United States Environmental Protection Agency

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

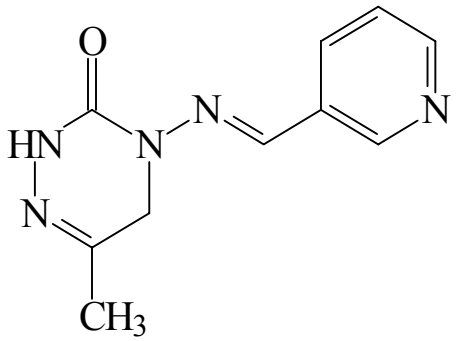
Pesticide Fact Sheet

Name of Chemical: Pymetrozine
Reason for Issuance: Conditional Registration
Date Issued: August 2000

I. DESCRIPTION OF CHEMICAL

Generic Name:	{1,2,4-triazin-3(2H)-one,4,5-dihydro-6-methyl-4-[(3-pyridinylmethylene) amino]}
Common Name:	Pymetrozine
Other Name:	CGA-215944
Trade Name:	Fulfill™, Endeavor™
EPA Shaughnessy (Active Ingredient Code):	101103
Chemical Abstracts Service (CAS) No.:	123312-89-0
Year of Initial Registration:	1999
Pesticide Type:	Insecticide
Chemical Family:	Pyridine Azomethines
U.S. Producer:	Syngenta Crop Protection, Inc. of Greensboro, North Carolina 27419

Structural Formula:



II. REGISTERED PRODUCTS, FORMULATIONS, USE PATTERNS, AND MODE OF ACTION

Registered Products and Formulations:

1. Pymetrozine Technical (EPA Reg No. 100-914)
   98% Granular Solid
2. Fulfill[R] Insecticide (EPA Reg. No. 100-912)
   50% Water-Dispersible Granule
3. Endeavor[TM] Insecticide (EPA Reg. No. 100-913)
   50% Water-Dispersible Granule

Use Patterns:

The following table lists the products, type of application, sites, maximum rates, and other restrictions for pymetrozine.

Table 1. Application Methods, Rates, and Restrictions for Pymetrozine Use Patterns

Product Name	Type of Application & Sites	Maximum Rates	Other Restrictions
Fulfill[TM] Insecticide	Ground, Aerial, and Chemigation (Foliar) Potatoes, Other Tuberous/ Corm Vegetables Tobacco	2.75oz product/A per application 5.5oz product/A per season	C 2 applications/year C 7 days between applications C Last treatment 14 days before harvest (14 day preharvest interval or PHI) C 12 hr before re-entry C Rotational (Plantback) Restrictions: all crops (30 days)
	Cotton	same as above	same as above but 21 days PHI
	Cole Crops Leafy Vegetables	same as above	same as above but 7 days PHI
	Cucurbits Fruiting Vegetables	same as above	same as above but 0 days PHI
	Hops	4-6oz product/A per application 18oz product/A per season	C 3 applications/year C 14 days between applications C 14 days PHI C 12 hr before re-entry C Rotational (Plantback) Restrictions: 30 days

Table 1. Application Methods, Rates, and Restrictions for Pymetrozine Use Patterns

Product Name	Type of Application & Sites	Maximum Rates	Other Restrictions
	Pecan	4oz product/A per application 8 oz product/A per season	C 2 applications/year C 7 days between applications C 14 days PHI C 12 hr before re-entry C Rotational (Plantback) Restrictions: 30 days
Endeaver ™ Insecticide	Ground (Foliar) Ornamentals	2.5 to 10.0 oz / A per application 48 oz/year-outdoor use 100 oz/year-indoor use (all states but California) 48 oz/year-indoor use(California only)	7 Days-severe insect pressure 14 days-normal insect pressure

Mechanism of Pesticidal Action:

The mode of action of pymetrozine in insects has not been precisely determined biochemically, but it may involve effects on neuroregulation or nerve-muscle interaction. Physiologically, it appears to act by preventing these insects from inserting their stylus into the plant tissue.

III. SCIENCE FINDINGS

A. Summary:

Pymetrozine is a new active ingredient from a chemical class (pyridine azomethines) not previously used as a pesticide. The Agency has reviewed product chemistry, environmental fate, residue chemistry, toxicology, and ecological effects data. Based on these data, pymetrozine has been determined to be of low acute toxicity to humans, birds, aquatic organisms, mammals, and bees. Acute toxicology studies place the technical-grade in Toxicity Categories III and IV. Dermal Absorption was estimated to be 1%.

Pymetrozine is not mutagenic. It produced some neurotoxic effects, but the frequency and magnitude were low. It produced developmental effects in pups, but only at levels toxic to parents. Pymetrozine is not expected to pose a risk of contaminating groundwater. The

Agency considers pymetrozine a replacement for organophosphate (OP) pesticides used for the same use patterns.

The EPA has classified pymetrozine as a "likely" human carcinogen because tumors occurred in two species (rat and mouse), in two sexes (mouse), and in two types (liver benign hepatoma and/or carcinoma). Mechanistic arguments have been advanced to explain the carcinogenicity. However, these have not been sufficient to eliminate the need for quantitative risk assessment. Because of the limited sites, low use rates, and low exposure, the risks to humans is below the level of concern.

The environmental fate profile for pymetrozine indicates no major issues in the areas of soil persistence, mobility, and fish bioaccumulation. Minimal environmental residues of this chemical in drinking water resources are expected.

