US Environmental Protection Agency
Office of Pesticide Programs

Petition for Etoxazole -
Tab E - Reduced Risk Petition/
OP Replacement Petition
MRID 45630502

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Tab E

Etoxazole: Reduced Risk Pesticide/OP Replacement Petition
MRID 45630502

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DATA SUBMISSION VOLUME _____

DATA REQUIREMENT:

None

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STUDY TITLE:

SECURE™ Miticide - Petition For Expedited Review as a Reduced Risk Pesticide/OP Replacement When Used On Pome Fruit, Cotton, and Strawberry Crops

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STATEMENT OF DATA CONFIDENTIALITY CLAIMS

Information claimed confidential on the basis of its falling within the scope of FIFRA Section 10 (d) (1) (A), (B), or (C) has been removed to a Confidential Business Information Attachment and is cited by a cross reference number in the body of the report.

■This statement supersedes any other claims of confidentiality found in this report.

Company: VALENT U.S.A. CORPORATION

Company Agent: James W. Pensyl

Title: Project Manager

Date: 2/15/2002

Signature:

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This report was not designed to meet FIFRA Good Laboratory Standards set forth in 40 CFR Part 160 for the following reason(s):

·No new data was generated

Sponsor/Submitter
James W. Pensyl
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Date 2/15/2002

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INTRODUCTION

Valent U.S.A. Corporation is pleased to petition the United States Environmental Protection Agency for a reduced-risk status for SECURE™ Miticide, a new product containing the active ingredient etoxazole. Valent is also requesting that SECURE Miticide be classified as an OP replacement, as well as a reduced-risk pesticide, because one of the key products that will be replaced by SECURE Miticide in the cotton market is an organophosphate insecticide. Valent further requests that the EPA consider the enclosed information for a Public Interest Finding (PIF) should a conditional registration for SECURE Miticide be required.

Valent is developing SECURE Miticide for use in IPM (Integrated Pest Management) and IRM (Integrated Resistance Management) programs for control of mites in pome fruit, cotton, and strawberry growing areas throughout the United States. Key mites controlled by SECURE Miticide include European red mite, Pacific spider mite, carmine spider mite, two-spotted spider mite, citrus red mite, McDaniel spider mite, and southern red mite. Etoxazole 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. Although the mode of action of etoxazole has not been defined, it clearly functions by a mechanism that differs from that of its competitors, making it a valuable new tool in existing IRM programs.

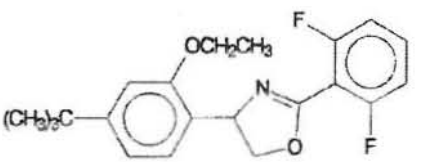
This document is being submitted in conjunction with applications to register the first food uses for etoxazole (SECURE Miticide), and with a petition to establish etoxazole tolerances in/on pome fruit, cottonseed, strawberries, and their associated processed commodities. The registration of etoxazole technical and TetraSan 5 WDG Miticide, containing etoxazole as the active ingredient, for non-food uses (greenhouse ornamentals) is currently pending at the Agency.

A. EXECUTIVE SUMMARY

1. **Chemical Name:** **Etoxazole**
   2-(2,6-difluorophenyl)-4-[4-(1,1-dimethylethyl)-2-ethoxyphenyl]-4,5-dihydrooxazole

2. **CAS Number:** **153233-9-1**

3. **Chemical Structure:**



4. **Chemical Class:** **Diphenyl Oxazoline**

5. **Mode of Action:**
The mode of action of etoxazole has not yet been determined but it appears to control susceptible mites by inhibiting the molting process through disruption of the cell membrane. Etoxazole has excellent contact activity against juvenile stages from egg to nymphs but has no acute toxicity to adult mites. In this petition, Valent is claiming that SECURE Miticide will replace a significant portion of the following chemicals currently registered for use on pome fruit, cotton, and strawberry crops: clofentezine, pyridaben, hexythiazox, fenbutatin-oxide, propargite, profenofos, docofol, and aldicarb. While the mode of action of etoxazole is uncertain, studies have been conducted suggesting that its mode of action is different from the mode of action of these competitive chemicals. These studies have shown that:

- three of the above products (fenbutatin oxide, propargite, and dicofol) show high adulticidal activity, suggesting that their mode of action is different from that of etoxazole, which has no adult activity.
- one of the above product (pyridaben) is an inhibitor of mitochrondrial electron transport complex I. Etoxazole was found to be effective against mites that are resistant to pyridaben, suggesting that etoxazole does not exhibit this mode of action.
- two of the above products (hexythiazox and clofentezine) are chitin synthesis inhibitors. Etoxazole was found to be effective against mites that are resistant to these products, suggesting that etoxazole does not function by this mode of action.
- the last two products listed above (profenofos and aldicarb) are cholinesterase inhibitors. The results of all of the toxicology studies done with etoxazole show no evidence of any endocrine-mediated effects and no pathology of the endocrine organs. Consequently, it can be concluded that etoxazole does not possess estrogenic or endocrine disrupting properties.

Etoxazole's unique mode of action will make SECURE Miticide a valuable new tool in the continuing effort to delay the development of resistance to existing miticides.

Etoxazole exhibits pronounced translaminar movement in plant leaves. Translaminar movement is important because a major obstacle to effective mite control is getting the product to where the pests are located on the plant, often the undersides of leaves.

6. Proposed Use Pattern:

SECURE Miticide is formulated as a water dispersible granule (WDG) product containing 72% active ingredient (a.i.). Application rates will be very low, ranging from 0.045 to 0.135 pounds active ingredient per acre (lbs. a.i./A). To minimize the development of resistance to the product, no more than two applications will be recommended per season to any of the proposed crops. Pre-harvest intervals range from one day for strawberries to 28 days for pome fruit and cotton. The following is a discussion of the crop specific use patterns, including a brief review of the current pome fruit, cotton and strawberry markets and how Valent believes SECURE Miticide will fit into those markets.

