United States Environmental Protection Agency | Office of Prevention, Pesticides and Toxic Substances Washington DC 20460 | EPA-737-F-96-005 May, 1996

Office of Pesticide Programs

[redacted]

New Pesticide Fact Sheet

1. Description of the Chemical:

Generic Name: 5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(1R,S)-(trifluoromethyl)sulfinyl]-1H-pyrazole-3-carbonitrile
Common Name: fipronil
Trade Name: Fipronil Technical; Chipco Choice Insecticide
EPA Shaughnessy Code (OPP Chemical Code): 129121
Chemical Abstracts Service (CAS) Number: 120068-37-3
Year of Initial Registration: MAY 1996
Pesticide Type: Insecticide
Chemical Family: Phenylpyrazoles
Producer: Rhone Poulenc Ag Company

2. Use Patterns and Formulations:

Application Sites: Golf Course Turf and Commercial Turf

Type and Method of Application: Application is made using slit-placement equipment which puts the product into the ground at the soil/thatch interface.

Type of Formulation: 0.1% flowable granular

Target Pest: Mole Cricket

Site: Golf Course and Commercial Turf

3. Science Findings:

Summary Statement: The end-use product, Chipco Choice Insecticide, has a low order of toxicity with respect to acute oral, dermal, inhalation, eye/skin irritation routes of exposure. It is not a sensitizer. The product is assigned to Toxicity Category III (**Caution**) based on the acute dermal route of exposure and eye irritation study. The technical product has a high order of toxicity to mammals with respect to acute oral, dermal, and inhalation routes of exposure and eye/skin irritation. It is not a sensitizer. The technical product is assigned to Toxicity Category II (**Warning**) based on the acute oral, dermal, and inhalation routes of exposure.

Fipronil has been classified as a Group C (Possible Human) Carcinogen based on an increase in thyroid follicular cell tumors in both sexes of the rat. The increase is statistically significant by both pair-wise and trend analyses. The RfD methodology was selected for quantification because the thyroid tumors appeared to be related to a disruption in the thyroid-pituitary status and there was no apparent concern for mutagenicity or available information from structurally related analogs.

An acceptable chronic rat feeding study identified the following effects: seizures, including seizures resulting in death, decreased body weight gain, decreased food consumption and food conversion efficiency, decreased hematology measures, alterations in clinical chemistry (cholesterol, calcium, and protein), alterations in thyroid hormones, alterations in urine chemistry, changes on gross necropsy, increase in liver and thyroid weights, and progressive senile nephropathy (kidney effects). The NOEL for systemic toxicity was 0.5 ppm. The LOEL of 1.5 ppm was based on an increase in incidence of clinical signs and alterations in clinical chemistry and thyroid parameters. Based on this study, the RfD Committee recommended that the RfD be established using the NOEL and an uncertainty factor of 100 to account for the interspecies extrapolation and intraspecies variability. The RfD was set at 0.0002 mg/kg/day.

In addition to the toxicity endpoints identified above, the toxic endpoint selection (TES) committee has identified the following endpoints and dose levels of concern. The acute dietary endpoint of concern is acute neurotoxicity. The NOEL is 0.5 mg/kg, and the LOEL is 5.0 mg/kg based on decreased hind leg splay observed at this level at seven hours post treatment. The TES committee also identified short and intermediate term occupational and residential exposure end points based on a 21-day dermal toxicity study. The NOEL was 5.0 mg/kg/day. The LOEL of 10.0 mg/kg/day was

based on decreased body weight gain and food consumption in rabbits.

An acceptable reproductive toxicity study in rats showed that fipronil is associated with reproductive effects. The NOEL for parental (systemic) toxicity was 3 ppm (0.25 mg/kg/day for males and 0.27 mg/kg/day for females). The LOEL for parental (systemic) toxicity was 30 ppm (2.54 mg/kg/day for males and 2.74 mg/kg/day for females) based on effects on the thyroid, liver, and pituitary gland. The NOEL for reproductive toxicity was 30 ppm (2.54 and 2.74 mg/kg/day for males and females respectively). The LOEL for reproductive toxicity was 300 ppm (26.03 mg/kg/day for males and 28.40 mg/kg/day for females based on clinical signs of toxicity, decreased litter size, decreased body weights, decrease in the percentage of animals mating, reduction in fertility index, reduced post-implantation survival and offspring postnatal survivability, and delay in physical development.

