chronic Toxicity to Wild Mammals

Etoxazole is practically nontoxic to mammals as demonstrated by the toxicological profile outlined in the previous human health summary.

2. Avian Acute and Subacute Toxicity

Etoxazole is classified as "practically non-toxic" to birds and poses minimal acute or chronic risk to avian species. See Appendix III for comparative risk assessment tables.

The acute oral LD_{50} of technical grade etoxazole in mallard ducks was >2000 mg/kg, the highest dose tested. No treatment related effects were noted in birds exposed to levels up to 2000 mg/kg. Etoxazole is classified as "practically non-toxic" to mallard ducks via oral exposure.

The dietary LC_{50} of technical grade etoxazole in bobwhite quail chicks and mallard ducklings was >5200 ppm. No effects were observed at levels up to and including 5200 ppm, the highest dose tested. Etoxazole is classified as "practically non-toxic" to bobwhite quail and mallard ducks via dietary exposure.

Summary of Etoxazole Avian Acute Toxicity

STUDY	RESULTS	TOXICITY CATEGORY/RISK	RQ	REFERENCE
Acute Oral Mallard Duck	LD_{50} = >2000 mg/kg	Practically Non-toxic	NA	MRID 45089908
Acute Dietary Bobwhite Quail	LC_{50} = >5200 mg/kg	Practically Non-toxic	>0.005	MRID 45089910
Acute Dietary Mallard Duck	LC_{50} = >5200 mg/kg	Practically Non-toxic	>0.005	MRID 45089909

NA - Not Applicable
RQ = EEC (maximum residue levels in avian food items - based upon 0.045-0.135 lb a.i./A, Kenaga nomogram with short-range grasses as food item) / LC_{50}

3. Avian Reproductive Toxicity

Definitive reproduction studies were conducted on mallard ducks using 18 pairs of breeding birds exposed for 23 weeks to nominal dietary feed concentrations up to 1000 ppm of technical grade etoxazole. Definitive reproduction studies were conducted on Bobwhite quail using 20 pairs of breeding birds exposed for 20 weeks to nominal dietary feed concentrations up to 1000 ppm of technical grade etoxazole. For both species, there were no treatment-related effects on mortality, clinical signs, behavior, bodyweight, or food consumption in adult birds. There were no adverse effects on the health or reproductive performance of adult birds or on the health and growth of their offspring. The NOECs for both studies were 1000 ppm resulting in a RQ << 1 when compared to maximum residue levels in feed items (Kenaga, 1973). Based upon these results, etoxazole poses "minimal chronic risk to birds."

Summary of Etoxazole Avian Reproductive Toxicity

STUDY	RESULTS	TOXICITY CATEGORY/RISK	RQ
Reproduction Bobwhite Quail	NOEL = 1000 ppm	Minimal Chronic Risk	0.03
Reproduction Mallard Duck	NOEL = 1000 ppm	Minimal Chronic Risk	0.03

RQ = EEC (maximum residue levels in avian food items - based upon 0.045-0.135 lb a.i./A, Kenaga nomogram with short-range grasses as food item) / NOEL

4. Fish and Aquatic Invertebrate Acute and Chronic Toxicity

For evaluation of ecological effects to non-target aquatic organisms, a simulation of expected environmental concentration (EEC) values in aquatic ecosystems has been performed using the GENEEC v.2.0. The results are found in Appendix III.

5. Honeybee Toxicity

A study was conducted to assess the acute oral and contact toxicity of etoxazole to honey bees. In this study, the test substance was administered as a solution in acetone and sucrose and the 48-hour oral LD_{50} was >200 µg/bee, the highest dose tested. The contact LD_{50} was determined to be >200 µg/bee.

6. Effects on Terrestrial Plant Growth

Tier I vegetative vigor and seedling emergence studies were conducted with etoxazole to evaluate the potential detrimental effects on 6 dicotyledonous plant species from 5 families and 4 monocotyledonous plant species from 2 families. Test endpoints were % emergence, % survival, phytotoxicity, plant height, and plant dry weight. The results indicated that no single endpoint was a sensitive indicator of adverse effects for all test species. There is no indication that etoxazole will have any effect on terrestrial plant growth. Field efficacy trials have not exhibited any phytotoxic effects.

7. Effects on Aquatic Plant Growth

A study was conducted to determine the acute toxicity of technical grade etoxazole to the freshwater alga, *Selenastrum capriconutum*. In this study, algal cells were exposed to 10 mg a.i./L (the maximum solubility achievable under the conditions of the study) for 72 hours. There was no significant inhibition of growth in any of the cultures. The 72-hour EC_{50} and the 72-hour No-Observed-Effect-Concentration (NOEC) was determined to be >10.0 mg/L.

8. Potential Exposure to Non-target Organisms

SECURE Miticide will not pose a threat to non-target species when used according to the label, due to its very low use rate and breakdown in the environment. Etoxazole is relatively short-lived in the environment under aerobic conditions and is not persistent.

9. Environmental Persistence (Soil and Water)

Etoxazole is stable to hydrolysis, with a half-life of 161 days at pH 7, but photodegrades in water with an average half-life of 17.4 days. The photolytic half-lives in soil were 9.5 and 9.7 days versus 118 and 392 days for the non-irradiated controls (difluorophenyl and butylphenyl labels, respectively).