Apples

SECURE Miticide will be applied to apples at a maximum application rate of 0.135 lbs. a.i./A using standard ground airblast equipment. A maximum of two applications per season at a minimum 21-day interval will be recommended on the proposed label. Preharvest interval will be 28 days. Apples will be treated beginning around May 15th and ending as late as November 15th. There are six major apple-producing areas in the U.S. and SECURE Miticide will potentially be used in all of them: Western New York, the Hudson and Champlain Valleys and New England, Mid Atlantic-Southeastern, Midwest, Pacific Northwest, and California. There are three mites of major importance to apple production in the U.S.: European red mite, twospotted spider mite, and the McDaniel spider mite, all of which are effectively controlled by SECURE Miticide.

The European Red Mite is established in most deciduous fruit growing areas and is considered the most important mite species attacking tree fruits in North America. Injury is caused by the piercing of the cell walls by the bristle-like mouth parts and the ingestion of their contents, including the chlorophyll. The injury results in off-color foliage, which in severe cases becomes bronzed as compared to uninfested foliage. The leaf efficiency and productivity is directly affected. Heavy mite feeding early in the season not only can reduce tree growth and yield but also drastically affect fruit bud formation, and thereby reduce yields the following year. Injury caused by European red mites does not lead to leaf drop but mite-injured leaves will not respond to growth regulators applied to delay harvest drop.

The twospotted spider mite (TSM) is an indirect pest that feeds by extracting leaf sap. The TSM and the McDaniel spider mite can cause almost complete defoliation of apple trees that exposes trees and fruit to sunburn, reduces fruit size and sugar, and interferes with coloring of fruit and with harvest and can cause preharvest drop. Species are favored by hot, dry conditions and, as the weather becomes warmer, the mites increase in numbers and move throughout the tree. Severe defoliation early in the season can reduce yield by 10% as well as interfere with production of sugars, size, and

color. Over the past 25 years, IPM practices have been adopted to manage mite populations through predators and selective use of insecticides and acaricides as growers learned that mites were rapidly developing resistance to commonly used miticides.

The current product of choice for control of mites in all apple-producing areas (except California) is Pyramite (pyridaben). Other major miticides currently being used in apple production are Agri-Mek (abamectin), Savey (hexythiazox), Apollo (clofentezine), Summer oil, Vendex (fenbutatin-oxide), and Kelthane (dicofol). **(Pyramite and Kelthane are neurotoxins and Savey and Kelthane are classified as "C" carcinogens).**

Pyramite should remain the leading miticide, but its number of treated acres probably will not increase in the future due to concern about mites developing resistance to this product. Both Vendex and dicofol will be used as alternatives to Pyramite for rescue applications and are expected to grow significantly in the near future.

Valent believes that SECURE Miticide can replace a significant amount of these products in the apple market for three reasons:

1. Etoxazole effectively controls the major mites infesting apples (European red mite, twospotted spider mite, McDaniel spider mite)
2. Etoxazole has a mode of action that is different than the products currently used on apples to control these mites, making it a good choice for growers looking for a new product for their IRM programs
3. The cost to treat an acre of apples with SECURE Miticide will be significantly less than Pyramite and comparable in price to the other products.

Valent's estimate of SECURE Miticide's penetration into the pome fruit market, with supporting marketing information, is discussed in Section E.3 of this document. See the Confidential Business Information Attachment.

Pears

SECURE Miticide will be applied to pears at a maximum application rate of 0.135 lbs. a.i./A using standard ground airblast equipment. A maximum of two applications per season at a minimum 21-day interval will be recommended on the proposed label. Preharvest interval will be 28 days. Pears will be treated beginning around May 15th and ending as late as November 15th.

The major pear producing areas of the U.S. are located on the Pacific slope. Fire blight, a bacterial disease, limits pear production east of the Rocky Mountains. The use of SECURE Miticide on pears will occur mostly in the west where 94% of the U.S. acreage is located, with Washington being the leading pear producing state in the U.S. The remaining pear production in the west is in California and Oregon.

The twospotted spider mite is the primary mite infesting pears in all regions. The Pacific spider mite occurs in California. The McDaniel spider mite attacks both pears and apples and is a major pest in Washington and in the Hood River district of Oregon. All of these mites are effectively controlled by etoxazole. In pears, mite feeding can affect the leaf color by reducing photosynthetic activity. Mites feed on leaves causing loss of green color followed by a characteristic blackening and eventual defoliation. Severe defoliation can cause decreased fruit size and may cause the tree to bloom in the fall. The European red mite can be a serious problem in some growing districts; it overwinters as eggs on the tree and feeds on the leaves causing mottling of the foliage that, in severe cases, become bronzed. This mite is also effectively controlled by etoxazole. Biological control of mites has not been successful in pears because insecticides used to control pear psylla and codling moth are very toxic to predator mites. Pears have a low threshold for spider mite feeding, substantially lower than on apples.

The three major products currently being used to control mites in pears are Apollo, Vendex, and Savey. **(Apollo and Savey are both classified as "C" carcinogens).** The use of Apollo and Savey is expected to increase significantly in the future with their treated acreage about equally divided as they are alternated to prevent the development of resistance. Vendex will be the other miticide used and its treatment acres are expected to increase by 10% as the principal rescue treatment. Valent believes that SECURE Miticide can replace a significant amount of these products in the pear market for three reasons:

1. Etoxazole effectively controls the the major mites infesting pears (twospotted spider mite, Pacific red mite, and the McDaniel spider mite)
2. Etoxazole has a mode of action that is different than the products currently used on pears to control these mites, making it a good choice for growers looking for a new product for their IRM programs
3. The cost to treat an acre of pears with SECURE Miticide will be comparable to the competitive products

Valent's estimate of SECURE Miticide's penetration into the pome fruit market, with supporting marketing information, is discussed in Section E.3 of this document. See the Confidential Business Information Attachment.

