United States
Environmental Protection
Agency

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

Pesticide Fact Sheet

Name of Chemical: Thiazopyr
Reason for Issuance: Registration of a New Chemical
Date Issued: February 20, l997

1. Description of the Chemical

Generic Name: 3-Pyridinecarboxylic acid, 2-(difluoromethyl)-5-(4,5-dihydro-2-thiazolyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-, methyl ester

Common Name: Thiazopyr
Trade Names: MANDATE, VISOR
EPA Shaughnessy Code (OPP Chemical Code): 129100
Chemical Abstracts Service (CAS) Number: 117718-60-2
Year of Initial Registration: February 20, 1997
Pesticide Type: Herbicide
Chemical Family: Pyridine
Producer: Rohm and Haas Company

2. Use Patterns and Formulations:

Application Sites: citrus

Type and Methods of Application: Spraying by ground equipment

Types of Formulations: 95.1 % a.i. Technical; EC formulation containing 22.3 % by weight of the new chemical, thiazopyr

Usual Carriers: Water

Target Pests: Preemergent weeds--annual grasses and certain broadleaf weeds

Annual grasses:

Alexandergrass	Crowfootgrass	Itchgrass
Barley, Little	Foxtail, Giant	Junglerice

Barnyardgrass	Foxtail, Green	Natalgrass
Brome, Ripgut	Foxtail, Yellow	Sandbur, Field
Canarygrass	Goosegrass	Shattercane
Crabgrass, Large	Guineagrass	Signalgrass, Broadleaf
		Sprangletop

Broadleaf Weeds		
Beggarweed, Florida	Malva	Redmaids
Carpetweed	Mustard species	Rocket, London
Chickweed	Nightshade, black	Shepherdspurse
Eclipta	Pigweed	Sowthistle, Annual
Groundsel, Common	Purslane,Common	Spurge (Anual Species)
Lambsquarters,Common		

Sites: Oranges and grapefruit

3. <u>Science Findings</u>

Summary Statement: The end-use (EP) product, MANDATE® 2E Herbicide or VISOR® 2E Herbicide, is slightly toxic by acute oral and inhalation exposure and practically nontoxic by acute dermal exposure. It is considered to be moderately irritating to the skin and substantially irritating to the eye. It is not a dermal sensitizer. The product is assigned to Toxicity Category Category II based on eye irritation. The technical is practically nontoxic by oral and dermal exposure, not significantly toxic by inhalation exposure, no more than slightly irritating to the skin, and slightly irritating to the eye. It, too, is not a dermal sensitizer. The technical is assigned to Toxicity Category III because of its inhalation toxicity and ocular irritation potential.

Thiazopyr technical produced organ toxicity following multiple exposures at high doses. The primary target organs for thiazopyr toxicity in the rat, mouse and dog were the liver, thyroid, kidney and blood, with the liver being the most sensitive indicator of toxicity. In chronic dietary feeding studies, the dog was the most sensitive species. An RfD for thiazopyr of 0.008 mg/kg/day was established by the RfD Committee of the USEPA Health Effects Division, based on the NOEL of 0.8 mg a.i./kg/day (20 ppm) from the chronic dog study and a 100-fold safety factor to account for intraspecies extrapolation and intraspecies variability.

There was no evidence of carcinogenic effects in an 18-month chronic/oncogenicity study in mice at dose levels up to and including 800 ppm (216 mg/kg/day). In rats, an increased incidence of thyroid follicular tumors in males at the two highest doses, 1000 (44.2 mg/kg/day, males) and 3000 ppm, (136.4 mg/kg/day) was observed, and there was a low incidence of renal tubular adenoma at the high dose only in females. The thyroid tumors were determined in three special thyroid function studies to be secondary to a disturbance of thyroid/pituitary homeostasis and were attributed to a hormonally-

mediated mechanism for thyroid tumor induction. The effects were dose-responsive and with the exception of thyroid weight, all effects were completely reversible when thiazopyr was removed from the diet. Based on limited evidence for carcinogenicity, thiazopyr is classified as Category C, possible human carcinogen, by the USEPA Health Effects Division Carcinogenicity Peer Review Committee. A NOEL of 4.4 mg/kg/day and a Margin of Exposure approach were selected for use in carcinogenicity risk assessment.