The soil metabolic half-life under aerobic conditions ranges from 9 to 52 days, depending on the soil type. A value of 28 days, based on an EPA t-test of eight values, was selected for modeling purposes in determining EEC's for this document. Under anaerobic conditions, the metabolic half-life was somewhat longer at 102-112 days. In aquatic environments, the half-life of etoxazole under anaerobic conditions is 133-142 days.

In both soil and water, in aerobic or anaerobic conditions, the degradation of etoxazole is extensive. In soil, under aerobic conditions, etoxazole degrades into eight identified metabolites, three of which exceeded 10% of the applied radioactivity (R-7, R-8, and R-13). Under anaerobic conditions, etoxazole degraded into four metabolites, two of which exceeded 10% of the applied radioactivity (R-8 and R-11). In water, under anaerobic conditions, etoxazole degraded into six metabolites, two of which exceeded 10% of the applied radioactivity (R-4 and R-11).

10. Mobility in Soil and Water

Dissipation studies conducted in California and Mississippi on bare ground following the cotton use pattern resulted in field half-lives of 6.2 and 0.8 days respectively.

An additional dissipation study conducted in Utah on bare ground in an apple orchard following the proposed apple use rate, resulted in a field half-life of 11.4 days. In all of the dissipation studies, no vertical movement of etoxazole or any of its soil metabolites was observed.

Laboratory leaching and adsorption/desorption experiments have been conducted on etoxazole and most of its soil metabolites to determine their mobility in soil. Soil/water partition coefficients (K_{oc}'s) were determined using the batch equilibrium method and/or the HPLC method. These studies were conducted on four European soils and four U.S. soils and included sandy loam, clay loam, loamy sand, sandy loam, and sand, all representatives of agricultural soils in regions where etoxazole will be used. The following table summarizes the adsorption equilibrium constants determined:

Summary of Adsorption Equilibrium Constants

Analyte Studied	K_{oc} By Batch Equilibrium		K_{oc} By HPLC	Mobility Classification
	EU Soils	U.S. Soils		
Etoxazole	4910-11,000	14,217-55,275[1]	71,000	Immobile
Metabolite R-3	-	-	5130	Immobile
Metabolite R-4	-	-	759	Low mobility
Metabolite R-7	1125-7540	-	79,400	Immobile
Metabolite R-8	103-351	-	-	Med. Mobility
Metabolite R-13	13,670-83,230	146,400	>427,000	Immobile

[1] A value of 17,150 was selected for use in modeling to determine EEC's (mean of 8 values).

Based on these results, etoxazole and most of its soil metabolites are considered immobile in most agricultural soils. Two metabolites, R-4 and R-8 show low and medium mobility, respectively. The mobility of these metabolites is not a cause for concern, however, as residues were not detected in field dissipation studies conducted in the U.S. The following table summarizes the environmental persistence data for etoxazole:

Summary of Environmental Persistence

Hydrolysis Half-life	161 days
Aqueous Photolysis Half-life	17.4 days
Soil Photolysis Half-life	9.6 days
Aerobic Soil Metabolism Half-life	28 days (EPA t-test of 8 values)
Anaerobic Aquatic Metabolism Half-life	142 days
Field Dissipation Half-life	0.8 to 11.4 days

11. Transport in Air (Spray Drift and Volatility)

Due to the extremely low vapor pressure of etoxazole (7×10^{-6} mm Hg at 25°C), it is not expected to volatilize into the atmosphere. Spray drift has been determined to be a generic issue and that factors influencing spray drift include wind, droplet size, crop canopy, and spray height. All of these factors play a role in managing off-target spray drift.

12. Bioaccumulation as Indicated by Octanol/Water Partition Coefficient

Bioaccumulation is not expected to a great extent with etoxazole despite the relatively large octanol/water partition coefficient (Log P_{ow} = 5.52 @ 20°C). In the bluegill trout bioaccumulation study, the bioconcentration factor (BCF) for etoxazole and its metabolites ranged from 1300 to 1500 in edible tissues, only slightly above the level of concern (i.e. 1000x). This BCF is not as large as would be predicted from the K_{ow} because bioaccumulation is limited by the organism's ability to eliminate the compound from its system, as measured in the bioaccumulation study.

In that study, total radioactivity in non-edible tissue was three times higher than in edible tissue, suggesting that etoxazole has collected in the digestive tract where it can be metabolized and excreted. Equilibrium was reached quickly (7-16 days) and, when transferred to clean water, depuration was rapid (half-life of 3-6 days). These observations are consistent with mammalian systems. For example, in rats 94-97% of an internal dose was excreted within seven days of dosing, most within the first two days. Thus, bioconcentration is minimized with bioaccumulation controlled through metabolism and excretion.

D. OTHER HAZARDS

1. Potential to Deplete Stratospheric Ozone

Neither etoxazole nor any of the SECURE Miticide formulation inerts are structurally related to known ozone depleting compounds. For this reason, SECURE Miticide does not appear to have the potential to deplete stratospheric ozone.

2. Potential to Present a Hazard through Storage, Transport, Mixing, Use or Disposal

SECURE Miticide is produced by Valent U.S.A. and the active ingredient is identified as etoxazole. The chemical abstract name for etoxazole is 2-(2,6-difluorophenyl)-4-[4-(1,1-dimethylethyl)-2-ethoxyphenyl]-4,5-dihydrooxazole. The end-use product is a water dispersible granule (WDG) that contains 72% active ingredient.

The key physical/chemical properties of etoxazole, summarized in the following table, contribute to the safety of the active ingredient and the formulated product.