Cotton

SECURE Miticide will be applied to cotton at a maximum application rate of 0.045 lbs.a.i./A using standard ground equipment. Aerial application to cotton is also permitted. A maximum of two applications per season at a minimum 21-day interval will be recommended on the proposed label. Preharvest interval will be 28 days. Cotton will be treated with SECURE Miticide beginning around May 1st and ending in late August.

SECURE Miticide use on cotton will, for the most part, be limited to California and primarily five counties of the San Joaquin Valley (King, Kern, Fresno, Merced, and Tulare). Although cotton is produced all across the south, including Texas, New Mexico and Arizona, except for occasional outbreaks during periods of drought, mites are generally only a problem cotton in California. Fifteen percent of U.S. produced cotton is grown in California.

Spider mites are the key arthropod pests in San Joaquin Valley cotton fields. Two species of spider mites are of major concern: twospotted spider mite and the Pacific spider mite. As mentioned previously, etoxazole effectively controls these mites. In general, spider mites are early to mid-season pests but late season problems can occur as a result of the use of broad-spectrum pesticides that eliminate the spider mites' natural enemies.

Spider mites are found on the undersides of leaves and reduce yields by removing the sap from the plant, which causes discoloration and early defoliation. Loss of leaf surface reduces energy available to maturing fruit, so squares and bolls may fail to develop and may eventually drop. Entire plants in heavily infested areas of the field may be defoliated.

The current product of choice for control of mites in California cotton is abamectin (Zephyr). Other major miticides currently being used in apple production are aldicarb (Temik), dicofol (Kelthane), oil, propargite (Comite), and profenofos (Curacron). [**Temik and Curacron (an OP) are both cholinesterase inhibitors while Comite and Kelthane are classified as "B2" and "C" carcinogens, respectively**]. Research has confirmed that populations of the twospotted and Pacific mites in some areas have developed resistance to dicofol (Kelthane), propargite (Comite), abamectin (Zephyr), or any combination of these. Valent believes that SECURE Miticide can replace a significant amount of these products in the cotton market for three reasons:

1. Etoxazole effectively controls the major mites infesting cotton in California (twospotted spider mite and the Pacific red mite)
2. Etoxazole has a mode of action that is different than the products currently used to control these mites in cotton, making it a good choice for growers looking for a new product for their IRM programs
3. The cost to treat an acre of cotton with SECURE Miticide will be slightly more expensive that the competitive products (except abamectin). We believe that the developing resistance to the current products makes the need for new miticides urgent and that growers will select SECURE Miticide for their IRM programs despite the added cost.

Valent's estimate of SECURE Miticide's penetration into the cotton market, with supporting marketing information, is discussed in Section E.3 of this document. See the Confidential Business Information Attachment.

Strawberry

SECURE Miticide will be applied to strawberries at a maximum application rate of 0.135 lbs. a.i./A using standard ground equipment. A maximum of two non-consecutive applications per season will be recommended on the proposed label. Preharvest interval will be one day. Strawberries will generally be treated during the early Spring. Although strawberry agriculture in the U.S. occurs in most states east of the Mississippi river, in the Pacific Northwest, and in California, most SECURE Miticide use on strawberries will occur in California and Florida where the majority of fresh and processed strawberries are produced (80% and 12%, respectively).

The twospotted spider mite (TSM) is the major mite pest in strawberries in both California and Florida. TSM damage to strawberries is expressed as stippling, scarring, and bronzing of the leaves and calyx. TSM feeding seriously interrupts photosynthesis and is particularly damaging during the first 4 to 5 months following transplanting in late summer, fall, or early spring, depending on the growing region. Mite feeding during this critical period of plant growth substantially reduces berry numbers per plant and overall yield.

The two major miticides applied to strawberries in California are abamectin (Zephyr) and hexythiazox (Savey); in Florida, the major products are abamectin and fenbutatin-oxide. **(Savey is classified as a "C" carcinogen).** Valent believes that SECURE Miticide can replace a significant amount of these products in the strawberry market for three reasons:

1. Etoxazole effectively controls the major mite infesting strawberries (TSM)
2. Etoxazole has a mode of action that is different than the products currently used to control this mite in strawberries, making it a good choice for growers looking for a new product for their IRM programs
3. The cost to treat an acre of strawberries with SECURE Miticide will be significantly less expensive that the competitive products (except abamectin)

Valent's estimate of SECURE Miticide's penetration into the strawberry market, with supporting marketing information, is discussed in Section E.3 of this document. See the Confidential Business Information Attachment.

7. Health, Ecological, and Environmental Fate Effects

The acute toxicity of etoxazole is low by all routes. Etoxazole is not a developmental or reproductive toxicant and is not mutagenic or oncogenic. EPA has not established toxicity endpoints for etoxazole but Valent is proposing a chronic population adjusted dose (cPAD) value of 0.04 mg/kg/day and an acute population adjusted dose (aPAD) of 2 mg/kg/day. These endpoints were based on the NOEL of 4.0 mg/kg/day from the rat two-year chronic/oncogenicity study and the NOEL from the rabbit oral developmental toxicity study (200 mg/kg/day), respectively. Both endpoints were derived by applying an uncertainty factor of 100 (to account for intra- and inter-species differences). Etoxazole is metabolized and excreted rapidly in mammals, indicating a low potential for bioaccumulation.