Thiazopyr was not teratogenic and was not embryofetotoxic below maternally toxic doses. In the rat, thiazopyr technical produced no reproductive effects in a two-generation study. Overall, thiazopyr was not associated with significant developmental or reproductive effects. Thiazopyr was not mutagenic or genotoxic in a battery of tests.

Pharmacokinetic and metabolism studies in the rat indicated that thiazopyr was rapidly metabolized and excreted, and does not accumulate in tissues.

Thiazopyr had low toxicity to birds, mammals, honeybees, and earthworms. It was moderately toxic to freshwater and marine fish and *Daphnia magna*, with moderate to high toxicity to marine invertebrates. Thiazopyr was highly to very highly toxic to nontarget terrestrial and aquatic plants, algae and diatoms.

Thiazopyr degrades relatively rapidly in the environment. It dissipates relatively quickly in soil with an average half life of 85 days.. The vertical mobility, even in sandy soils with low organic content, did not exceed 12 inches, and thiazopyr was usually only detectable in the 0-6 inch layer of soil. The major soil metabolite, monoacid, was detected only in very low amount in the top soils. The monoacid dissipates as fast or faster than thiazopyr itself in the field.

Thiazopyr has a very low water solubility and a low potential for vertical movement. It is hydrolytically stable, but degrades rapidly by photolysis. The dynamic fish bioaccumulation study demonstrated that it should not bioconcentrate.

Plant metabolism studies have been conducted on three crops (lemon, peanut, and cotton), as well as three mammals (goat, hen, and rat). The metabolic pathway has been well defined and is similar. Thiazopyr is extensively degraded.

Residue studies conducted on citrus indicate that the residues in the crops are below the limit of quantitation and tolerances are proposed at the LOQ.

Chemical Characteristics: **(Technical Grade)**

Physical:	Granular Solid	
Color	Light tan	
Odor:	Sulfurous	
Melting Point:	77.3-79.1 C	
Boiling Point:	Not applicable	
Density:	1.3777 g/ml @ 25 C	
Molecular Formula:	C16H17F5N2O2S	
Vapor Pressure:	2.04 x 10-6 mm Hg @ 25 C	
Solubility:	Water	2.29 x 10-4 g/100 ml @ 20 C
	Hexane	3.06 g/ 100 ml @ 20 C
	Methanol	28.7 g/100 ml @ 20 C
Octanol/Water Partition Coefficient:	log:	3.89
	$K_{ow:}$	7,729
pH:	5.39 @ 25 C	

Toxicology Characteristics:

Technical Formulation:

Acute Oral Toxicity (Rat): LD_{50} =>5.0 g/kg. Toxicity Category IV.

Acute Dermal Toxicity (Rat): LD_{50} =>5.0 g/kg.. Toxicity Category IV.

Acute Inhalation Toxicity (Rat): LC_{50} =>1.2 mg/L (highest concentration which could be generated in this study). Toxicity Category III.

Primary Eye Irritation (Rabbit): slightly irritating. Toxicity Category III.

Skin Irritation (Rabbit): Practically non-irritating. Toxicity Category IV.

Dermal Sensitization (Guinea Pig): Not a sensitizer

21-Day Dermal (Rat): NOEL =100 mg/kg/day. The LOEL was 500 mg/kg/day based on minimal hepatocellular vacuolation in females.

90-day Oral (Rat): NOEL (systemic) =100 ppm (6.60 mg /kg/day and 7.99 mg/kg/day for males and females, respectively). The LOEL was 1000 ppm (68 - 79 mg/kg/day in males and females, respectively) based on increased liver, thyrid and kidney weights, changes in clinical chemistry and hematological parameters and on gross and microscopic changes observed in the liver and thyroid at does levels of 68 mg/kg/day and higher. At the 201 mg/kg/day dose diffused thyroid follicular cell hypertrophy/ hyperplasia was observed.