Developmental toxicity studies in rats and rabbits showed that fipronil was not associated with significant developmental toxicity. Several mutagenicity tests were negative. They include two Salmonella typhimurium/mammalian microsome reverse gene mutation assays with and without S-9 activation, an in vitro cytogenics assay using human lymphocytes, two Chinese hamster forward gene mutation assays, and a mouse micronucleus test.

Available environmental fate lab data indicate that, below the soil surface, fipronil dissipates by soil binding followed by slower biotic mediated processes. However, on the soil surface the major route of degradation may be slow photolysis and/or soil binding followed by slower biotic mediated processes. In addition, lab data indicate that fipronil has low mobility in soils and degrades slowly under alkaline hydrolytic conditions. Fipronil is stable to hydrolysis at mildly acid to normal pH.

The field data support the lab data. Half lives for fipronil of 1.1 to 1.5 months were reported for bare soil and 0.4 to 0.5 for turfed soil. In bare soil, residues were found only in the top 6 inches of soil. The potential for ground water contamination is considered low.

The ecological effects data show that fipronil is highly toxic to upland game birds on an acute oral basis, very highly toxic on a subacute dietary basis, and is practically non-toxic to waterfowl on both an acute and subacute basis. The chronic (avian reproduction) studies show no effects at the highest levels tested in mallards (NOEC) = 1000 ppm) or quail (NOEC = 10 ppm). The metabolite

MB 46136 is more toxic than the parent to avian species tested (very highly toxic to upland game birds and moderately toxic to waterfowl on an acute oral basis). Fipronil is very highly toxic to bluegill sunfish and highly toxic to rainbow trout on an acute basis. The results of a fish early life-stage toxicity study in rainbow trout show that fipronil affects larval growth with a NOEC of 0.0066 ppm and an LOEC of 0.015 ppm. The metabolite MB 46136 is more toxic than the parent to freshwater fish (6.3 times more toxic to rainbow trout and 3.3 times more toxic to bluegill sunfish). Based on an acute daphnia study using fipronil and three supplemental studies using its metabolites, fipronil is characterized as highly toxic to aquatic invertebrates. An invertebrate life cycle daphnia study showed that fipronil affects length in daphnids at concentrations greater than 9.8 ppb. A life cycle study in mysids shows fipronil affects reproduction, survival and growth of mysids at concentrations less than 5 pptr. Acute studies of estuarine animals using oysters, mysids, and sheepshead minnows shows that fipronil is highly acutely toxic to oysters and sheepshead minnows, and very highly toxic to mysids. Metabolites MB 46136 and MB 45950 are more toxic than the parent to freshwater invertebrates (MB 46136 is 6.6 times more toxic and MB 45950 is 1.9 times more toxic to freshwater invertebrates).

Chemical Characteristics: Technical Grade fipronil

Physical: Powder
Color: White
Odor: Moldy
Melting Point: 195.5 to 203 deg. C
Density: 1.6262 g/ml at 20 deg. C
Molecular Formula: $C_{12}H_4Cl_2F_6N_4OS$
Vapor Pressure: 2.8×10^{-9} mm Hg at 25 deg. C
Octanol/Water Partition Coefficient: log $P_{o/w}$ = 4.01
pH: 5.9 to 6.1 at 23 deg. C (1% w/v water)

Solubility:

Solvent	Solubility, g/l
water pH 5	0.0024
water pH 9	0.0022
acetone	545.9
2-propanol	36.2
dichloromethane	22.3
ethyl acetate	264.9
hexane	0.028
methanol	137.5
toluene	3.0
octanol	12.2

Stability: degraded slightly by sunlight; stable at normal temperatures for one year; not stable in presence of metal ions.

Toxicology Characteristics: Technical Grade Fipronil

Acute oral (Rat): LD50 97 mg/kg; Tox Category II

Acute dermal (Rabbit): LD50 354 mg/kg; Tox Category II

Acute dermal (Rat): LD50 > 2000 mg/kg; Tox Category III

Acute inhalation (Rat): LC50 0.39mg/L; Tox Category II

Primary eye irritation (Rabbit): Mild transient eye irritation clearing by 24 hours; Tox Category III

Primary dermal irritation (Rabbit): Slight dermal irritation; Tox Category IV

Dermal sensitization (Guinea Pig): Not a sensitizer

Acute Neurotoxicity (Rat): NOEL = 0.5 mg/kg for males and females. LOEL 5.0 mg/kg for males and females based on decreased hind leg splay at the 7 hour post treatment evaluation in males and females.