Summary of Physical/Chemical Properties

GUIDELINE		TEST	RESULT	REFERENCE
Old	New			
63-2	830.6302	Color	Munsell: N9.5/	MRID 45089903
63-3	830.6303	Physical State	Lumpy powder at 20°C	MRID 45089903
63-4	830.6304	Odor	Musty	MRID 45089903
63-5	830.7200	Melting Point	101.5-102.5°C	MRID 45089902
63-6	830.7220	Boiling Point	Not Applicable (N/A)	---
63-7	830.7300	Density	1.2389 g/ml at 25°C	MRID 45089902
63-8	830.7840	Solubility	0.0704 mg/L in water at 20°C 309 g/L in acetone at 20°C 104 g/L in methanol at 20°C 18.7 g/L in n-heptane at 20°C 252 g/L in xylene at 20°C	MRID 45089902 and 45089903
63-9	830.7950	Vapor Pressure	7×10^{-6} mm Hg at 25°C	MRID 45089902
63-10	830.7370	Dissociation Const.	No measurable pK_a	MRID 45089902
63-11	830.7570	Octanol/Water Partition Coeff.	Log P_{ow} = 5.52 at 20°C	MRID 45089902
63-12	830.7000	PH	6.2 at 25°C (1% aqueous suspension)	MRID 45089905
63-13	830.6313	Stability	Stable at elevated temperature. Stability to metal and metal ions not required-contact during storage not likely	MRID 45089904
63-14	830.6314	Oxidizing/Reducing Action	Not oxidizing	MRID 45089903
63-15	830.6315	Flammability	Not flammable	---
63-16	830.6316	Explosivity	No thermal or impact explosive behavior	MRID 45089903
63-17	830.6317	Storage Stability	Stable at ambient temperature for 1 year	MRID 45089906
63-18	830.7100	Viscosity	N/A	---
63-19	830.6319	Miscibility	N/A	---
63-20	830.6320	Corrosion Characteristics	Not required-lack of extreme pH, dry powder packaged in inert polyethylene	---
63-21	830.6321	Dielectric Breakdown Voltage	N/A	---

3. Potential to Affect Endangered and/or Threatened Plant and Animal Species

Using laboratory data and very conservatively calculated EEC values, the potential for acute and chronic effects on sensitive aquatic invertebrates may exist with etoxazole. However, the low use rate, low potential for runoff and fairly rapid degradation in water (photolysis) will reduce this risk to aquatic species. In addition, etoxazole has demonstrated a very low potential to affect plants and terrestrial animals in laboratory studies.

Valent is a member of the FIFRA Endangered Species Task Force. In the event that an assessment of endangered species effects becomes necessary, Valent will follow the procedures agreed upon by the task force and the EPA.

4. PBT/POP Classification

Because of its relatively short half-life in soil (28 days), etoxazole should **not** be classified under TOSCA as a Persistent Biological Toxicant (PBT), also known as Persistent Organic Pollutant (POP).

E. RISK DISCUSSION

1. SECURE Miticide Reduced-Risk Claims

Reduced Risk Claim 1: **SECURE Miticide will reduce the environmental burden in pome fruit, cotton, and strawberry crops by offering growers an alternate pest control tool that will limit the use of carbamate, organophosphate, and other "toxic" insecticides.**

SECURE Miticide is applied to pome fruit, cotton, and strawberry crops at a very low rate. The maximum rate per application is 0.135 pounds active ingredient per acre. This application rate is lower than the rate for all eight of the selected competitive products that Valent believes will be displaced by SECURE Miticide in these markets. Therefore, the use of SECURE Miticide in favor of any of these products will have the effect of reducing the overall chemical burden in the environment. The introduction of SECURE Miticide will not only result in less chemical introduced into the environment but also less risk to the environment. Etoxazole is practically non-toxic to mammals, birds and bees, and has no effects on avian reproduction. Etoxazole's expected environmental concentration (EEC) is lower than the acute toxicity endpoints (LC_{50} or EC_{50}) for fish and freshwater invertebrates so it clearly does not pose an acute risk to these organisms. EEC's for etoxazole use on pome fruit and strawberries (but not cotton) do exceed the acute LC_{50} (or EC_{50}) for saltwater invertebrates, but etoxazole's risk quotients (RQ's) calculated from these EEC's are lower than all of available competitor RQ's, except for one.

Further, Valent believes that growers will have important incentives to use SECURE Miticide:

- etoxazole has been shown to be efficacious against mites that are of economic importance to pome fruit, cotton, and strawberry growers
- etoxazole will be priced to compete with the existing products
- growers urgently need new products to alternate with existing products to combat the serious and growing problem of mite resistance to established miticides.

Spider mites have historically demonstrated a propensity for developing resistance quickly, particularly to products used in tree and vine crops. Research has confirmed that populations of various mite species in some areas have developed resistance to some commonly used miticides such as dicofol (Kelthane), propargite (Comite), abamectin (Zephyr), or combinations of these. Kelthane and Comite are classified by EPA as "C" and "B2" carcinogens, respectively. Once again, they are becoming tolerant to the latest group of products introduced. The few that remain effective do so because of strict resistance management strategies.