The ecological effects data showed that pymetrozine is practically non-toxic to terrestrial and aquatic vertebrates, and honeybees. In addition, the data showed that this pesticide is only slightly to moderately toxic to aquatic invertebrates. All of the risk assessments were below EPA's level of concern. Further, endangered species will not be adversely affected.

B. Chemical Characteristics:

The following table lists the properties of the technical and end-use formulations for pymetrozine.

Table 2. Properties of Technical and End-Use Formulations for Pymetrozine.

Property	Technical	End-Use
Physical State	crystalline (granular) solid	water-dispersible granule
Color	white to beige	N/A
Odor	slightly sweet	N/A
Melting Point	217°C (decomp.)	N/A
Density	1.36g/mL @ 23°C	0.479g/cm
Solubility (Water)	0.29g/L@pH6.4-6.5@25°C	N/A
Vapor Pressure	$<4 \times 10^{-6}$ Pa @ 25°C	N/A
Octanol/Water Partition Coefficient	log P_{ow} = -0.18	N/A
pH	5.6@25C	7-11 (1% water dispersion@25C)

C. Toxicology Characteristics:

1. Acute Toxicity

Technical pymetrozine has low acute toxicity, being classified as Toxicity Category III for acute dermal and primary eye irritation studies and Toxicity Category IV for acute oral, acute inhalation and primary dermal studies. It is a slight sensitizer. Table 3 provides a summary of acute tests.

Table 3. Acute Toxicity of Pymetrozine Technical

Guideline Number	Study Type	MRID Number	Results	Toxicity Category
81-1	Acute Oral (rat)	44024926	Oral LD_{50}: Males: 5693 mg/kg Females: 5955 mg/kg Combined: 5820 mg/kg	IV
81-2	Acute Dermal (rat)	44024928	Dermal LD_{50}: Males: > 2.0 g/kg Females: > 2.0 g/kg	III
81-3	Acute Inhalation (rat)	44024930	Inhalation LC_{50}: Males: >1.8 mg/L Females: > 1.8 mg/L Combined: > 1.8 mg/L	IV
81-4	Primary Eye Irritation (Rabbit)	44024932	Is a slight ocular irritant. Primary Irritation Score (PIS): 12.8 at 1 hour; 1.0 at 72 hours.	III
81-5	Primary Dermal Irritation (Rabbit)	44024934	Primary Irritation Index (PII): 0.0 Is not a dermal irritant.	IV
81-6	Dermal Sensitization (Guinea Pig)	44024936	Is a slight dermal sensitizer with intradermal challenge.	N/A
81-8	Acute Neurotoxicity (rat)	44411317	NOAEL (both sexes) < 125 mg/kg (LDT) LOAEL (both sexes) = 125 mg/kg	N/A

2. Subchronic and Chronic Toxicity

Table 4 summarizes the results of the subchronic and chronic toxicity, metabolism, and dermal penetration studies in animals.

Table 4. Subchronic and Chronic Toxicity, Metabolism, and Dermal Penetration Studies in Animals of Pymetrozine Technical

Study Type	MRID No.	Results (NOAEL & LOAEL in mg/kg/day)
82-1a, Subchronic-Feeding-Rat	44024939	NOAEL: males = 32.5; females = 33.9 LOAEL: males = 360; females = 370
82-1b, Subchronic-Feeding-Dog	44572201	NOAEL: males = 3.12; females = 3.12 LOAEL: males = 14; females = 14

Table 4. Subchronic and Chronic Toxicity, Metabolism, and Dermal Penetration Studies in Animals of Pymetrozine Technical

Study Type	MRID No.	Results (NOAEL & LOAEL in mg/kg/day)
82-1c, Subchronic-Feeding-Mouse	44024938	NOAEL: males & females = Not established LOAEL: males & females = 125 (LDT)
82-2, 28-Day Dermal Toxicity-Rat	44024942	Systemic/Dermal Irritation NOAEL = 1000 (both sexes) Systemic/Dermal Irritation LOAEL > 1000 (both sexes)
82-7, Subchronic neurotoxicity - rat	44411318	NOAEL: males = 68; females = 81 LOAEL: males = 201; females = 224
83-1, Chronic-Feeding-Dog	44024943	NOAEL: males = 5.33; females = 5.33 LOAEL: males = 27.8; females = 27.8
83-2, Carcinogenicity-Mouse	44024944	NOAEL: males & females = 12 LOAEL: males & females = 250 liver benign hepatomas and/or carcinomas combined in both sexes
83-3a, Developmental Toxicity-Rat	44024948	Maternal NOAEL = 30; Maternal LOAEL = 100 Developmental NOAEL = 100; Developmental LOAEL = 300
83-3b, Developmental Toxicity-Rabbit	44024949	Maternal NOAEL = 10; Maternal LOAEL = 75 Developmental NOAEL = 10; Developmental LOAEL = 75
83-4, Reproductive Toxicity - Rat	44024950	Parental Systemic NOAEL: males = 1.4; females = 1.6 Parental Systemic LOAEL: males = 13.9; females = 16.0 Offspring Syst./Develop. NOAEL: males = 13.9; females = 16.0 Offspring Syst./Develop. LOAEL: males = 136.9; females = 151.6 Reproductive NOAEL: males = 136.9; females = 151.6 Reproductive LOAEL: males > 136.9; females = 151.6 (HDT)
83-5, Chronic toxicity/ Carcinogenicity-Rat	44024951	NOAEL: males = 0.377; females = 4.48 LOAEL: males = 3.76; females = 46.26 liver benign hepatomas and/or carcinomas combined in females
84-2, Gene Mutation - *Salmonella* & E. Coli	44024952	Non-mutagenic (±) activation in *Salmonella* and *E.* coli.
84-2, Gene Mutation - HGPRT with V79 cells	44024954	Non-mutagenic up to the solubility limit (±) activation.
84-2, *In vitro* cytogenetics assay in CHO cells	44024953	Not clastogenic up to the solubility limit of the test substance.
84-2, Micronucleus Assay-Mice	44024955	No clastogenic response at any dose or sacrifice time.
84-2, Unscheduled DNA Synthesis-Primary Rat Hepatocytes	44024956	No evidence of induced UDS.