Etoxazole is practically non-toxic to mammals, birds and bees, and no effects were observed in avian reproduction studies. Etoxazole's acute toxicity to aquatic organisms ranges from moderate to very highly toxic. However, results of modeling simulations of estimated exposure concentrations (4-day average EEC) in aquatic ecosystems yield EEC's which are less than 2% of the acute LC_{50} (or EC_{50}) for both fresh and saltwater fish and less than half of the acute LC_{50} (or EC_{50}) for freshwater invertebrates. Therefore, etoxazole clearly does not pose an acute risk to these aquatic organisms. EEC's for etoxazole use on pome fruit and strawberries (but not cotton) 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.

Chronic aquatic exposures are expected to exceed the aquatic invertebrate maximum acceptable toxicant concentration (MATC) based on very conservative GENEEC calculated EEC values. However, etoxazole risk quotients (RQ's) are lower than most of the competitor RQ's. Valent does not believe that etoxazole will pose a significant risk to aquatic ecosystems.

In a bioaccumulation study conducted with rainbow trout, the mean bioconcentration factor of ^{14}C was 2700-3000 for whole fish and 1300-1500 for edible tissue. The ^{14}C depuration half-life was 2.6-6.3 days for all tissues, with neither etoxazole nor any of its metabolites accumulating irreversibly.

In water, etoxazole is very slowly hydrolyzed at pH 7, with a half-life of 161 days, but photodegrades with an average half-life of 17.4 days. Etoxazole's half-life in acidic water is much shorter (9.6 days at pH 5). In soil, the average photolytic half-life is 9.6 days. The soil metabolic half-life under aerobic conditions is 28 days. In aquatic environments, the half-life of etoxazole averaged 138 days under anaerobic conditions.

In field dissipation studies conducted following use patterns consistent with cotton and strawberry agriculture in California and Mississippi, etoxazole half-lives were 6.2 and 0.8 days, respectively. No vertical movement of etoxazole or metabolite residues in the soil profile was observed. In a field dissipation study conducted in an apple orchard in Idaho, utilizing the proposed use rates for apples, etoxazole's estimated half-life was 11.4 days. No vertical movement of the residues in the soil profile was observed.

8. FQPA Criteria

Valent believes SECURE Miticide meets all four of the FIFRA §3(c)(10) criteria for expedited review in that:

- SECURE Miticide reduces the risks to human health from the use of pesticides by offering growers a low toxicity alternative to more toxic insecticides, including four carcinogens, two neurotoxins, a carbarmate, and an organophosphate insecticide.
- SECURE Miticide reduces the risk of pesticides to nontarget organisms through its very low use rates and rapid breakdown in the environment. In particular, SECURE Miticide has very low toxicity to insect pollinators and many beneficial predator species.
- SECURE Miticide degrades rapidly in surface waters and has been shown to have a low leaching potential in laboratory and field studies. Both of these attributes reduce the potential for contamination of groundwater and surface water resources.
- SECURE Miticide, with a mode of action that is different than competitive products, will provide growers with an important new tool for integrated pest management and insect resistance management programs.

9. Reduced-Risk Statement

SECURE Miticide is a product that offers a unique mode of action providing reduced risk to human health, endangered or threatened species and beneficial organisms. Its low use rates, fairly rapid degradation, and low leaching potential result in a reduced risk to the environment and low potential for runoff and groundwater impacts. SECURE Miticide will be an important tool for IPM and IRM programs in pome fruit, cotton, and strawberry agriculture. The specific claims to support reduced risk status are:

- 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 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 can be used as an important partner with existing Integrated Pest Management Programs, reducing the grower's dependence on more toxic products.

- 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).

Valent believes that the use of SECURE Miticide on pome fruit, cotton, and strawberry crops qualifies for consideration under the Voluntary Reduced Risk Pesticide Initiative. Because one of the products that will be displaced by SECURE Miticide is an organophosphate insecticide (profenofos), Valent also believes that SECURE Miticide qualifies as an OP replacement.

10. Data Matrix

A data matrix containing references to all regulatory studies submitted to EPA in support of the registration of etoxazole and SECURE Miticide is attached as Appendix I.

B. HUMAN HEALTH

1. Acute Toxicity

The acute toxicity of etoxazole is low by all routes, classified as Category III for acute dermal and inhalation toxicity, and Category IV for acute oral toxicity and skin/eye irritation. The end use product, SECURE Miticide, is less acutely toxic than the technical grade material by dermal route (Category IV) but slightly more acutely toxic for eye irritation (Category III). Etoxazole is not a skin sensitizing agent. The following tables summarize the acute toxicity of Etoxazole Technical and SECURE Miticide:

Summary of Acute Toxicity – TGAI

Study Description	LD_{50}/LC_{50} Observation	Toxicity Category	Reference MRID #
Oral Toxicity	>5 g/kg	IV	45089919
Dermal Toxicity	>2 g/kg	III	45089921
Inhalation Toxicity	>1.09 mg/l	III	45089923
Eye Irritation	Mild eye irritation, clearing within 24 hrs.	IV	45089925
Skin Irritation	No skin irritation	IV	45089927
Dermal Sensitization	No skin sensitization	---	45089929

Summary of Acute Toxicity - SECURE Miticide

Study Description	LD_{50}/LC_{50} Observation	Toxicity Category
Oral Toxicity	>5 g/kg	IV
Dermal Toxicity	>5 g/kg	IV
Inhalation Toxicity	>2.28 mg/l	IV
Eye Irritation	Moderately irritating	III
Skin Irritation	Slightly irritating	IV
Dermal Sensitization	No skin sensitization	-

2. Reproductive, Developmental, Mutagenic and Neurotoxic Properties

Etoxazole is not a developmental or reproductive toxicant, is not mutagenic, and there are no data to indicate that etoxazole is a neurotoxicant.

Etoxazole is metabolized and excreted rapidly in mammals (most of the radioactivity was eliminated within 48 hours of dosing), indicating low potential for bioaccumulation. In the rat teratology study, maternal toxicity was observed at doses of 1000 mg/kg/day and greater; the NOEL for prenatal developmental toxicity was 1000 mg/kg/day. A rabbit teratology study resulted in NOEL's of 200 mg/kg/day for both maternal and prenatal developmental toxicity.