The most important tool in managing mite resistance is rotating or mixing products from different classes based on modes of action. Rotation of recently registered miticides with the older miticides may help to reduce resistance to any one of them and slow the development of resistance in areas where it is not yet a problem. With multiple applications per year, products with different classes should be alternated so that only one generation of mites per crop year is exposed to a particular class of chemical. When only one application is made, products should be rotated from different classes from year to year to reduce selection pressure. Because etoxazole acts by a mode of action that is different than that of the available alternates, SECURE Miticide will provide growers with a new product that can be rotated with the existing products to mitigate the development of resistance.

The use of SECURE Miticide will also allow growers to effectively control mite populations with fewer applications of traditional broad-spectrum insecticides which can disrupt the life cycle of many beneficial mites and insects. This principle has been clearly demonstrated in commercial practice with the introduction of another Valent product, Knack Insect Growth Regulator, for control of whitefly in Arizona cotton and red scale in California citrus. In both instances, introduction of the new insecticidal mode of action resulted in a dramatic decrease in usage of traditional insecticides. SECURE Miticide's low use rates coupled with the decrease in usage of toxic insecticides will decrease the overall pesticide environmental burden in pome fruit, cotton, and strawberry growing regions.

Reduced Risk Claim 2: **SECURE Miticide will reduce exposure to hazardous carcinogenic and/or neurotoxic insecticides, with an overall benefit to mixer, loader, applicators, and workers reentering the treated orchards and fields.**

SECURE Miticide does not pose a toxicological hazard to mammalian systems when used according to label directions. Chronic exposures to consumers and workers are negligible, and thus the risks entailed with the use of the product are minimal. Four miticides commonly used in cotton, pome fruit, and strawberry crops that will be displaced by SECURE Miticide are either "Group B2" (probable human) or "Group C" (likely human) carcinogens. Also, two other miticides commonly

used in these crops are cholinesterase inhibitors (one organophosphate and one carbamate). The carbamate (aldicarb) has an acute toxicity to rats (LD_{50}) of 1 mg/kg/day. As the use of these insecticides is reduced by the availability of SECURE Miticide, the overall exposure to these hazardous materials by mixer, loader, applicators and workers reentering treated fields and orchards will be reduced.

Reduced Risk Claim 3: **SECURE Miticide can be used as an important partner with Integrated Pest Management Programs, reducing the grower's dependence on more toxic products.**

IPM is an approach that combines various tools and methods, including chemical and biological products, natural pest enemies, and cultural methods such as sanitation, crop rotation, and resistant crop varieties, to manage pests at an economically acceptable level. Etoxazole is well suited for use in IPM programs because it shows high selectivity to harmful mite species such as the twospotted spider mite, European red mite, Pacific spider mite, McDaniel spider mite, and the carmine spider mite. But, SECURE Miticide has no hazardous effects on many beneficial insects and mites. Insect predators or parasites which are generally unaffected by etoxazole include: *Anthocoris melanocerus* (Pear Psylla predator), *Encarsia formosa* (Whitefly parasite), *Neoseiulus californicus* (predatory mite), *Aleochara bilineata* (predaceous beetle), *Aphidius rhopalosiphi* (parasitic wasp), and *Scolothrips takahasii* (predaceous thrips). In pome fruit, cotton, and strawberry crops, the major non-chemical IPM tool is the use of beneficial insect predators. SECURE Miticide very effectively compliments the use of this tool because it selectively controls susceptible mite species without interrupting the life cycle of the above beneficial insects and mites.

Release of parasitoids such as *Aphytis melinus* has proven to be effective for scale control when scale populations are relatively low and there is not any pressure from other pests. *Aphytis* is very susceptible to neurotoxic insecticides and requires elimination of broad-spectrum pesticides. In addition, the cost for *Aphytis* averages approximately $90.00 per acre. SECURE Miticide provides an excellent fit in this release program by allowing the grower to concurrently control mites while avoiding unwanted impact on beneficial insects and mites.

Reduced Risk Claim 4: **With a mode of action that is different than that of competitive products, SECURE Miticide will be an important tool in management of developing insect resistance (IRM programs).**

Organophosphate (OP) insecticides have been used in orchard crops to control insect pests for over 30 years. The result of such long-term exposure to these materials has been the development of OP resistance by many tree crop pests. Also, laboratory bioassays have demonstrated that dicofol (Kethane) and/or propargite (Comite) resistance has been detected in 25% of twospotted spider mite and 40% of Pacific mite populations. To maintain effective control of resistant species, growers have increased the rates and frequency of pesticide applications. While control can be achieved with increased rates and number of applications, this type of program tends to select for rapid increases in resistance.

A side effect of developing resistance is the development of cross-resistance to other insecticides. Cross-resistance is when a single resistance mechanism allows an insect to survive a normally lethal dose of another pesticide with a different mode of action. There appears to be at least partial cross-resistance between the organophosphate and the carbamate insecticides and, thus, resistance cannot be reduced by alternation of these compounds.

Insect resistance management programs are designed to slow resistance and decrease the potential for cross-resistance between currently used insecticides primarily by rotating between miticides with different modes of action. Because SECURE Miticide has a mode of action that is different from currently used miticides, it is well suited to fit into this IRM strategy. It can be applied in combination or alternation with currently available miticide/insecticide products to control target mites. Etoxazole's unique chemistry and pest-specific mode of action will provide a valuable tool to breaking the cycle of mite resistance. Ultimately, this will help maintain longevity of miticides currently labeled for use.