90-day Oral (Dog): NOEL (systemic) =10 ppm. (0.2 mg/kg/day(m); 0.3 mg/kg/day(f)), based on decreased body weight gain and increased SGPT levels at 3 and 6 m/kg/day for males and females, respectively and above; decreased total protein and albumin concentration and albumin/globulin ratio, increased AP, hepatocytic hypertrophy, oval cell proliferation and increased hepatocytic fatty content at 35 mg/kg/day and above; and decreased calcium concentration which is thought to be related to hypoalbuminemia, decreased cholesterol and triglyceride concentrations, slightly increased GGT and SGPT, follicular hyperplasia of thyroid, increased colloid content in follicles and increased relative thyroid weight at 175 mg/kg/day.

A 3 week dermal study in rabbits at 0, 100, 500 and 1000 mg/kg/day with a NOEL of 100 mg/kg/day. The effects were increased mean absolute and relative kidney weights and minimal multifocal or periportal hypatocyte vacuolation.

A 1 year feeding study in dogs at 0, 0.8, 7.8, 86.0 with males, and 0.8, 8.8, and 78.0 with females with a NOEL of 0.8 mg/kg/day. The Loel was based on hepatocellular hypertrophy and hyperplasia. A 10% increase in prothrombin time and several and several changes in blood chemistry: increased SGOT, SGPT, GGT and ALK levels and decreased cholesterol, albumin and total protein and calcium were observed in high-dose dogs. There were increases in absolute weights, liver and body weight and liver to brain weight, heptotoxicity characterized by enlargement and/or discoloration in some high dose animals and by hepatocellular hypertrophy/hyperplasia in the 0.8 and 7.8 mg/kg/day dogs. The NOEL was based on hepatocellular hypertrophy and hyperplasia.

A developmental toxicity study in rats at 0, 10, 100 and 250 mg/kg/day with a maternal toxicity NOEL of 100 mg/kg/day. The effect were increased liver weight, increased slivation, significantly decreased body weight gain and decreased food consumption. The developmental NOEL was also 100 mg/kg/day. The effects at the high dose were increased incidence of unossified sternebrae and 7th cervical rib variation. No development effects were observed below the maternally toxic doses.

A developmental toxicity study in rabbits at 0, 10, 75 and 175 mg/kg/day with a maternal toxicity NOEL of 75 mg/kg/day. The effects were reduced body weight gain and reduced food consumption. The developmental NOEL was greater that 175 mg/kg/day, the highest dose tested.

A two-generation reproductive in rats at 0, 0.75, 7.5 and 75.0 mg/kg/day with a parental toxicity NOEL of 7.5 mg/kg/day. The toxic effects were increased absolute and relative liver weight, hepatic discoloration, histologic evidence of hepatic hypertrophy and vacuolization in females in both generations. No adverse efects were ob served in adults or their offspring up to 75 mg/kg/day, the highest dose tested.

A mouse carcinogenicity study at doses of 0, 0.17, 1.6, 16.9, 66.3 or 128.4 mg/kg/day (males) and 0,0.24, 2.6, 26.8, 108.1 or 215.9 mg/kg/day (female) with a systemic NOEL of 0.1 mg/kg/day. The effects were hepatocellular hypertropy and amyloid deposition. At 66.3 mg/kg/day the same lesions plus increased liver weights, random and periportal hepatocellular vacuolation were observed. At 128.4 mg/kg/day the same lesions plus distended abdonen, slight increase in ALP, SGOT and SGPT, abnormal coloration and enlargement of liver, decrease in absolute and relative spleen weights, increase in absolute and relative kidney weights, increase in eosinophilia in hepatocytes, kidney nephropathy and lymphocytic hyperplasia of the nesenteric lymph nodes were observed. There was no evidence of oncoenicity at any dose level.

A two year rat carcinogenicity study at doses of 0, 0.04, 4.4, 44.2 or 136.4 mg/kg/day (Males) 0, 0.06, 0.6, 5.6, 56.3 or 177.1 mg/kg/day (female) with a NOEL of 4.4 mg/kg/day. The effects were protruding eyes, evidence of mild anemia, increased GGT and cholesterol, increased absolute and relative liver, kidney and thyroid weights and significant increase in microscopic lesions in the liver (hypertrophy and vacuolar changes), kidney (nephropathy) and thyroid (hypertrophy and hyperplasia); decreased mean body weight and body weight gain and food consumption. A statistically significant increase in thyroid follicular cell adenomas/cystadenomas were observed in males at 44.2 and 136.4 mg/kg/day. A nonsignificant increase in renal tubular adenomas in high-dose females was considered to be equivocal.