Table 4. Subchronic and Chronic Toxicity, Metabolism, and Dermal Penetration Studies in Animals of Pymetrozine Technical

Study Type	MRID No.	Results (NOAEL & LOAEL in mg/kg/day)
85-1, Metabolism-Rat	44024957 44517720	• Absorption and excretion studies, oral & iv doses. • Recovered radioactivity 7 days post-dosing: urine (56.3-80.3%), expired air (0.2-1.4%), tissues (0.3-3.8%), feces (15.4-38.9%), and cage washes (0.2-0.7%). • Both sexes excreted more via the kidneys after a high dose (M/F: 72.5%/78.3%) than low dose (M/F: 56.3%/ 62.1%). • 12 urinary & fecal metabolites identified after a high dose. High level of unchanged test material in the urine. • 3 major metabolic pathways found. • Max.blood conc.: low dose (15 min, 0.3 ppm) & high dose (4 hrs (60 ppm). • Calculated half life: 1 to 2 hours at 0.5 mg/kg dose (both labels) and from 2 to 11 hours (100 mg/kg dose). • Tissue residue levels (ppm) were highest in the kidneys and liver. For the low/high doses, the peak kidney levels were 0.6/75 ppm (triazine) and 0.6/101 ppm (pyridine).
85-3, Dermal absorption	44024958	The percent of dose absorbed after 10 hour application: 0.01% (low-dose), 0.01% (mid-dose), and <0.005% (high-dose).

These tests suggest that pymetrozine targets three major areas in the body: the liver, the hematopoietic system and the lymphatic system. In addition, both the subchronic and chronic dog studies suggest that this chemical affects muscle tissue, perhaps secondarily. The most significant effects in these areas are tumors in the livers of mice and rats, necrosis of the liver of mice and dogs, hyperplasia in the bile ducts of dogs, anemia in dogs, atrophy in the thymus of young rats and dogs, and myopathy in the muscle of dogs. Hepatocellular hypertrophy is often related to induction of drug metabolizing enzymes. The red blood cell effects in rats and mice were somewhat minor.

3. Carcinogenic Effects

The EPA has classified pymetrozine as a "likely" human carcinogen, based on male mouse liver benign hepatoma and/or carcinoma. Mechanistic arguments have been advanced to explain the carcinogenicity. However, these have not been sufficient to eliminate the need for quantitative risk assessment. Because of the limited sites, low use rates, and low exposure, the actual risks to humans is below the level of concern.

4. Developmental/Reproductive Effects

In the rat, developmental toxicity was observed only at maternally toxic dose levels: (maternal NOAEL: 30 mg/kg/day, LOAEL: 100 mg/kg/day (reduced body weight gains and food consumption); developmental NOAEL: 100 mg/kg/day, LOAEL: 300 mg/kg/day (increased incidence of skeletal anomalies)). In the rabbit, developmental toxicity was also observed

only at maternally toxic dose levels: (maternal NOAEL: 10 mg/kg/day, LOAEL: 75 mg/kg/day (reduced body weight gains and reduced food consumption and efficiency); developmental NOAEL: 10 mg/kg/day, LOAEL: 75 mg/kg/day (increased incidence of skeletal anomalies)).

In the rat reproduction study, systemic/developmental toxicity for the pups was observed at parentally toxic dose levels (parental systemic NOAEL:1.4 mg/kg/day for males, 1.6 mg/kg/day for females, LOAEL: 13.9 mg/kg/day for males, 16.0 mg/kg/day for females (liver effects in the F0 and F1 males); offspring systemic/developmental NOAEL: 13.9 mg/kg/day for males, 16.0 mg/kg/day for females, LOAEL: 136.9 mg/kg/day for males, 151.6 mg/kg/day for females (decreased pup weight and delay in eye opening in both F1 and F2 litters)). There was no reproductive toxicity at dose levels up to 136.9 mg/kg/day for males and 151.6 mg/kg/day for females.

5. Mutagenic Effects

Pymetrozine is not considered to be of mutagenic concern.

6. Neurotoxic Effects

In the acute mammalian neurotoxicity study, there was a transient decrease in the body temperature and indications of decreased activity in the FOB and motor activity assessments at a dose level of 125 mg/kg, the lowest dose tested. In the subchronic mammalian neurotoxicity study, stereotypy in males and tiptoe gate or walking on toes in females were observed when administered dose levels of 201 mg/kg/day (males) or 224 mg/kg/day (females). The frequency and magnitude of these effects were low.