2. Risk Comparison to Registered Pesticides and Pest Control Practices

Tables 1-4 provide a comparison of the use pattern, toxicity, and technical attributes of SECURE Miticide and those products expected to be displaced by SECURE Miticide. These tables were constructed from product labels, MSDS's and Pesticide Fact Sheets as well as other agrochemical references such as *The Pesticide Manual, Farm Chemicals Handbook, Agrochemcials Desk Reference,* and *Crop Protection Reference*. See References for other sources. Information is extremely limited and, in many instances, qualitative in nature.

Table 5 lists the trade names and EPA Chemical Number for each of the active ingredients compared. A summary of the environmental fate characteristics of each of these products is provided in Appendix IIII. The following table highlights a few parameters that emphasize the differences in relative toxicity and environmental persistence between etoxazole and its selected competitors:

Active Ingredient	Max. Rate lb. a.i./A	RfD (mg/kg/day)	K_{oc}	Additional Risk Factors
Etoxazole	**0.135**	**0.04**[1]	**17,150**	
Clofentezine	0.25	0.013	11,000	Carcinogen
Pyridaben	0.50	0.005	NA	Neurotoxin
Hexythiazox	0.19	0.025	6200	Carcinogen, possible neurotoxin
Fenbutatin-Ox	1.5	0.05	2300	Toxic to birds
Propargite	1.6	0.04	2963	Carcinogen
Profenofos	1.0	0.00005	840	OP, cholinesterase inhibitor
Dicofol	3.0	0.0004	5868	Carcinogen, neurotoxin
Aldicarb	20	0.00125	30	Carbamate, cholinesterase inhibitor

[1] Proposed by Valent. EPA has not reviewed toxicity data.

Note that etoxazole has the lowest maximum application rate of any of the competitive products and a reference dose (RfD), which represents EPA's assessment of its mammalian toxicity, that is the nearly the same or higher than all of the competitive products. Etoxazole also has the highest K_{oc} among the selected competitors, indicating its low potential to leach into groundwater. Two of the currently registered products are neurotoxicants and four are potential human carcinogens, all of which present a greater potential risk to workers compared to etoxazole, which is neither oncogenic nor neurotoxic. Although not summarized above, some of the products, unlike etoxazole, are also toxic to bees and beneficial insects.

The following table summarizes the ecological risks associated with the use of SECURE Miticide and each of its selected competitors. These risks are characterized using EPA's Risk Characterization (minimal, potential, high), based on the Risk Quotients (RQ's) calculated from the EEC's and the ecotoxicology endpoints for each chemical as described in Appendix III.

Active Ingredient	Acute Risk		Chronic Risk	
	Fish	Invertebrates[1]	Fish	Invertebrates[1]
Etoxazole	**Minimal**	**Potential**	**Minimal-Potential**	**High**
Clofentezine	Minimal	High	Minimal	Minimal
Pyridaben	Potential-High	High	Potential	High
Hexythiazox	Minimal	Minimal	NA	Minimal
Fenbutatin-Ox	Potential-High	Potential	High	Potential-High
Propargite	High	Potential-High	High	High
Profenofos	High	High	High	High
Dicofol	Minimal-Potential	Minimal	High	NA
Aldicarb	High	High	NA	NA

[1] Freshwater invertebrates only-all of these products (except dicofol) represent high acute and chronic risk to saltwater invertebrates.
NA=not available. RQ could not be calculated because endpoint not available.

In most cases, SECURE Miticide will offer a "safer" alternative compared to the key products, whether the criteria are human health effects or environmental/ecological impact. The low rate range of 0.045 to 0.135 lb a.i./A, maximum seasonal use rate of 0.27 lb a.i./A, coupled with its fairly rapid environmental breakdown and minimal toxicity to animals, makes SECURE Miticide worthy of consideration for expedited review as a reduced-risk pesticide.

One of the products that will be displaced by SECURE Miticide in the cotton market (profenofos) is an organophosphate insecticide. For this reason, Valent believes that etoxazole should also be classified as an OP replacement, which also qualifies it for expedited review.

3. Economic Analysis – Market Impact

This discussion has been removed to the Confidential Business Information Attachment, Cross Reference Number 1.

F. PEST RESISTANCE AND MANAGEMENT

Insect resistance management programs include the use of diverse chemistry, a limitation on the use of sprays and careful application timing. These programs are designed to slow resistance and decrease the potential for cross-resistance. A key factor in managing insect resistance is complete knowledge of the insect's life cycle. With this knowledge, crop protection scientists can develop programs that will target specific pest stages and counter the resistance problem.

Two spotted spider mites in particular have a history of developing resistance to miticides rapidly when a miticide is applied repeatedly to the same population. Alternating the use of miticides that have different modes of action helps reduce the development of resistances to a specific miticide. Organophosphate, carbamate, and pyrethroid insecticide applications can stimulate TSM outbreaks by disrupting the balance with beneficial insects.

As described previously, SECURE Miticide appears to act by inhibiting the molting process through disruption of the cell membrane. Etoxazole has excellent contact activity against juvenile stages from egg to larvae and nymphs but has no acute toxicity to adult insects. To manage insect resistance, new insecticide chemistry and changes in control practices are required. Etoxazole's unique chemistry and pest-specific mode of action will provide the crucial link to breaking the cycle of developing insect resistance.

G. COMPARATIVE PERFORMANCE DATA

The following is a brief overview of the results of efficacy studies that Valent has conducted with etoxazole in the U.S. since 1996. These studies demonstrate that etoxazole effectively controls certain mite species and that it, in general, performs as well or better than the products that were considered standards at the time the studies were conducted. Further details of these studies can be found in **Appendix IV**.

