United States
Environmental Protection
Agency

Office of Prevention, Pesticides
and Toxic Substances
(7501C)

**Pesticide
Fact Sheet**

Name of Chemical: Etoxazole
Reason for Issuance: Conditional Registration
Date Issued: August 2002

1. DESCRIPTION OF CHEMICAL

Generic Name:	2-(2,6-difluorophenyl)-4-[1,1-dimethylethyl) -2-ethoxyphenyl]-4,5-dihydrooxazole
Common Name:	Etoxazole
Trade Name:	TetraSan™ 5 WDG
EPA PC Code:	107091
Chemical Abstracts Service (CAS) Number:	153233-91-1
Year of Initial Registration:	2002
Pesticide Type:	Miticide/Ovicide
Chemical Class:	Diphenyl Oxazoline
U.S. Producer:	Valent USA Corporation

2. USE PATTERNS AND FORMULATIONS

Application Sites:	Ornamental plants grown in greenhouses, shadehouses, and lathhouses.
Types of Formulations:	95.4% technical product 5.0% water dispersible granular end-use product
Types and Methods of Application	Compressed air sprayers, hydraulic sprayers or ground boom sprayers.

Application Rates: An application rate of 8 to 16 ounces of product per 100 gallons of water (which equates to 0.025 to 0.05 pounds of active ingredient/100 gallons or 16 to 32 ounces/acre). A second application can be applied 14 days after the first application if necessary. No more than two (2) applications per cropping season or two (2) applications in six (6) months are allowed.

Carrier: Water

3. SCIENCE FINDINGS

Etoxazole is a member of the diphenyl oxazoline class of insecticides. Available product chemistry, toxicology, ecological effects and environmental fate data supporting the ornamental use pattern has been reviewed. The data and estimated risks to human health and the environment from its use on ornamental plants grown in greenhouses, shade, and lathhouses are summarized below.

Chemical Characteristics

Table 1. Chemical Characteristics

Property	Technical	End-Use
Color	Munsell color notation N9.5 (TGAI) White N 9.5/with 90% reflectance (PAI)	Brown
Physical State	Lumpy powder (TGAI) Free Flowing crystalline Powder (PAI)	Brown granules
Odor	Musty odor (TGAI) No obvious odor(PAI)	N/A
Oxidation/reduction: Chemical incompatiblity	TS was found not having any oxidizing properties	No reaction was observed
Flammability/Flame Extension	Non flammable	N/A
Explodability	Non-explosive	Not explosive
Storage Stability	Stable for one year under warehouse conditions	In progress. Study initiated 3/9/00.
Miscibility	N/A	N/A

Property	Technical	End-Use
Corrosion Characteristics	In progress. Study initiated 3/9/00.	In progress. Study initiated 3/9/00.
pH	6.2	5.94
Melting Point	101.5 to 102.5C (PAI)	N/A
Density	37.6 lbs / cu. ft. (TGAI) 1.2389 (Relative density of PAI)	34.2 lb./ft^3 at 21° C
Solubility (Water) Column elution method; shake flask method	3.99×10^{-5} g/l in distilled water at 10° C 7.04×10^{-5} g/l in distilled water at 20° C 6.69×10^{-5} g/l in distilled water at 30° C	N/A
Vapor Pressure	7.0×10^{-6} pascals @ 25° C (PAI)	N/A

[1] Technical Grade Active Ingredient
[2] Pure Active Ingredient

Toxicology Characteristics

Table 2. Acute Toxicity Data on Etoxazole Technical

Guideline No.	Study Type	Results	Toxicity Category
OPPTS 870.1100	Acute Oral - Mouse	LD_{50} > 5000 mg/kg	IV
OPPTS 870.1100	Acute Oral - Rat	LD_{50} > 5000 mg/kg	IV
OPPTS 870.1200	Acute Dermal - Rat	LD_{50} > 2000 mg/kg	III
OPPTS 870.1300	Acute Inhalation - Rat	LC_{50} > 1.09 mg/L	III
OPPTS 870.2400	Primary Eye Irritation - Rabbit	Not an eye irritant	IV
OPPTS 870.2500	Primary Skin Irritation - Rabbit	Not a dermal irritant	IV
OPPTS 870.2600	Dermal Sensitization - Guinea Pig	Not a dermal sensitizer	N/A