Summary of Developmental Toxicity Studies:
Etoxazole has been tested in developmental toxicity studies with rats (MRID 45090005) and rabbits (MRID 45090003). In the rat developmental toxicity study, with doses administered during gestation days 6-15, there were no mortalities or treatment-related adverse effects in any dose group. The maternal NOEL was therefore set at 200 mg/kg/day, based on decreased food consumption at the next highest dose level (1000 mg/kg/day). The NOEL for prenatal developmental toxicity was 1000 mg/kg/day, the highest dose tested.

In the rabbit developmental toxicity study, with doses administered during gestation days 6-18, no treatment-related adverse effects on clinical signs were noted on maternal rabbits in any dose group. The maternal NOEL was set at 200 mg/kg/day, based on decreased body weight gain and food consumption, and liver enlargement at oral doses of 1000 mg/kg/day. The NOEL for developmental toxicity in rabbits was 200 mg/kg/day, based on a statistically significant increased incidence of 27 presacral vertebrae with 13th ribs in fetuses at 1000 mg/kg/day.

Summary of Reproductive Toxicity Studies:
Etoxazole did not produce reproductive toxicity in rats. In a two-generation rat study, the parental NOEL was 400 ppm (17 mg/kg/day). No effects on reproduction were produced even at 2000 ppm, the highest dose tested. Adult systemic toxicity (increased liver weight) was produced at the 2000 ppm dose in males. The pup NOEL was 400 ppm (37.9 mg/kg/day) based on decreased viability and body weight at 2000 ppm in the F_1 pups. The reproductive NOEL was determined to be 2000 ppm (86.4 mg/kg/day), the highest dose tested (MRID 45090007).

Summary of Mutagenicity Studies:
Etoxazole was negative in the following tests for mutagenicity: Ames assay with and without S9, *in vitro* chromosomal aberration test in Chinese hamster lung cells with and without S9, *in vivo* micronucleus test in CD-1 mice, and *in vivo/vitro* unscheduled DNA synthesis in CD rat liver cells (MRID 45250905, 45090015, 45250904, 45090010, 95090014). Etoxazole tested positive in an *in vitro* gene mutation test with mouse lymphoma L5178Y cells but, in the absence of metabolic activation, only at highly toxic doses. In this test, it was concluded that etoxazole was mutagenic but only in the presence of metabolic activation (MRID 45090013). Etoxazole does not present a genotoxic hazard.

Summary of Reproductive, Developmental and Mutagenicity Studies

STUDY	ENDPOINT	MRID REFERENCE	COMMENTS
Rat Developmental Tox. Oral	NOEL (maternal)=200 mg/kg/day; evidence of maternal toxicity at the high dose (decreased food consumption). NOEL (fetus developmental)=1000 mg/kg/day; no effects observed at the highest dose tested.	45090005	Dose levels (mg/kg/day): 0, 40, 200, 1000 (Days 6-15 of Gestation)
Rabbit Developmental Tox. Oral	NOEL (maternal)=200 mg/kg/day; evidence of maternal toxicity at the high dose (decreased body-weight gain and food consumption and liver enlargement). NOEL (developmental)=200 mg/kg/day; evidence of developmental toxicity at the high dose (increased incidence of 27 presacral vertebrae with 13th ribs in fetuses).	45090003	Dose levels (mg/kg/day): 0, 40, 200, 1000 (Days 6-18 of Gestation)
Rat Reproduction Dietary	NOEL (parental)=400 ppm (17 mg/kg/day); increased relative liver weights. NOEL (adult reproductive)=2000 ppm (86.4 mg/kg/day), the highest dose tested; NOEL (pup developmental)=400 ppm (37.9 mg/kg/day); decreased pup viability and body weight.	45090007	Dose levels (ppm): 0, 80, 400, 2000
Bacterial Mutation	Negative tests with *E. Coli* or *Salmonella* strains conducted with and without S9 metabolic activation.	45250905, 45090015	—
In Vitro Mammalian Cell Gene Mutation	Positive response with mouse lymphoma L5178Y cells in the presence of metabolic activation. In the absence of metabolic activation, only at highly toxic doses.	45090013	—
In Vitro Chromosome Aberration Assay	No increase in the frequency of chromosomal aberrations or polyploid cells, with or without metabolic activation.	45250904	—
In Vivo Micronucleus Assay	No increase in the incidence of micronucleated PCE's.	45090010	
DNA Damage/ Repair	No mutagenic potential toward rat liver cells (etoxazole did not induce *in vivo/in vitro* UDS in hepatocytes)	45090014	—

3. Oncogenic and Other Subchronic and Chronic Effects

Studies with etoxazole show that repeated high dose exposures produce changes in the liver, kidney and red blood cells, but did not produce cancer in test animals. No oncogenic responses were observed in rat two-year chronic feeding/oncogenicity or mouse 18-month oncogenicity studies. In the first two-year chronic/oncogenicity study in rats (dose levels: 4.01, 16.1, and 64 mg/kg/day), an increased incidence of interstitial cell tumors in the testes of male rats was observed but these were

believed to be incidental. A repeat study (dose levels: 50, 5000 and 10000 ppm or 1.83, 187, and 386 mg/kg/day for males, 2.07, 216, and 445 mg/kg/day for females) confirmed the conclusion that etoxazole is not a tumorigenic compound.