Cotton

A total of nineteen (19) trials have been conducted since 1996 to study the control of mites in cotton with etoxazole. Trials were located in major cotton areas impacted by mites. Etoxazole was evaluated as a single application with rates ranging from 0.03 to 0.045 lbs a.i./A, applied alone. Treatments were applied by ground in standard water volumes of approximately 8 to 76 GPA. One trial was conducted to evaluate the efficacy of aerial application to cotton. This aerial trial was conducted using 3.39 GPA.

Etoxazole at rates of 0.03 lbs a.i./A or higher consistently provided good to excellent control of twospotted spider mites (*Tetranychus urticae*). Control was equal to the standards, including the following chemicals: dicofol, hexythiazox, propargite, chlorfenapyr, amitraz, bifenthrin, abamectin, pyridaben, and fenpropathrin. See **Appendix IV** for a list of tradenames associated with these active ingredients.

Single or multiple trials were also conducted to evaluate control of carmine spider mite (*Tetranychus cinnabarinus*) with etoxazole. Control was good to excellent at 0.03 to 0.045 lbs. a.i./A. However, it has been observed that the 0.045 lb. rate is more consistent across trials. Etoxazole applied aerially at 0.045 lbs. a.i./A also provided good control of carmine spider mite. Control is this case was equal to the standards, including dicofol, bifenthrin, chlorfenapyr, and fenpropathrin. See Appendix IV for a list of tradenames associated with these active ingredients.

The addition of various surfactants/adjuvants (vegetable oil, non-ionic surfactants, methylated seed oil, petroleum crop oil concentrate) generally did not improve the efficacy of etoxazole over etoxazole applied alone.

Pome Fruit

A total of twenty three (23) trials have been conducted since 1996 to study the control of mites in pome fruit with etoxazole. Trials were conducted in the major growing areas including California, Michigan, Pennsylvania, Oregon, Washington, New York, and North Carolina. Etoxazole was evaluated as a single application with rates generally ranging from 0.045 to 0.18 lbs active/acre applied alone or as a tank mix. Treatments were applied by ground in standard water volumes of approximately 40 to 400 gallons water per acre (GPA)(most often between 100 and 200).

Etoxazole applied at rates of 0.065 lb. a.i./A or higher consistently provided good to excellent control of twospotted spider mites (*Tetranychus urticae*) and European red mite (*Panonychus ulmi*). Control was usually equal to or superior to the standards that included the following chemicals: pyridaben, abamectin, bifenazate, hexythiazox, and clofentezine. See Appendix IV for a list of tradenames associated with these active ingredients. Trials to evaluate the effectiveness of tankmixing etoxazole with fenpropathrin indicate no economic benefit over using etoxazole alone.

Two trials were conducted to evaluate the effect of etoxazole on the predatory mite *Amblyseius fallacis* in pome fruit. Some reduction was noted with etoxazole and all other treatments including the standards, but there were no differences between treatments, which ranged from at 0.078 to 0.09 lbs. a.i./A. In a single trial, etoxazole did have a significant negative effect on the predatory mite (*Typhlodromus occidentalis*) compared to the control. In a separate trial, there was no apparent effect on predaceous mites (*Typhlodromus pyri*) under low numbers. In separate trials etoxazole applied at 0.065 to 0.135 lbs. a.i./A reduced western predatory mites (*Galandromus occidentalis*), the mite predator (*Hyaliodes vitripennis*), and the mite predator (*Stethorus punctum*) compared to the control but was no different than other treatments in the tests.

Strawberry

A total of eight (8) trials have been conducted since 1996 to study the control of mites in strawberries with etoxazole. Trials were located in California and Oregon. Etoxazole was evaluated as a single application with rates ranging from 0.018 to 0.268 lbs. a.i./A, applied alone or as a tank mix. Treatments were applied by ground in standard water volumes of approximately 100 to 250 GPA.

Etoxazole at rates of 0.03 lbs. a.i./A or higher consistently provided good to excellent control of twospotted spider mites (*Tetranychus urticae*) in strawberries. Control was equal to the standards (pyridaben, chlorfenapyr, abamectin, and fenpropathrin). Trials evaluating the efficacy of tankmixing etoxazole with fenpropathrin showed no benefit over treating with etoxazole alone.

Two trials were conducted to evaluate the effect of etoxazole on the predatory mite *Amblyseius fallacis* in strawberries. Some reduction was noted with etoxazole and all other treatments including the standards, but there were no differences between treatments, which ranged from at 0.018 to 0.03 lbs. a.i./A. In a single trial, etoxazole did have a significant negative effect on the western predatory mite (*Typhlodromus occidentalis*) compared to the control. In a separate trial, there was no apparent effect on predaceous mites (*Typhlodromus pyri*) under low numbers.

H. OTHER INFORMATION

Proposed Product Label

A copy of the proposed product label can be found in Appendix III of this petition.

Letters of Support

Copies of letters from a pest consultant and a field research specialist supporting the registration of SECURE Miticide are included in Appendix V of this petition.

I. REFERENCES

C&P Press, *Crop Protection Reference*, 2000.

Meister Publishing Company, *Farm Chemicals Handbook*, 2000.

Montgomery, John H., *Agrochemicals Desk Reference, Environmental Data*. 1993.