The EPA Health Effects Division Carcinogenicity Peer Review Committee classified thiazopyr as a Group C, possible human carcinogen and recommended that for the purpose of risk characterization a Margin of Exposure (M.O.E.) approach should be used in evaluation of the consequences of human exposure.

An acceptable study for inducing reverse mutation in Ames Salmonella strains of bacteria exposed with or without activation at doses up to 10,000 micrograms per plate. The study showed negative results.

An acceptable study for inducing micronuclei in bone marrow cells of mice treated up to a lethal dose of 800 mg/kg. The study showed negative results.

A mutagenic study with Chinese hamster ovary cells exposed **in vitro** with or without activation to doses up to 1000 micrograms, the hightest dose tested. The study showed negative result for inducing forward mutation at the hypxanthine guanine phosphoribosyl transferase locus (HGPRT). On the basis of the studies on mutagenicity and genotoxicity, it is concluded tht thiazopyr is not a mutagenic or genotoxic chemical.

An acute neurotoxicity in rats at doses of 0, 100, 500 and 2000 mg/kg with a NOEL of 500 mg/kg. The LOEL of 1000 mg/kg was based on transieent differences in functional observational battery (FOB) and motor activity compared to control groups. The results of the study were considered to be inconclusive for neurotoxicity. At the highest dose (2000 mg/kg) it was not possible to distinguish betweem neurotoxicity and general systemic toxicity.

Two metabolism studies were conducted in rats with radio- labeled thiazopyr. One with the 14C at the 4 position of the pyridine ring and one with the 14C at the 4' and 5' positions of the thiazole ring. The absorption of an orally administered dose was about 90%. The overall radiolabel recovery for all study groups was 88.9, plus or minus 0.65%. No significant sex-related differences were observed in the total percent recovery. However, the distribution of recovery was sex-related. There was little radiolabel detected in tissues at study termination. Preferential sites for localization of the radiolabel included liver, adipose tissue, muscle and bone. The metabolic pathway is essentially an oxidative pathway. Vulnerable sites of the molecule are the thiazoline ring, the isobutyric side chain and the pyridine rings. Thiazapyr appears to be rapidly and extensively eliminated with low amounts of residues remaining in the tissues and carcasses. The percentage of radiolabel remaining in the carcasses following feeding thiazoline labeled thiazopyr was beween 6.9 and 10.8%.

Special mechanistic studies for mode of toxic action on thyroid function. The results of three studies on the effects of thiazopyr on thyroid function and mechanisms involved in the disposition of T4 in rats were reviewed. These studies are described below:

a. Thiazopyr was administered through the diet at 0 and 150 mg/kg/day rats to determine the subchronic effect on hormone level and other biochemical endpoints. Animals were assayed at 7, 14, 28, 56 or 90 days. Significant decreases in body weight gain were observed at 90 days. Early in the study the treated rats showed increases in TSH (ranging from 133 to 200% of controls) and decreases in T4 (ranging from 43% to 76% of controls). In addition there were increases in liver and thyroid weights and increases in thyroid follicular cell hypertrophy/hyperplasia. Reverse T3 was increased at 28 days, and T3 was either not

affected or increased. There were indications of increases in hepatic UDPGT activity and significant increases in T4 UDPGT activity. Hepatic 5'-monodeiodinase activity was either not affected or decreased. The effects observed in this study were supportive of the theory that thiazopyr may induce thyroid tumors through a disruption in the thyroid-pituitary hormonal feedback mechanisms.