Summary of Subchronic Studies

STUDY	ENDPOINT	MRID No.	COMMENTS
28-day dermal (Rat)	NOAEL=1000 mg/kg. No treatment related changes in any of the parameters	45089941	Dose levels: 30, 100,1000 mg/kg/day
Subchronic 4 Weeks (Rat)	NOAEL=80 ppm (6.1 mg/kg/day males, 6.4 mg/kg/day female; EFFECTS: anemia at ≥ 2000 ppm (males) and ≥400 ppm (females);liver swelling at 2000 and 10,000 ppm (both sexes); liver /adrenal weight changes at ≥400 ppm (both sexes)	45089934	Dose levels (ppm): 0, 80, 400, 2000, 10000
Subchronic 13 Weeks Dietary (Rat)	NOAEL=100 ppm (6.12 mg/kg/day (males) and 300 ppm (20.5 mg/kg/day) females. Hematological parameters altered at 1000 and 3000 ppm (males); clinical chemistry parameters altered at 3000 ppm (both sexes); liver enlargement at 3000 ppm (males) and 1000 and 3000 ppm (females); organ weight changes at ≥ 300 ppm (males) and ≥1000 ppm (females); centrilobular hepatocellular swelling at ≥ 1000 ppm (males) and at 3000 ppm (females).	45089935	Dose levels (ppm): 0, 100, 300, 1000, 3000
Subchronic 13 Weeks Dietary (Rat)	Hematological parameters altered at 5000 and 10000 ppm (both sexes); clinical chemistry effects ≥ 5000 ppm (both sexes); increased liver weight (both sexes) at 5000 and 10000 ppm, kidney weight (females), thyroid weight (males) at 10000 ppm; centrilobular hepatocellular hypertrophy (both sexes, both doses).	45089931	Dose levels (ppm): 0, 5000, 10000
4-Week Feeding (Mouse)	Blood biochemical parameters were altered and dark colored livers in males were observed at 10000 ppm; liver weight increases in both sexes at 2000 and 10000 ppm.	45089938	Dose levels (ppm): 0, 80, 400, 2000, 10000
13-Week Feeding (Mouse)	NOAEL=400 ppm (55.1 mg/kg/day) for males and 1600 ppm (251 mg/kg/day) for females. Increased alkaline phosphatase at 6400 ppm (both sexes); increased liver weights at 6400 ppm (both sexes) and 1600 ppm (males); enlarged liver in females at 6400 ppm; centrilobular hepatocellular swelling at 6400 ppm (both sexes) and 1600 ppm (males).	45089936	Dose levels (ppm): 0, 100, 400, 1600, 6400
4-Week Feeding (Dog)	At all doses and in both sexes, increased alkaline phosphatase levels, liver weights and centrilobular hepatocellular swelling.	45089932	Dose levels (ppm): 0, 1000, 3000, 10000, 30000
13-Week Feeding (Dog)	NOAEL=200 ppm (5.3 mg/kg/day for males and 5.4 mg/kg/day for females). Clinical chemistry changes, liver weights increased, and histopathology changes (centrilobular hepatocellular swelling) at ≥ 2000 ppm (both sexes).	45089933	Dose levels (ppm): 0, 200, 2000, 10000

Summary of Chronic and Oncogenicity Studies

STUDY	ENDPOINT	MRID No.	COMMENTS
Chronic Feeding 12-Month (dog)	NOAEL=200 ppm (4.62 mg/kg/day for males and 4.79 mg/kg/day for females). Hematological and pathological parameters altered at 5000 ppm; blood chemistry changes, liver weight increases and centrilobular hepatocellular swelling at ≥ 1000 ppm.	45089942	Dose levels (ppm): 0, 200, 1000, 5000
Chronic Feeding /Oncogenicity 104 Weeks (Rat)	NOAEL=4.01 mg/kg/day for males and 16.1 mg/kg/day for females. Hemoglobin decreased, centrilobular hepatocellular swelling, testicular masses at 64 mg/kg/day (males); clinical chemistry changes, increased liver weights and hepatic enlargement at ≥ 16 mg/kg/day; and testicular interstitial (Leydig) cell tumors at ≥ 4 mg/kg/day. No oncogenic response.	45250903	Dose levels (mg/kg/day): 0, 4, 16, 64
Chronic Feeding /Oncogenicity 104 Weeks (Rat) **Repeat Study**	NOAEL= 50 ppm (1.8 mg/kg/day for males and 2.07 mg/kg/day for females). Decreased body weight, food consumption/efficiency, increased urine protein (females) at 10000 ppm; hematological and clinical chemistry changes, liver weight increases (both sexes) at 5000 and 10000 ppm; adrenal and epididymides weight increases (males); centrilobular hepatocellular hypertrophy (both sexes) at 10000 ppm and effects on the incisors. **Testicular interstitial (Leydig) cell tumors, observed in the initial study, were not observed.**	Not assigned	Dose levels (ppm): 0, 50, 5000, 10000
18-Month Dietary (Mice)	NOAEL=60.1 mg/kg/day for males and 60.5 mg/kg/day for females. Non oncogenic. Slight with occasional significant differences in body weight of both sexes, increased liver weights of females at 240 mg/kg/day after 52 weeks; histopathology parameters were altered for males at 240 mg/kg/day; no alterations for females; no neoplastic lesions noted.	45090001	Dose levels (mg/kg/day): 0, 15, 60, 240
18-Month Dietary (Mice) 2nd Study	NOAEL=2250 ppm (242 mg/kg/day for males and 243 mg/kg/day for females). Non oncogenic. Increase in liver weights of females at 4500 ppm; histopathology parameters were altered for males at 4500 ppm; no alterations for females; no neoplastic lesions noted.	Not assigned	Dose levels (mg/kg/day): 0, 2250, 4500

4. Toxicity of Mammalian and Plant Metabolites

Metabolism studies of etoxazole in rats, goats and hens, as well as a fish bioaccumulation study demonstrate that the parent is very rapidly metabolized and eliminated. In the rat, most of the administered dose (94-97%) was excreted in the urine and feces within seven days of dosing, most within the first two days. Seven days after dosing, tissue residues were low, accounting for no more than 0.6% of the dosed ^{14}C. Because parent and metabolites are not retained in the body, the potential for acute toxicity is low. The potential for chronic toxicity is adequately tested by chronic exposure to the parent at the MTD and consequent chronic exposure to the internally formed metabolites.