D. Toxicological Endpoints and Exposure Doses:

Based on its review of the toxicological data, the Agency selected specific studies, end points (adverse biological effects), a Lowest Observed Adverse Effect Level (LOAEL), and several No Observed Adverse Effect Levels (NOAELs), and modified by several safety (SF) or uncertainty factors (UF), to derive acceptable exposure doses in mg/kg/day for use in acute and chronic risk assessments. Table 5 lists the studies, endpoints, exposure doses, uncertainty/safety factors, and exposure profiles that the Agency used in these risk assessments.

Table 5. Summary of Toxicological Endpoints for Use in Human Risk Assessment			
EXPOSURE PROFILE	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary Females 13+	NOAEL= 10 UF = 100 FQPA SF = 3	Reduced body weight gain, food consumption and feed efficiency. Also, increased incidence of skeletal anomalies in pups.	Rabbit Developmental (MRID No.: 44024949)
	Acute RfD (Females 13+) = 0.10 mg/kg **Acute Population-Adjusted Dose (Females 13+) = 0.033 kg/kg**		
Acute Dietary General Population including Infants and Children	LOAEL = 125 UF = 300 FQPA SF = 3 (Infants, Children)	Decreased body temperature, decreased motor activity and FOB parameters associated with decreased activity.	Acute Neurotoxicity (MRID No.: 44411317)
	Acute RfD (General Population) = 0.42 mg/kg **Acute Population-Adjusted Dose (General Population) = 0.42 mg/kg** **Acute Population-Adjusted Dose (Infants and Children) = 0.14 mg/kg**		
Chronic Dietary	NOAEL = 0.377 UF = 100 FQPA SF = 3 (Females 13+, Infants, Children)	Liver hypertrophy and pathology supported by the rat chronic feeding and multigeneration reproduction studies and dog subchronic and chronic studies.	Rat Chronic Feeding (MRID No.: 44024951)
	Chronic RfD = 0.0038 mg/kg/day **Chronic Population-Adjusted Dose (General Population) = 0.0038 mg/kg/day** **Chronic Population-Adjusted Dose (Females 13+, Infants, Children) = 0.0013 mg/kg/day**		
Short-& Intermediate Term (Dermal)	NOAEL= 1000	No effects at the highest dose tested.	Rat Dermal Toxicity (MRID No.: 44024942)
Short -Term (Inhalation)[a]	Oral NOAEL = 10	Reduced body weight gain, food consumption and feed efficiency. Also, increased incidence of skeletal anomalies in pups.	Rabbit Developmental (MRID No.: 44024949)
Intermediate Term (Inhalation)[a]	Oral NOAEL = 0.377	Liver hypertrophy and pathology supported by the rat chronic feeding and multigeneration reproduction studies and dog subchronic and chronic studies.	Rat Chronic Feeding (MRID No.: 44024951)
Long-Term (Dermal and Inhalation)	The current use pattern does not indicate a concern for long-term dermal or inhalation exposure potential, therefore, these risk assessments are NOT required.		

a = Since oral values were selected, 100% inhalation absorption factor (default) value should be used in route-to-route extrapolation/risk assessment.

E. Residue Chemistry

The pyridine containing metabolites such as nicotinyl alcohol and trigonelline are not of toxicological concern at the levels observed in tomatoes (ca 0.01-0.1 ppm). This is in part based on the recommended daily dietary allowance for nicotinic acid being 6-19 mg. Concentrations of nicotinamide and nicotinic acid compounds in ruminants are similar to those observed in tomatoes and, therefore, are also not of toxicological concern.

The triazine containing metabolites (CGA-294849 and GS-23199) are likely to be of toxicological concern. It was noted that these compounds are azapyrimidines and analogs of thymine and uracil. The uracil analog of GS-23199 is a mutagen. The metabolite GS-23199 can serve as a marker for CGA-215525, CGA-249257, and CGA-294849 for risk assessment purposes. These compounds are all "azauracils" that may lend to the carcinogenic nature of pymetrozine.

Tolerances will be set in terms of only the parent compound for enforcement purposes. Triazine containing metabolites are included in the risk assessment for plants with their levels estimated using GS-23199 as a marker in field trials. Additionally, the metabolite CGA-313124 (both free and phosphate-conjugated) would be included in any risk assessment for livestock commodities due to its structural similarity to pymetrozine.

The Agency has established permanent tolerances for **residues** of **pymetrozine per se** in three Final Rules in the Federal Register on September 29, 1999 (64 FR 52438-50), August 9, 2000 (65 FR 48626-34), and December 27, 2001 (66 FR 66786-94, as indicated in the following table. The tolerance level and pre-harvest interval (PHI) for each commodity is expressed in terms of the parent insecticide only, which serves as an indicator of the use of pymetrozine of these raw agricultural commodities. The following table lists each commodity and its tolerance level and pre-harvest interval (PHI).

Table 6. Food commodities, Tolerance Levels, Pre-Harvest Intervals for Pymetrozine.