Table 3. Acute Toxicity Data on TetraSan™ 5 WDG Insecticide

Guideline No.	Study Type	Results	Toxicity Category

OPPTS 870.1100	Acute Oral - Rat	LD_{50} = 4274 mg/kg	III
OPPTS 870.1200	Acute Dermal - Rat	LD_{50} > 5000 mg/kg	IV
OPPTS 870.1300	Acute Inhalation - Rat	LC_{50} > 2.05 mg/L	IV
OPPTS 870.2400	Primary Eye Irritation - Rabbit	Conjunctivitis in 3/3 eyes at one hour after instillation. All irritation resolved by 48 hours.	III
OPPTS 870.2500	Primary Skin Irritation - Rabbit	Not a dermal irritant	IV
OPPTS 870.2600	Dermal Sensitization - Guinea Pig	Not a sensitizer	N/A

Table 4. Subchronic/Chronic Toxicity Data on Technical Etoxazole

Guideline No./ Study Type	Results (mg/kg/day)
870.3100 90-Day Feeding Rat	NOAEL = not determined LOAEL = 300.4/336.6 (M/F), based on clinical signs, clinical chemistry, increased liver weights, and histopathology
870.3100 90-Day Feeding Rat	NOAEL = 18.3/20.5 (M/F) LOAEL = 183.7/204.8 (M/F) based on increase in hepatic enzyme levels, increased liver weights and centrilobular hepatocellular swelling in both sexes and liver enlargement in females only
870.3150 90-Day Feeding Mouse	NOAEL = 213.6/250.5 (M/F) LOAEL = 878.4/994.5 (M/F), based on periportal hepatocellular necrosis, increased alkaline phosphatase levels, accompanied by increased relative liver weight, liver enlargement, and centrilobular hepatocellular swelling
870.3150 90-Day Feeding Dog	NOAEL = 5.33/5.42(M/F) LOAEL = 53.7/55.9 (M/F), based on clinical signs (vomiting foamy fluid and mucous stool), clinical chemistry, increased liver weights, and on centrilobular hepatocellular swelling in the liver and acinar cell atrophy in the prostate.
870.3200 21-Day Dermal Tox Rat	NOAEL = 1000 LOAEL > 1000, no effects noted.
870.3700 Developmental Tox Rabbit	NOAEL = Maternal: 200 Developmental: 200 LOAEL = Maternal: 1000, based on liver enlargement and decreased body weight gains and food consumption Developmental: 1000, based on increased incidences of 27 presacral vertebrae and 27 presacral vertebrae with 13 ribs (skeletal variations) in the fetuses

Guideline No./ Study Type	Results (mg/kg/day)
870.3700 Developmental Tox Rat	NOAEL = Maternal: 1000 Developmental: 1000 LOAEL = Maternal: not determined Developmental: not determined
870.3800 2-Gen Reproduction Rat	NOAEL = Parental Systemic: 20 Offspring Systemic: 20 Reproductive : 100 LOAEL = Parental Systemic: 100, based on increased liver weights in the P and F males and increased adrenal weights in the P females Offspring Systemic: 100, based on pup mortality Reproductive: Not determined
870.4100 1-Year Feeding Dog	NOAEL = 4.62/4.79 (M/F) LOAEL = 23.5/23.8 (M/F), based on increased alkaline phosphates activity, increased liver weights, liver enlargement (females), and incidences of centrilobular hepatocellular swelling in the liver
870.4200 78 - Week Carcinogenic Mouse	NOAEL = 241/243 (M/F) LOAEL = Not determined, No evidence of carcinogenicity
870.4300 2-Year Feed/Carcinogenic Rat, 52- week interim report	NOAEL = 2.05/2.4 (M/F) LOAEL = 208/247 (M/F) based on increased absolute and relative liver weight and elongation, whitening and abrasion of the incisors in both males and females, Y - glutamyl transpeptidase in males only, and urinary volume, chronic nephropathy, total protein and proteinuria in females only