Tomlin, Clive D. S., *The Pesticide Manual, 11th Edition*, The British Crop Protection Council. 1997.

Whiting, Rick J. *Office of Pesticide Programs Reference Dose Tracking*. February 25, 1997.

ECOTOX: Ecotoxicology Database, Office of Research and Development, National Health and Environmental Effects Research Laboratory,.

Environmental Fate & Effects Division, PESTICIDE ENVIRONMENTAL FATE ONE LINE SUMMARY

OSU Extension Pesticide Properties Database (http://ace.orst.edu/info/nptn/ppdmove.htm)

USDA Crop Profiles (Office of Pest Management Policy and Pesticide Impact Assessment Program)

Insecticide and Acaricide Usage on Tree Fruit, Vines, Citrus and Nuts, Richard F. Buhn, 2000.

Summary of Pesticide Use Report Data, Preliminary Data, 1998, 1999, 2000, California Department of Pesticide Regulation.

Table 1. Comparison of Etoxazole to Other Pome Fruit, Cotton, and Strawberry Active Ingredients

Active Ingredient	Chemical Class	Mode of Action	Crop	Rate lb ai/A	Pest
Clofentezine	Tetrazine	Chitin syntheses inhibitor	Pome Fruit	0.25	European red mite, Pacific spider mite, two-spotted spider mite
Etoxazole	Diphenyl oxazoline	Inhibits molting	Pome Fruit, Cotton, Strawberry	0.135	European red mite, Pacific spider mite, two-spotted spider mite, carmine spider mite, citrus red mite, southern red mite
Pyridaben	Pyridazinone	Mitochondrial electron transport Complex 1	Pome Fruit	0.50	European red mite, Pacific spider mite, two-spotted spider mite
Hexythiazox		Chitin syntheses inhibitor	Pome Fruit, Cotton, Strawberry	0.19	European red mite, Pacific spider mite, two-spotted spider mite
Fenbutatin-oxide	Organotin	Adulticidal activity	Pome Fruit, Strawberry	1.5	European red mite, two-spotted spider mite
Propargite	Organosulfite	Adulticidal activity	Cotton, Strawberry	1.6	Pacific spider mite, two-spotted spider mite, European red mite, Pacific spider mite, Mcdaniel strawberry mite
Profenofos	Organophosphate	Cholinesterase Inhibition	Cotton	1.0	Mites
Dicofol	Organochlorine	Adulticidal activity	Pome Fruit, Cotton, Strawberry	3.0	European red mite, Pacific spider mite, two-spotted spider mite
Aldicarb	Carbamate	Cholinesterase Inhibition	Cotton	20	Mites

Table 2. Comparison of Etoxazole to Other Pome Fruit, Cotton, and Strawberry Active Ingredients

Active Ingredient	Toxicology Signal Word	Toxicity Class	Restricted Entry Interval (hours)	Formulation Type (Liquid, Dry, Both)
Clofentezine	Caution	III	12	Liquid
Etoxazole	Caution	III	12	Dry
Pyridaben	Warning	II	12	Dry
Hexythiazox	Caution	IV	12	Both
Fenbutatin-oxide	Danger	I	48	Both
Propargite	Danger	I	168	Liquid
Profenofos	Warning	II	72	Liquid
Dicofol	Warning	II	12	Both
Aldicarb	Danger	I	48	Dry

Table 3. Technical Attributes and Comparative Analysis of Etoxazole to Other Pome Fruit, Cotton, and Strawberry Active Ingredients

		Human Health Effects			Environmental Fate and Ecological Effects						
Active Ingredient	Appl. Rates >¼ lb. ai/A	Possible Carcinogen /Oncogen	Terato-genic Effects	Neuro-toxicant	Hydrolysis $t_{1/2}$ > 7 days	Soil $t_{1/2}$ >14 days	Leaching Potential	Avian Effects Potential	Aquatic Effects Potential	Toxicity to Bees	Toxicity to Beneficial Predators
Clofentezine	Yes	Yes	Yes	No	No	Yes	No	No	No	No	No
Etoxazole	No	No	No	No	Yes	Yes	No	No	Yes	No	No
Pyridaben	Yes	No	No	Yes	Yes	Yes	No	No	Yes	Yes	
Hexythiazox	No	Yes	No	Maybe	Yes	Yes		No	No	No	
Fenbutatin-oxide	Yes	No	No		Yes	Yes	No	Yes	Yes	No	No
Propargite	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	No	Yes
Profenofos	Yes	No	No	No	Yes	No	No	Yes	Yes	Yes	
Dicofol	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes[1]
Aldicarb	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes

[1] Dicofol is toxic to predaceous mites but relatively non-toxic to beneficial insects.