Commodity	Tolerance Level (ppm)	Pre-Harvest Interval (PHI)
Brassica, head and stem , subgroup (Crop Subgroup 5-A)	0.5	7
Brassica, leafy greens, subgroup (Crop subgroup 5-B)	0.25	7
Cotton gin byproducts	2.0	21
Cotton, undelinted seed	0.3	21
Hops, dry cones	6.0	14

Table 6. Food commodities, Tolerance Levels, Pre-Harvest Intervals for Pymetrozine.		
Commodity	**Tolerance Level (ppm)**	**Pre-Harvest Interval (PHI)**
Pecans	0.02	14
Turnip, greens	0.25	7
Vegetable, fruiting, group (Crop Group 8)	0.2	0
Vegetable, cucurbit, group (Crop Group 9)	0.1	0
Vegetable, leafy, except *Brassica*, group (Crop Group 4)	0.6	7
Vegetable, tuberous and corm, subgroup (Crop Subgroup 1-C)	0.02	14

Because of a metabolite of concern, the label also includes a plant back restriction of 30 days for all crops.

F. Human Risk Assessments:

The Agency conducted several acute, chronic, and cancer human risk assessments for different population subgroups and exposure profiles. These were all below the Agency's level of concern. The Agency also conducted risk assessments that aggregated (combined) dietary, drinking water, and residential exposure for acute, chronic, and cancer scenarios. Initially, the aggregate cancer assessment produced a possible level of concern because of high theoretical levels in drinking water, resulting in a request for drinking water monitoring data. However, later, the Agency discovered that the original Cancer Q^* value was too high. Once it used the correct value, the aggregate cancer no longer exceeded its level of concern, and the drinking monitoring studies were no longer needed. A detailed discussion of the risk assessments may be found in the Final Tolerance Rules published in the Federal Register on September 29, 1999, August 9, 2000, and December 27, 2001.

1. Aggregate Risks and Determination of Safety

Tables 7 and 8 show the Drinking Water Levels of Comparison (DWLOC's) for acute and chronic exposure.

Table 7. Acute Drinking Water Levels of Comparison for Aggregated Exposures

Scenario/Population Subgroup	aPAD mg/kg/day	Food Exposure, mg/kg/day	Maximum Water Exposure, mg/kg/day	SCI-GROW (groundwater) ppb	PRZM/ EXAMS (surface water) ppb	DWLOC * : g/L
U.S. Population	0.42	0.002119	0.41788	0.02	5.23	15,000
All Infants (<1 year)	0.14	0.001404	0.13860	0.02	5.23	1,400
Children (1-6 yrs)	0.14	0.003517	0.13648	0.02	5.23	1,400
Children 7-12 years	0.14	0.002615	0.13739	0.02	5.23	1,400
Females 13-50	0.033	0.001939	0.031061	0.02	5.23	930
Males 13-19	0.42	0.001722	0.41828	0.02	5.23	15,000
Males 20+ years	0.42	0.001807	0.41819	0.02	5.23	15,000
Seniors 55+	0.42	0.002035	0.41797	0.02	5.23	15,000

* DWLOC = Maximum Water Exposure (mg/kg/day) × 1000 : g/mg × body weight (70 kg general population/males 13+, 60 kg females 13+, 10 kg infants and children) ÷ Water Consumption (2 L/day adults, 1 L/day infants and children). The acute EEC is 5.23 : g/L.

Table 8. Chronic Drinking Water Levels of Comparison for Aggregated Exposures

Scenario/Population Subgroup	cPAD mg/kg/day	Food Exposure, mg/kg/day	Maximum Water Exposure, mg/kg/day	SCI-GROW (groundwater) ppb	PRZM/ EXAMS (surface water) ppb	DWLOC* : g/L
U.S. Population	0.0038	0.000034	0.003766	0.02	1.58	130
All Infants (<1 year)	0.0013	0.000018	0.001282	0.02	1.58	13
Children (1-6 yrs)	0.0013	0.000045	0.001255	0.02	1.58	13
Children 7-12 years	0.0013	0.000040	0.001260	0.02	1.58	13
Females 13-50	0.0013	0.000029	0.001271	0.02	1.58	38
Males 13-19	0.0038	0.000024	0.003776	0.02	1.58	130
Males 20+ years	0.0038	0.000034	0.003766	0.02	1.58	130
Seniors 55+	0.0038	0.000036	0.003764	0.02	1.58	130

* DWLOC = Maximum Water Exposure (mg/kg/day) × 1000 ：g/mg × body weight (70 kg general population/males 13+, 60 kg females 13+, 10 kg infants and children) ÷ Water Consumption (2 L/day adults, 1 L/day infants and children). The chronic and cancer EEC is 1.58 ：g/L.

a. *Acute risk*.

The Tier 1 exposure estimates provided by the acute dietary analysis are based on the assumption that tolerance-level residues are present in/on all commodities on which pymetrozine will be used and that 100% of these commodities are treated. The exposure estimates are therefore conservative ones. As shown in Table 7, the acute EECs for pymetrozine are below EPA's level of concern. That is, they are below the DWLOC values calculated for the various population subgroups. Thus, residues of pymetrozine in food and drinking water do not exceed EPA's level of concern (100% of the aPAD) for acute aggregate exposure for any of the population subgroups. Based on its assumptions and underlying data, this risk assessment is considered confident, very conservative, and highly protective of human health.

b. Chronic risk.