Carcinogenicity

Classification of the carcinogenic potential of etoxazole is not required at this time as all human exposures will be short-term (no more than 2 applications per cropping season or 6-month period). Although they are not required at this time, carcinogenicity studies have been submitted for Agency consideration in connection with pending food uses for etoxazole; the pending food uses will be evaluated at a later date. Preliminary results suggest that there is no evidence of carcinogenicity in the rat or mouse as a result of oral administration of etoxazole. The rat and mouse carcinogenicity studies listed in Table 2 are separate studies submitted previously. Although these studies showed no evidence of carcinogenicity up through the highest dose tested, adequately high doses were not tested.

Mutagenicity

The Agency has concluded that there is not a concern for mutagenicity resulting from exposure to etoxazole. Six acceptable genetic toxicology studies were available for review. The results from these studies indicate that etoxazole was not mutagenic in *Salmonella typhimurium*,

Escherichia coli, and L5178Y TK $^{+/-}$ mouse lymphoma cell assays. There was also no evidence of clastogenicity *in vitro*, and etoxazole gave a negative response for the induction of micronucleated polychromatic erythrocytes in bone marrow. Also, etoxazole did not induce unscheduled DNA synthesis. Overall, the data suggest that etoxazole is negative for mutagenicity *in vitro* and *in vivo*.

Toxicological Endpoints

The dose at which no adverse effects are observed (the NOAEL) from the toxicology study identified as appropriate for use in risk assessment is used to estimate the toxicological level of concern (LOC). The lowest dose at which adverse effects of concern are identified (the LOAEL) is sometimes used for risk assessment if no NOAEL was achieved in the toxicology study selected. An uncertainty factor (UF) is applied to reflect uncertainties inherent in the extrapolation from laboratory animal data to humans and in the variations in sensitivity among members of the human population as well as other unknowns. An UF of 100 is routinely used, 10X to account for interspecies differences and 10X for intra species differences.

The acute, sub-chronic and chronic (non-cancer) toxicological endpoints that have been established for etoxazole are summarized in the Table 5.

Table 5. Acute, Sub-chronic and Chronic (non-cancer) Toxicological Endpoints

Exposure Scenario	Dose (mg/kg/day) UF /MOE	Hazard Based Special FQPA Safety Factor	Endpoint for Risk Assessment
Dietary Risk Assessments			
Acute Dietary	N/A Non-food use only.		
Chronic Dietary	N/A Non-food use only.		
Incidental Oral	N/A No residential uses.		
Non-Dietary Risk Assessments			
Dermal All durations (1 day $ 6 months)	No hazard quantitation required.		**28-Day Dermal Study-Rat** NOAEL = 1000 mg/kg/day No systemic effects noted up to 1000 mg/kg/day.
Residential	N/A	N/A	
Occupational	N/A	N/A	
Inhalation All durations[3] (1 day $ 6 months)	Oral NOAEL = 4.62		**Chronic Oral Toxicity Study - Dog** LOAEL=23.5 mg/kg/day based on increased alkaline phosphatase activity, increased liver weights, liver enlargement (females), and incidences of centrilobular hepataocellular swelling in the liver
Residential	N/A	N/A	
Occupational	100	N/A	

Exposure Scenario	Dose (mg/kg/day) UF /MOE	Hazard Based Special FQPA Safety Factor	Endpoint for Risk Assessment
Cancer	N/A Non - food use only.		

[3] Since an oral endpoint was selected, an inhalation factor of 100% should be used in route-to-route extrapolation.