b. A second study on the effects of thiazopyr on the biochemical mechanisms of thyroid toxicity in rats at doses of 0, 0.5, 1.5, 5, 15, 50 or 150 mg/kg/day was conducted. Dose response effects on various biochemical parameters were observed. Two groups of the rats in the study were observed for reversibility of effects observed up to 56 and 112 days. Doses at 15, 50 and 150 mg/kg/day significantly increased the liver weights. Thyroid weights were increased at doses of 50 and 150 mg/kg/day. There were no significant effect on body weight or body weight gains during the study. The T4 UDPGT levels were increased by 117 and 376% above controls at the 50 and 150 mg/kg/day dosages. Effects of 150 mg/kg/day were increases in T3, TSH and rT3 serum concentrations, and increased incidence of follicular cell hypertrophy/hyperplasia at the 150 mg/kg/day dose. A NOEL of 1.5 mg/kg/day was determined based on liver weight increases. Thyroid weight was the only parameter that did not return to those similar to the controls. At the 56 and 112 day recovery periods the thyroid weights were 120 and 123% of control values, respectively.

c. A third thyroid function study on the biochemical mechanisms involved with disposition of T4 in rats fed dosages of 0 and 150 mg/kg/day for 56 days was conducted. Rats feed thiazopyr had increase T4 UDPGT activity and total deiodinase activity in their livers. There was also a two-fold increase in mixed function oxidase enzyme activity.

Results of the three studies suggest that increased glucuronidation, deiodination of T4 and T3, and increased rate of clearance of T4 from the blood and excretion of the hormone and its metabolites in the bile could significantly reduce the level of circulating T4 in the male rat. Results of these studies support the hypothesis tht thiazopyr may induce thyroid tumors through a disruption of the thyroid-pituitary hormonal feedback mechanism circulating T4 in the male rat.

<u>End-Use Formulation:</u>

Acute Oral Toxicity (Rat): (male and female combined) LD_{50} =2180 mg/kg. Toxicity Category III.

Acute Dermal Toxicity (rat): (male and female combined) LD_{50} = >5.0 g. Toxcicty

Category IV.

Acute Inhalation (Rat): (male and female combined) LC_{50} =2.9 mg/L. Toxicity Category III.

Primary Eye Irritation (Rabbit): Substantially irritating, but completely reversible within 14 days. Toxicity Category II.

Primary Dermal Irritation (Rabbit): Moderately irritating. All animals were essentially free of dermal irritation by day 14. Toxicity Category III.

Dermal Sensitization: Not a dermal sensitizer.

Residue Chemistry

Nature of residues

Plant:

The metabolic fate of thiazopyr was investigated in lemon, cotton, and peanuts. There was extensive degradation with over 40 metabolites quantitated in each study, ranging from 0.01 to 13.7% of the dose level. In all plants studied, the metabolism profiles were the same.

Magnitude of residues:

20 field trials were conducted in four major citrus growing states using the 2E formulation at 2 lb ai/acre. Residues of thiazopyr and its metabolites were measured. No detectable residue from any trial was found above 0.05 ppm, the limit of quantitation of the residue analytical method.

Proposed tolerance

The proposed tolerance of 0.05 ppm is acceptable.

Directions for use

The proposed labeling is acceptable and adequately reflects the application pattern used to generate the residue data.

Analytical method

An enforcement analytical method which quantifies thiazopyr and its metabolites by gas chromatography with a mass spectrometry detector was proposed. The limit of quantitation of the method is 0.025 ppm. This method was successfully validated and has been determined to be suitable for enforcement of a 0.05 ppm tolerance for the raw agricultural commodity, citrus.

Chemical identity

The chemical nature of thiazopyr has been adequately addressed.

Reasonable grounds in support of petition

The data submitted adequately support the tolerance.

Ecological Effects Characteristics:

(Technical Formulation)

Avian Acute Oral: Slightly toxic

Bobwhite Quail: LD_{50} = 1814 mg/kg

Avian Dietary: Practically non toxic

Bobwhite quail and mallard duck: LC_{50}'s = 5328 mg/kg

Avian Reproduction:

There were no apparent treatment-related effects on any reproductive parameters in the bobwhite quail up to the maximum dose tested (1200 ppm). In the mallard duck, no effects were observed on any measured parameter up to and including 300 ppm.