The Tier 3 exposure estimates provided by the chronic dietary analysis are based on anticipated residues and projected percent crop treated data. Anticipated residues (average field trial values) were calculated for the crops. The resulting exposure estimates are therefore refined ones. The chronic EECs for pymetrozine are below the Agency's level of concern. That is, as shown in Table 8, they are below the DWLOC values calculated for the various population subgroups. Thus, residues of pymetrozine in food and drinking water do not exceed the Agency's level of concern (100% of the cPAD) for chronic aggregate exposure for any of the population subgroups.

c. Short-term risk

Short-term aggregate exposure takes into account residential exposure plus chronic exposure to food and water (considered to be a background exposure level). In aggregating short-term risk, the Agency considered background average dietary exposure and short-term, non-dietary oral exposure. Non-dietary oral exposure may occur with toddlers as hand-to-mouth transfer of residues from ornamental plants or incidental ingestion of treated ornamental plants and/or surrounding soil. The highest estimated exposure via these routes is 0.0046 mg/kg/day which results from hand-to-mouth transfer of residues. Combining this exposure with the chronic dietary exposure estimate of 0.000045 mg/kg/day results in an aggregate exposure of 0.0046 mg/kg/day. In the absence of a short-term oral endpoint, EPA has used the acute dietary endpoint for infants and children (125 mg/kg/day) to estimate aggregate short-term risk. Note that this endpoint is based on a LOAEL and therefore has a 300-fold uncertainty factor associated with it. Combining the exposure estimate with the toxicological endpoint gives an MOE of 27,000. For this scenario, the Agency would be concerned with an MOE of less than 900; thus, this exposure is below EPA's level

of concern. Aggregated short-term exposure results in a DWLOC of 1400 ppb. This value is in excess of the peak EEC of 5.23 ppb for pymetrozine. Therefore, the short-term aggregate risk is below the Agency's level of concern.

d. *Intermediate-term risk*.

Intermediate-term aggregate exposure takes into account residential exposure plus chronic exposure to food and water (considered to be a background exposure level). There are no intermediate-term residential exposure scenarios for pymetrozine based on the current uses. Therefore, aggregate intermediate-term risks do not exceed the the Agency's level of concern.

e. *Aggregate cancer risk for U.S. population*

As with the chronic dietary exposure analysis, the cancer risk assessment is also based on a Tier 3 estimate of dietary exposure. The cancer aggregate risk consists of chronic dietary exposure as well as non-occupational exposure resulting from pruning and planting treated ornamental plants. The sum of the food and residential exposure is 0.000034 (food) + 0.0000012 (residential) = 3.5×10^{-5} mg/kg/day. Assuming a cancer risk limit of 1×10^{-6}, the cancer dose of concern is 8.4×10^{-5} mg/kg/day ($0.000001/Q_1^*$ = 0.000001/0.0119). As 3.5×10^{-5} mg/kg/day is less than 8.4×10^{-5} mg/kg/day, the aggregate food and residential exposure is below the level of concern. With respect to drinking water, the cancer DWLOC is calculated to be 1.7 ppb. The highest EEC for any of the crops in these petitions is 1.6 ppb (pecans). As a result, the aggregate cancer risk resulting from use of pymetrozine is below the Agency's level of concern.

f. Determination of safety

Based on these risk assessments, EPA concludes that there is a reasonable certainty that no harm will result to the general population, and to infants and children from aggregate exposure to **pymetrozine** residues.

G. Environmental Characteristics:

The following table summarizes the results of major environmental fate studies conducted on pymetrozine.

Table 9. Results of Major Environmental Fate Studies Conducted on Pymetrozine.

Study Type	Half Life/Other Result
Hydrolysis (Half Life)	<14 days (pH 5, 25C); >80 days (pH 7) >86 days (pH 9)
Photolysis in Water (Half Life)	about 2 days (pH 7)
Photolysis on Soil (Half Life)	>30 days
Aerobic Soil Metabolism (Half Life)	Biphasic: 1. primary (0 to 30 days): <1 week 2. secondary (30 days to 357 days): about 1 year
Aerobic Aquatic Metabolism (Half Life)	Graphical DT_{50} = 5 months
Anaerobic Aquatic Metabolism (Half Life)	4 months
Mobility- Leaching (Parent)	Mobility - negligible (K_{OC} = 7.4 to 38 mL/g) substantiated in field studies (most residues found in upper 6-inches of soil)
Mobility- Leaching (Metabolites)	Mobility - some mobility into upper 12 in of soil, not environmentally significant because of low application rate/low concentration of degradates relative to the parent (<10% in field studies).
Bioaccumulation	Pymetrozine should not significantly bioconcentrate in fish due to its low octanol/water partition coefficient.
Terrestrial Field Dissipation* (Half Life)-tests in five locations	Biphasic: 1. Primary (0-14 days): 8 to 138 days, depending on soil and location. 2. Secondary (14-180 days): 103 to 1269 days depending on soil and location.

1. Water Resources Assessment

Based on the FIRST, SCI-GROW, and PRZM/EXAMS models the estimated environmental concentrations (EECs) of **pymetrozine** for acute exposures are estimated to be **5.23** parts per billion (ppb) for surface water and <0.02 ppb for ground water. The EECs for chronic exposures are estimated to be **1.58** ppb for surface water and <0.02 ppb for ground water, as shown in Tables 5 and 6 above. See the December 27, 2001, Final Tolerance Rule (66 FR 66789-90 for a detailed description of the models and have the Agency calculated the EEC values.