Two metabolites of etoxazole, R-3 and R-7 HCl salt, have been tested for mutagenicity (Ames) and acute oral toxicity to rats. The acute toxicity of these metabolites did not appear to markedly differ from etoxazole, with all metabolites having acute oral LD_{50} values greater than 5000 mg/kg bw. In Ames assays with and without S9 at doses up to 5000 micrograms per plate, neither metabolite induced any significant increases in revertant colonies in any of the test strains. It was concluded that R-3 and R-7 HCl salt were not mutagenic in any strain tested in the presence or absence of metabolic activation.

5. Dietary Exposure and Risk Assessment

Tier 1 acute and chronic dietary exposure analyses were performed for etoxazole using tolerance level residues and assuming that 100 percent of the crops are treated. This analyses was performed for Valent by Novigen Sciences, Inc. and detailed in the report entitled "Tier 1 Chronic and Acute Dietary (Including Drinking Water) Exposure Analyses for Potential Residues of Etoxazole in/on Cotton, Pome Fruits, Strawberries, Imported Mandarin Oranges, Beef Fat, and Milk Fat", Study No. ETOXAZOLE 01-02.

The crops included in these analyses are the raw agricultural commodities apples, pears (representing pome fruit), cotton, strawberry, and oranges. Also included are the processed products from these crops and the resulting secondary residues in meat, milk, and eggs. EPA has not established a toxicity endpoints for etoxazole but Valent is proposing a chronic population adjusted dose (cPAD) value of 0.04 mg/kg/day and an acute population adjusted dose (aPAD) of 2 mg/kg/day. These endpoints were based on the NOEL of 4.0 mg/kg/day from the rat two-year chronic/oncogenicity study and the NOEL from the rabbit oral developmental toxicity study (200 mg/kg/day), respectively. Both endpoints were derived by applying an uncertainty factor of 100 (to account for intra- and inter-species differences). These endpoints were used to assess the risks due to dietary exposure to etoxazole.

Acute dietary exposure to etoxazole residues were calculated for the U.S. population and 9 population subgroups assuming tolerance level residues and 100 percent of the crop treated. The results from several representative subgroups are listed below. Acute dietary exposure was at or below 0.5 % of the aPAD with all proposed uses. Generally speaking, the Agency has no cause for concern if total residue contribution for published and proposed tolerances is less than 100 percent of the aPAD.

Tier I Calculated **Acute** Dietary Exposures to the Total U.S. Population and Selected Sub-Populations to Etoxazole Residues in Food
95th Percentile

Population Subgroup	Exposure (mg/kg bw/day)	Percent of aPAD
U.S. Population	0.002572	0.13
Females (13+)	0.001449	0.07
Females (13-50 Years)	0.001597	0.08
Males (20+ years)	0.001285	0.06
Children (1-3 Years)	0.010040	0.50
Children (1-6 Years)	0.008294	0.41
All Infants (<1 Year Old)	0.007451	0.37
Non-Nursing Infants (<1 Year Old)	0.007956	0.40
Nursing Infants (<1 Year Old)	0.004682	0.23

Chronic dietary exposure to etoxazole residues were calculated for the U.S. population and 25 population subgroups assuming tolerance level residues and 100 percent of the crop treated. The results from several representative subgroups are listed below. Chronic dietary exposure was at or below 5.7 % of cPAD with all proposed uses. Generally speaking, the Agency has no cause for concern if total residue contribution for published and proposed tolerances is less than 100 percent of the cPAD.

Tier I Calculated **Chronic** Dietary Exposures to the Total U.S. Population and Selected Sub-Populations to Etoxazole Residues in Food

Population Subgroup	Exposure (mg/kg bw/day)	Percent of cPAD
Total U.S. Population (all seasons)	0.000574	1.4
Females (13+/Nursing)	0.000534	1.3
Females (20+ years, not preg. or nursing	0.000310	0.8
Children (1-6 Years)	0.002293	5.7
All Infants (<1 Year Old)	0.001812	4.5
Non-Nursing Infants (<1 Year Old)	0.002084	5.2
Nursing Infants (<1 Year Old)	0.000883	2.2

The dietary exposure analyses indicate that a reasonable certainty that no harm will result from the use of etoxazole on pome fruit, cotton, and strawberry or the consumption of imported mandarin oranges treated with etoxazole. The results are very conservative because it was assumed that 100 percent of the commodities were treated and contained tolerance level residues of etoxazole. Because of the lack of consumption data for mandarin oranges, data for all oranges was used in this dietary risk assessment. This assumption makes the assessment additionally conservative.

6. Worker Exposure and Risk

An assessment has been prepared to estimate the exposure and potential risk to workers resulting from the use of SECURE Miticide on cotton, pome fruits, and strawberry crops. Using EPA's PHED Surrogate Exposure Guide, taken from the Pesticide Handlers Exposure Database (PHED, version 1.1), estimates were prepared for workers performing the following activities:

- open-pour mixing/loading of a dry-flowable formulated end-use product
- aerial applications of a liquid using fixed-wing aircraft with enclosed cockpit
- flagging, associated with the aerial applications
- open-cab groundboom applications
- open-cab airblast applications

A NOEL of 1000 mg/kg/day from the rat subchronic dermal toxicity was used for short-term (daily) dermal risk assessment, and a NOEL of 5.33 mg/kg/day from the 90-day oral toxicity study in rats was used for short term (daily) inhalation risk assessment. To assess the long-term (seasonal) risk to workers exposed to SECURE Miticide, the 5.33 mg/kg/day NOEL from the 90-day oral toxicity study in rats was used for both dermal and inhalation exposure. A summary of absorbed doses and the calculated Margins of Exposure (MOE's) for each of four possible use scenarios is presented in the following tables:

Absorbed Doses and Calculated MOE's for Cotton Use (Aerial Application)

			Mixer/Loader	Applicator (Pilot)	Flagger
Acute Dermal and Inhalation Exposure and Risk Calculations	Dermal exposure	Calculated Doses Mg/kg/day	0.0939	0.00711	0.00457
		MOE	10648	140556	219048
	Inhalation Exposure	Calculated Doses Mg/kg/day	0.0011	0.000097	0.000145
		MOE	4865	55085	36694
	Combined MOE		**3339**	**39575**	**31429**
Seasonal Dermal and Inhalation Exposure and Risk Calculations	Dermal exposure	Calculated Doses Mg/kg/day	0.0167	0.00126	0.000812
		MOE	319	4214	6567
	Inhalation Exposure	Calculated Doses Mg/kg/day	0.000195	0.0000172	0.0000258
		MOE	27364	309855	206402
	Combined MOE		**316**	**4157**	**6365**

Absorbed Doses and Calculated MOE's for Cotton Use (Ground Application)

			Mixer/Loader	Applicator
Acute Dermal and Inhalation Exposure and Risk Calculations	Dermal exposure	Calculated Doses mg/kg/day	0.0157	0.0033
		MOE	63889	301190
	Inhalation Exposure	Calculated Doses mg/kg/day	0.000183	0.000173
		MOE	29188	30371
	Combined MOE		**20035**	**27589**
Seasonal Dermal and Inhalation Exposure and Risk Calculations	Dermal exposure	Calculated Doses mg/kg/day	0.00278	0.00059
		MOE	1915	9030
	Inhalation Exposure	Calculated Doses mg/kg/day	0.0000325	0.0000312
		MOE	164183	170839
	Combined MOE		**1893**	**8577**

Absorbed Doses and Calculated MOE's for Pome Fruit Use

			Mixer/Loader	Applicator
Acute Dermal and Inhalation Exposure and Risk Calculations	Dermal exposure	Calculated Doses mg/kg/day	0.00939	0.0512
		MOE	106481	19522
	Inhalation Exposure	Calculated Doses mg/kg/day	0.00011	0.00064
		MOE	48647	8324
	Combined MOE		**33392**	**5836**
Seasonal Dermal and Inhalation Exposure and Risk Calculations	Dermal exposure	Calculated Doses mg/kg/day	0.00167	0.00911
		MOE	3192	585
	Inhalation Exposure	Calculated Doses mg/kg/day	0.0000195	0.000114
		MOE	273638	46823
	Combined MOE		**3156**	**578**

Absorbed Doses and Calculated MOE's for Strawberry Use

			Mixer/Loader	Applicator
Acute Dermal and Inhalation Exposure and Risk Calculations	Dermal exposure	Calculated Doses mg/kg/day	0.0235	0.00498
		MOE	42593	200794
	Inhalation Exposure	Calculated Doses mg/kg/day	0.000274	0.000262
		MOE	19459	20248
	Combined MOE		**13357**	**18393**
Seasonal Dermal and Inhalation Exposure and Risk Calculations	Dermal exposure	Calculated Doses mg/kg/day	0.00417	0.000885
		MOE	1277	6020
	Inhalation Exposure	Calculated Doses mg/kg/day	0.0000487	0.0000468
		MOE	109455	113893
	Combined MOE		**1262**	**5718**

As can be seen in the above tables, all the MOE's calculated for this assessment are significantly greater than 100. For an endpoint, EPA generally considers an MOE of 100 to be protective of human health. Even though the MOE's are acceptable, it is important to note that the short-term and intermediate risk estimates are conservative and overestimate the likely risk of exposure for the following reasons:

- The inhalation exposure dose was based on the default assumption of 100% absorption through inhalation when oral toxicity endpoint was used.
- The seasonal dermal exposure was based on the default assumption of 100% absorption when oral toxicity endpoint was used.
- The seasonal application frequency was conservatively estimated to be 16 days.
- The maximum daily use rate, based on the proposed label use directions, was used in all calculations.
- Very conservative daily acreage estimates, taken from the Draft Policy of the Science Advisory Council for Exposure, Agricultural Default Daily Acres Treated, were also used in all calculations.

Based on the fact that all MOE's associated with the use of SECURE Miticide greatly exceed 100, it can be concluded that the registration of etoxazole will not present unacceptable risks to workers handling SECURE Miticide for use on cotton, pome fruit, or strawberry crops.

An assessment of the exposure and risks associated with post-application activities has also been performed. Etoxazole exhibits extremely low dermal toxicity, both on an acute basis and on a subchronic basis. For example the NOEL from a 28-day dermal toxicity study was >1000 mg/kg/day (MRID 45089941). Using extremely conservative assumptions, the maximum daily exposure to a worker entering a field that had been treated with etoxazole is estimated to be 3.18 mg/kg/day. This exposure value was calculated from a worse-case dislodgeable foliar residue (DFR) value of 3.02 $\mu g/cm^2$ by assuming that the maximum seasonal use rate (0.27 lbs. a.i. per acre) was applied at one time to a flat even surface. This is the highest DFR that could be obtained from this application rate since the surface area of a flat acre must be less than an acre covered with foliage, especially considering the fact that each leaf of foliage has two sides. Comparison of this estimated exposure to the 1000 mg/kg/day dermal endpoint yields a worse-case margin of exposure (MOE) of 314. Since EPA generally considers a MOE of 100 to be protective of human health, this result supports the conclusion that post-application exposure to etoxazole represents minimal risks to workers.