Bobwhite quail:	NOEL = 1000 ppm
	LOEL = >1200 ppm
Mallard duck:	NOEL = 300 ppm
	LOEL = >1200 ppm

Freshwater Fish: moderately toxic

Rainbow trout: LC_{50} = 3.4 mg/L

Bluegill Sunfish: LC_{50} = 3.5 mg/L

Aquatic Invertebrate: moderately toxic

Daphnia magna: LC_{50} = 6.1 mg/L

Mollusc Shell Deposition: highly toxic

Eastern Oyster: EC_{50} = 0.82 mg/L

Estuarine Invertebrate Acute Toxicity: Moderately toxic

Mysid Shrimp: LC_{50} = 2.0 mg/L

Fish Early Life Stage Toxicity

Rainbow trout:	NOEL = 0.55 mg/L
	MATC = 0.74 mg/L

Aquatic Invertebrate Life Cycle Toxicity

Daphnia magna: NOEL = 0.11 mg/L
MATC = 0.16 mg/L

Aquatic Plant Growth and Reproduction

Selenastrum capricornutun:EC_{50} = 0,043 mg/L
NOEL = 0.018 mg/L

Honey Bees: Relatively Non Toxic

LD_{50} = > 100 µg/bee

Environmental Fate: **(Technical Formulation)**

Hydrolysis:

Thiazopyr is stable in sterile aqueous buffered solutions at pH 4 and 5. Hydrolysis was observed at pH 7 and 9, with predicted half-lives of thiazopyr of 3394 days and 64 days, respectively. In both cases, the product of the hydrolysis was thiazopyr monoacid.

Photodegradation in Water:

Thiazopyr degraded with half-lives of 7.8 and 20.8 days, respectively, in unsensitized and humic acid sensitized sterile aqueous pH 5 buffer solutions using artificial sunlight at 25 C.

Photodegradation on soil:

Thiazopyr degrades very slowly in soil, with an extrapolated half life of 1373 days.

Aerobic soil metabolism:Thiazopyr degraded with half-lives of 111 and 437 days in loam soil and in and sandy loam soil, respectively.obility (Leaching/SorptionOnce adsorbed to soil, thiazopyr desorbed less readily than it adsorbed. The major soil metabolite, monoacid, however, was adsorbed to only a slight extent by the soils. The soil adsorption/desorption study indicated that mobility of thiazopyr and the monoacid might be moderate or greater in soil.

Bioaccumulation in fish:

A dynamic fish bioaccumulation study showed that thiazopyr should not bioconcentrate, with bioconcentration factors ranging from 11 to 400X for different fish tissues.

Terrestrial field dissipation:

Thiazopyr dissipated relatively quickly, with an average half life from 14 field dissipation studies across the country of 85 days. The vertical mobility, even in sandy soils with low organic content, did not exceed 12 inches, and thiazopyr was usually only detectable in the 0-6 inch layer of soil. The major soil metabolite, monoacid, was detected only in very low amount in the top soils. The monoacid dissipates as fast or faster than thiazopyr itself in the field.

4. **Summary of Data Gaps**

. Rohm and Haas will develop a method for thiazopyr and/or any metabolites of concern b January, l998 with a sensitivity as low as possible. The sensitivity must be of 0.1 ppb or less.

. Rohm and Haas will develop with the states of Florida and California a water sampling program to sample for the monoacid of thiazopyr. The monoacid will be used as a surogate for thiazopyr and its metabolites. The final sampling program, agreed to by the states, must be submitted to EPA by October 30, l997. Rohm and Haas will work with the states to develop a monitoring program acceptable to the states and Rohm and Haas. The complete sampling program will start by March 1, l998. At a minimum, 10 wells per state will be required.

. An aerobic aquatic metabolism study.

. Available water balance data to further assess field dissipation studies. This would include: pan evaporation data, daily rainfall, and irrgation data. Additional dissipation studies may be required if after further review current dissipation studies are found unacceptable.

. An aquatic plant study.

5. **Required Unique Labeling Summary**

. Groundwater advisory statements under the label Environmental Hazards section.

. A " Proper Handling Instructions" section to prevent mixing, loading, rinsing or washing of product within 50 feet of any well, unless conducted on an impervious pad constructed to withstand the weight of the heaviest load that may be positioned on or moved across the pad. The pad construction and use is described.

. Do not contaminate irrigation water or water used for domestic purposes.

. Do not feed or allow any animals to graze on any areas treated with product.

. Endangered Species advisory.

6. **Contact Person at EPA**

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