2. Potential to Contaminate Drinking Water

Based upon proposed uses and fate characteristics, EPA does not expect pymetrozine to reach drinking water resources in significant quantities.

3. Ecological Risk Characterization:

The available data indicate that the use of pymetrozine to control aphids and whiteflies on the approved sites (food crops, tobacco, and ornamentals) listed under "II" above should not pose any significant risk concerns to terrestrial plants, aquatic plants, birds, mammals, fish, and aquatic invertebrates.

4. Endangered Species Concerns

The proposed product labels are not likely to result in any endangered plant species exposed to pymetrozine.

5. Toxicity to Nontarget Organisms

a. Toxicity to Terrestrial Animals

The following tables summarize the toxicity data for nontarget organisms.

i. Birds, Acute and Subacute

Table 10. Avian Acute Oral Toxicity of Pymetrozine.

Species	*% ai*	*LD_{50} (mg/kg)*	*Toxicity Category*	*MRID No. (Author/Year)*	*Study Classification*
Northern bobwhite quail *(Colinus virginianus)*	98.0	>2000 [1]	practically nontoxic	440249-08 (Hakin, 1993)	core

Table 10. Avian Acute Oral Toxicity of Pymetrozine.

Species	*% ai*	*LD_{50} (mg/kg)*	*Toxicity Category*	*MRID No. (Author/Year)*	*Study Classification*
Mallard duck *(Anas platyrhynchos)*	98.0	not determined [2]	not determined	440249-07 (Hakin, 1993)	supplemental [3]

[1] No mortality.
[2] One mortality in control group. Vomiting occurred at doses greater than 31 mg/kg; no mortality noted at that level.
[3] An LD_{50} could not be determined because several test birds in the three highest test concentrations ($ 125 mg/kg) regurgitated within one hour of dosing.

Table 11. Avian Subacute Dietary Toxicity of Pymetrozine.

Species	*% ai*	*LC_{50} (ppm)*	*Toxicity Category*	*MRID No. (Author/Year)*	*Study Classification*
Northern bobwhite quail *(Colinus virginianus)*	98.0	>5130 [1]	practically nontoxic	440249-09 (Hakin, 1992)	core
Mallard *(Anas platyrhynchos)*	98.0	>5010 [1]	practically nontoxic	440249-10 (Hakin, 1992)	core

[1] One mortality in the control and one mortality at 2,550 ppm (not considered treatment-related).
[2] No mortality.

ii. Birds, Chronic

Table 12. Avian Reproduction Studies for Pymetrozine.

Species/Study Duration	*% ai*	*NOEC/LOEC (ppm)*	*LOEC Endpoints*	*MRID No. (Author/Year)*	*Study Classification*
Northern bobwhite quail *(Colinus virginianus)*/ 20 weeks	98.5	NOEC = 100 LOEC = 300	14-day old survivors of eggs set	440249-11 (Taliaferro & Brewer, 1996)	core
Mallard duck *(Anas platyrhynchos)*	98.4	N/A	N/A	444113-04 (Taliaferro, 1997)	invalid [1]

[1] The percentage of normal hatching of eggs laid and eggs set in control group were lower than treatment groups.

iii. Mammals, Acute

Table 13. Mammalian toxicity of Pymetrozine.

Species/ Study Duration	% ai	Test Type	Toxicity Value	Affected Endpoints or Toxicity Category	MRID No.
Laboratory rat *(Rattus norvegicus)*	98.0	Acute Oral	LD_{50}= 5955 mg/kg	IV[1]	440249-26
		Acute Dermal	LD_{50}= >2000 mg/kg	III[2]	440249-28
		Acute Inhalation	LC_{50}= 1.8 mg/L	IV[1]	440249-30
		Parental Offspring	NOAEL= 2000 ppm LOAEL= >2000 ppm NOAEL= 200 ppm LOAEL= 2000 ppm	Reproduction Body weight	440249-50

[1] Least toxic and no irritation. Use restriction as on the label
[2] Less toxic and can be used for homeowners generally with only restriction as on the label.

iv. Insects

Table 14. Nontarget Insect Acute Contact Toxicity.

Species	*% ai*	*LD50 (ug/bee)*	*Toxicity Category*	*MRID No. (Author/Year)*	*Study Classification*
Honeybee (Apis mellifera)	98.0	>200 [1]	practically nontoxic	440249-61 (Decker, 19993)	Core

[1] One mortality at 10 *u*g/bee (not considered treatment-related).

b. Toxicity to Freshwater Aquatic Animals

i. Fish, Acute

Table 15. Freshwater Fish Acute Toxicity of Pymetrozine.

Species	*% ai*	*96-h LC_{50} (ppm)*	*Toxicity Category*	*MRID No. (Author/Year)*	*Study Classification*
Rainbow trout *(Oncorhynchus mykiss/ flow-through)*	98.5	>128 (measured)	practically nontoxic	440249-13 (Boeri et al., 1994)	Core
Bluegill sunfish *(Lepomis macrochirus/flow-through)*	98.5	>134 (measured)	practically nontoxic	440249-12 (Boeri et al., 1994)	Core

ii. Fish, Chronic

Table 16. Freshwater Fish Early Life-Stage Toxicity Study of Pymetrozine.