Table 4. Technical Attributes and Comparative Analysis of Etoxazole to Other Pome Fruit, Cotton, and Strawberry Active Ingredients

Active Ingredient	Restricted Use	Acute LD_{50} Mg/kg (rat)	OPP RfD Mg/kg/day	Avian Acute mg/kg	Aquatic Acute LC_{50} ppb
Clofentezine	No	>5200	0.013	>750 to >3000	0.84 to >24000
Etoxazole	No	>5000	0.04	>2000	1.2 to 2800
Pyridaben	No	570	0.005	>2250 to >2500	0.47 to 13.3
Hexythiazox	No	>5000	0.025	>2510	530 to >1000
Fenbutatin-oxide	**Yes**	4400	0.05	>2510	0.4 to 31
Propargite	No	2800	0.04	3401 to >4640	31 to 118
Profenofos	**Yes**	358	0.00005	56 to 70	0.93 to 263
Dicofol	No	570	0.0004	265	15.1 to 510
Aldicarb	**Yes**	1.0	0.00125	1.0 to 2.0	50 to 411

Table 5. Chemical, Trade, and EPA Chemical Codes for Pome Fruit, Cotton, and Strawberry Products

Active Ingredient	Trade Name	EPA Chemical Code
Clofentezine	Apollo	125501
Etoxazole	Secure	107091
Pyridaben	Pyramite	129105
Hexythiazox	Savey	128849
Fenbutatin-oxide	Vendex	104601
Propargite	Comite, Omite	097601
Profenofos	Curacron	111401
Dicofol	Kelthane	010501
Aldicarb	Temik	098301

APPENDIX I -DATA MATRIX FOR SECURE ™ Miticide

Form Approved OMB No. 2070-0040

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
401 M Street, S.W.
WASHINGTON, D.C. 20460

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DATA MATRIX

Date 2/15/02		EPA Reg No./File Symbol 59639-	Page 1 of 11
Applicant's/Registrant's Name & Address	Valent U.S.A. Corporation 1333 North California Blvd., Suite 600 Walnut Creek, CA 94596	Product Secure Miticide	

Ingredient

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
NONE	Summary of Data Supporting the Registration of Etoxazole Technical and the Use of Tetrasan™ 5 WDG on Greenhouse Ornamentals	45089901	Valent USA Corporation	OWN	
NONE	Etoxazole Supplemental Information: Statutory Findings and Information Summaries to Comply with The Food Quality Protection Act of 1996 in Support of Registration and Tolerances on Pome Fruit, Cotton, Strawberry, and Oranges		Valent U.S.A. Corporation		
NONE	SECURE Miticide - Petition For Expedited Review as a Reduced Risk Pesticide/OP Replacement When Used On Pome Fruit, Cotton, and Strawberry Crops		Valent U.S.A. Corporation	OWN	
NONE	Summary of Data and Tolerance Petition Supporting the Registration of Etoxazole Technical and the Use of SECURE Miticide on Cotton, Pome Fruit, Strawberries, and Oranges		Valent U.S.A. Corporation	OWN	
NONE	Tier 1 Chronic and Acute Dietary (Including Drinking Water) Exposure Analyses for Potential Residues of Etoxazole in/on Cotton, Pome Fruites, Strawberries, Imported Mandarin Oranges, Beef fat, and Milk fat		Valent U.S.A. Corporation	OWN	

2/15/02 Product: SECURE Miticide Active Ingredient: Etoxazole

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
830.1550 830.1600 830.1620 830.1650 830.1670 830.1700 830.1750 830.1800 830.1900 830.6303 830.6314 830.7000 830.7300	U.S. EPA Product Properties Test Guidelines - Group A and Group B of V-1283 72 WDG		Valent U.S.A. Corporation	OWN	
830.1550 830.1600 830.1620 830.1670	Product Identity and Composition Description of Materials Used to Produce the Product Description of Production Process for the Technical YI-5301 Discussion of Formation of Impurities		Valent USA Corporation	OWN	
830.1700 830.1750 830.1800	Analysis of S-1283, and its Production Process Impurities in S-1283 Technical (830.1700) Certification of Ingredient Limits of S-1283 Technical (830.1750) Determination of S-1283 in S-1283 Technical (830.1800) Determination of Methoxyoxazoline and DFBA-Ox	45250901	Valent USA Corporation	OWN	
63-02 63-03 63-04 63-05 63-08 63-09 63-10 63-11 63-12	S-1283 (Pure) Physicochemical Properties	45089902	Valent USA Corporation	OWN	

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
63-02 63-03 63-04 63-14 63-15 63-16	S-1283 (Technical) Physicochemical Properties	45089903	Valent USA Corporation	OWN	
830.6303 830.6314 830.7000 830.7300	Physical and Chemical Properties of V-1283 72 WDG		Valent U.S.A. Corporation	OWN	
NONE	Tank Mix Stability of Etoxazole in Water Dispersions of S-1283 38 SC		Valent U.S.A. Corporation	OWN	
830.6313	Elevated Temperature Shelf-Life Storage Stability Characteristics of Etoxazole Technical	45089904	Valent USA Corporation	OWN	
830.7000 830.7300	Physical and Chemical Properties of S-1283	45089905		OWN	
830.6317	Shelf Life Storage Stability Characteristics of S-1283 Technical Grade	45089906	Valent USA Corporation	OWN	
830.1550 830.1600 830.1650 830.1670 830.1700 830.1750 830.1800 830.1900 830.6303 830.6314 830.7000 830.7300	U.S. EPA Product Properties Test Guidelines - Group A and Group B of TetraSan 5 WDG	45250902	Valent USA Corporation	OWN	
830.6303 830.6314 830.7000 830.7300	Physical and Chemical Properties of TetraSan 5 WDG	45089907	Valent USA Corporation	OWN	
71-1	S-1283 Acute Oral Toxicity (LD50) to Mallard Duck	45089908	Valent USA Corporation	OWN	
71-2	S-1283 Dietary LC50 to the Mallard Duck	45089909	Valent USA Corporation	OWN	
71-2	YI-5301 Subacute Dietary Toxicity (LC50) to the Bobwhite Quail	45089910	Valent USA Corporation	OWN	