Human Exposures and Risks

Acute and Chronic Dietary Risk: Not applicable, since there are no food uses of etoxazole.

Occupational Risk: Estimated margins of exposure (MOE) for all handlers greatly exceed the target MOEs of 100 in all cases provided handlers wear baseline personal protective equipment (PPE) of long-sleeved shirt, long pants and shoes plus socks and a 12-hour restricted entry interval (REI) is observed. The end-use label includes both requirements. Two handler occupational activities are indicated from the use of etoxazole, mixing and loading the pesticide and applying the pesticide. The end-use product is packaged in water-soluble bags thus greatly reducing exposure during mixing and loading (estimated MOE = 2,700,000). Although many large "houses" utilize automated spray systems whereby no individual is involved in the actual spraying procedure, and the end-use label allows for no less than a 25-gallon tank mixture, MOEs were calculated for applicators using low- and high-pressure hand-held spray wands as the application scenarios of highest exposure. The MOE for the low-pressure hand-held spray wand is estimated to be 1,700, the MOE for the high-pressure hand-held spray wand is estimated to be 8,000. Thus, the Agency's level of concern is not exceeded for any application method. Post-application exposure to re-entry workers was not assessed because no dermal toxicity endpoints were identified. A restricted entry interval of 12 hours is required.

Environmental Characteristics

Available environmental fate data indicate that etoxazole degrades at moderate rates at pH 5 (approximately10 days), and it is relatively stable between pH 7 and 9. Etoxazole showed moderately rapid biodegradation in a variety of soils ranging from a variety of characteristics, a total of seven values available yielded a mean half-life of 20.5 days. Etoxazole is immobile in several soils tested, with $K_{f,OC}$>5000 in seven out of eight soils tested. There appears to be little potential for etoxazole to be transported with water, although transport of residues adsorbed to the eroding soil is possible. Based on etoxazole's greenhouse, shadehouse, and lathhouse use sites, environmental exposure should be limited.

Ecological Characteristics/Risk

Available ecological effects data indicate that etoxazole is practically non-toxic to birds in both acute oral basis (LD_{50} > 2000 mg/kg) and sub-acute basis (LC_{50} >5000 ppm). Based on etoxazole's use sites, significant exposure to non-target organisms is not expected to occur. Therefore, chronic testing was not required.

In contrast, etoxazole is considered very highly toxic to aquatic invertebrates in acute testing. Acute toxicity tests of etoxazole with freshwater fish are considered invalid for reasons including solubility problems and failure to use flow-through test methods, among others. Additional studies are required to characterize acute toxicity on freshwater fish. As with avian risk, however, significant exposure to aquatic, non-target organisms is not expected to occur. Therefore, chronic testing is not required.

4. SUMMARY OF REGULATORY POSITION AND RATIONALE

Available data provide adequate information to support the conditional registration of etoxazole technical and end-use products for use on ornamental plants grown in greenhouses, shadehouses, and lathhouses.

Use, Formulation, Manufacturing Process or Geographic Restrictions

Use Directions - General Precautions

Do not apply through any type of irrigation or chemigation system.

Do not apply this product in a way that will contact workers or other persons, either directly or through drift. Only protected handlers may be in the area during application.

Do not enter or allow worker entry into treated areas during the restricted entry interval (REI) of 12 hours.

Do not contaminate water, food or feed by storage or disposal.

Do not contaminate water when disposing of equipment washwaters.

Use Directions - Ornamentals Grown in Greenhouses, Shadehouses, and Lathhouses

Apply no more than two times per cropping cycle.

Apply no more than two times per six months.

5. SUMMARY OF DATA GAPS

Corrosion characteristics (Guideline 830.6320) and storage stability (Guideline 830.6317) on technical etoxazole and end-use product

Freshwater fish acute toxicity (Guideline 850.1075) on technical etoxazole

90-Day subchronic inhalation study on rats (Guideline 870.3465) on technical etoxazole

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