Species / Test Conditions	*% ai*	*NOEC/LOEC (ppm)*	*MATC (ppm) [1]*	*Endpoint Affected*	*MRID No. (Author/ Year)*	*Study Classification*
Rainbow trout *(Oncorhynchus mykiss/flow-through)*	98.5	NOEC = 11.7 LOEC > 11.7 [2]	Not Determined	None	440249-18 (Boeri et al., 1995)	Supplemental[3]

[1] Maximum Allowed Toxic Concentration, defined as geometric mean of the NOEC and LOEC.
[2] Highest test concentration.
[3]No effects at any test concentrations; MATC could not be determined.

iii. Invertebrates, Acute

Freshwater Invertebrate Acute Toxicity

Table 17. Freshwater Invertebrate Acute Toxicity of Pymetrozine.

Species/Test Conditions	*% ai*	*48-hour EC_{50} (ppm)*	*Toxicity Category*	*MRID No. (Author/ Year)*	*Study Classification*
Waterflea (Daphnia magna/flow-through)	98.5	87.0 (measured)	Slightly Toxic	440249-14 (Boeri et al., 1994)	Core [1]

[1] Dechlorinated tap water was used.

iv. Invertebrates, Chronic

Table 18. Freshwater Aquatic Invertebrate Life-Cycle Toxicity.

Species / Test Conditions	*% ai*	*21-day NOEC/LOEC (ppm)*	*MATC (ppm) [1]*	*Endpoint Affected*	*MRID No. (Author/ Year)*	*Study Classification*
Waterflea *(Daphnia magna / flow-through)*	98.5	NOEC = 0.025 LOEC = 0.052 (measured)	0.036	Reproduction, Growth, and Survival	440249-19 (Boeri et al., 1995)	Core [1]

[1] Maximum Allowed Toxic Concentration, defined as geometric mean of the NOEC and LOEC

c. Toxicity to Estuarine Marine Animals

i. Fish, Acute

Table 19. Estuarine/Marine Fish Acute Toxicity of Pymetrozine..

Species / Test Conditions	*% ai.*	*96-h LC_{50} (ppm)*	*Toxicity Category*	*MRID No. (Author/Year)*	*Study Classification*
Sheepshead minnow *(Cyprinodon variegatus)/ flow-through*	98.5	>117 (measured)	practically non-toxic	440249-16 (Boeri et al., 1994)	Core

ii. Invertebrates, Acute

Table 20. Estuarine/Marine Invertebrate Acute Toxicity of Pymetrozine.

Species	*% ai.*	*96-hour EC_{50}/ LC_{50} (ppm)*	*Toxicity Category*	*MRID No. (Author/Year)*	*Study Classification*
Eastern oyster (shell deposition) (*Crassostrea virginica)/*flow-through	98.5	3.05 (measured)	moderately toxic	440249-17 (Boeri et al., 1994)	Core
Mysid *(Americanysisbahia)*/flow-through	98.5	66.9 [2] (measured)	slightly toxic	440249-15 (Boeri et al., 1994)	Supplemental[1]

[1] Age of the test mysids was not reported; appeared to be greater than 10 days old.
[2] One mortality in control group.

d. Toxicity to Aquatic Plants

i. Terrestrial

Currently, terrestrial plant testing is not generally required for insecticides, unless there is a known concern about phytotoxicity.

ii. Aquatic Plants

Table 21. Nontarget Aquatic Plant Toxicity (Tier II) of Pymetrozine.

Species	*% ai*	*EC_{50} (ppm)*	*NOEC (ppm)*	*MRID No. Author/Year*	*Study Classification*
Vascular Plants					
Duckweed *Lemna gibba*	98.5	>109 (initial measured)	49	440249-60 (Boeri et al., 1995)	Supplemental[1]
Nonvascular Plants					
Green algae *Kirchneria subcapitata*	98.5	17.0 (initial measured)	6.28	440249-59 (Boeri et al., 1995)	Core

[1] Test material was unstable and was not detected by test termination. The test solutions should have been renewed every few days.

IV. SUMMARY OF REGULATORY POSITION AND RATIONALE

The Agency has established permanent tolerances for **residues** of **pymetrozine per se** in the food crops listed in Table 4 above It most recently published a Final Rule in the Federal Register on December 27, 2001 (66 FR 66786-94). All of these tolerance will appear in the 2002 version of the Code of Federal Regulations under 40 CRF 180.556 (Pymetrozine; tolerances for residues). Table 4 of this document lists the commodities and their tolerance levels and pre-harvest intervals (PHI). Because of a metabolite of concern, the label also includes a plant back restriction of 30 days for all crops.

Available data provide adequate information to support the conditional registrations of pymetrozine technical, Fulfill® on food crops and tobacco, and Endeavor® on ornamentals.

V. SUMMARY OF DATA GAPS

Chemistry Data (due December 2000);

- Storage Stability Data
- Corrosion Characteristics Data

Toxicology Data: (due October 2001)

- Developmental Neurotoxicity Study (870-6300 or 83-6)

Environmental Fate Data:

- Drinking water monitoring (originally due October 2002 but the requirement was no longer applicable after the Cancer Q^* was revised downward)
- Photodegredation on Soil (due October 2000)

Ecological Effects Data:

- Acute Estuarine/Marine Toxicity (shrimp), 72-3(c), due October 2000
- Avian Reproduction (mallard), 71-4(b), due November, 2003

VI. CONTACT PERSON AND MAILING ADDRESS AT EPA

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