Subchronic Toxicity (Dog): NOEL = 2.0 mg/kg/day for males and 0.5 mg/kg/day for females. LOEL = 10.0 mg/kg/day for males (based on clinical signs of toxicity and 2.0 mg/kg/day for females (based on clinical signs of toxicity and decreased body weight gain).

Subchronic Toxicity (Rat): NOEL = 5 ppm for males (0.33 mg/kg/day) and females (0.37 mg/kg/day. LOEL 30 ppm for males (1.93 mg/kg/day) and females (2.28 mg/kg/day) based on alterations in serum protein values and increased weight of the liver and thyroid.

Subchronic Neurotoxicity (Rat): NOEL = 5.0 ppm (0.301 mg/kg/day for males and 0.351 mg/kg/day for females). LOEL = 150 ppm (8.89 mg/kg/day for males and 10.8 mg/kg/day for females) based on increased incidence of no urination and increased incidence of exaggerated tail pinch response in males, increased incidence of exaggerated startle responses in males and females, and increased forelimb grip strength at week 13 in females.

21-Day Dermal Toxicity (Rabbit): Systemic NOEL = 5.0 mg/kg/day; Dermal irritation NOEL >= 10.0 mg/kg/day. Systemic LOEL = 10 mg/kg/day based on decreased body weight gain and food consumption; Dermal irritation LOEL > 10 mg/kg/day.

Chronic Toxicity (Dog): NOEL 0.2 mg/kg/day. LOEL 2.0 mg/kg/day based on clinical signs of neurotoxicity and abnormal neurological examinations.

Chronic Toxicity (Dog): NOEL = 0.3 mg/kg/day in females and 1.0 mg/kg/day in males. LEL is 1.0 mg/kg/day in females and 2.0 mg/kg/day in males based on clinical signs of neurotoxicity.

Carcinogenicity (Mouse): NOEL = 0.5 ppm (0.055 mg/kg/day for males and 0.063 mg/kg/day for females). LOEL = 10 ppm (1.181 mg/kg/day for males and 1.230 mg/kg/day for females) based on decreased body weight gain, decreased food conversion efficiency (males), increased liver weights and increased incidence of hepatic histopathological changes. The study demonstrated that technical fipronil is not carcinogenic when administered at doses of 30 ppm or greater to CD-1 mice.

Combined Chronic Toxicity/Carcinogenicity (Rat): NOEL = 0.5 ppm for males (0.019 mg/kg/day) and females (0.025 mg/kg/day). LOEL 1.5 ppm for males (0.059 mg/kg/day) and females (0.078 mg/kg/day) based on an increased incidence of clinical signs and alterations in clinical chemistry and thyroid parameters. The study demonstrated that fipronil is carcinogenic to rats at doses of 300 ppm in males (12.68 mg/kg/day) and females (16.75 mg/kg/day).

Developmental Toxicity (Rat): Maternal toxicity NOEL = 4 mg/kg/day. Maternal toxicity LOEL = 20 mg/kg/day based on reduced body weight gain, increased water consumption, reduced food consumption and reduced food efficiency. Developmental toxicity NOEL is 20 mg/kg/day or higher. Developmental toxicity LOEL is greater than 20/mg/kg/day.

Developmental Toxicity (Rabbit): Maternal toxicity NOEL < 0.1 mg/kg/day. Maternal toxicity LOEL is equal to or less than 0.1 mg/kg/day based on reduced body weight gain, reduced food consumption and efficiency. Developmental toxicity NOEL is equal to or greater than 1.0 mg/kg/day. Developmental toxicity LOEL is greater than 1.0 mg/kg/day.

Multigeneration Reproduction Study (Rat): NOEL for parental (systemic) toxicity was 3 ppm (0.25 mg/kg/day for males and 0.27 mg/kg/day for females). LOEL for parental (systemic) toxicity was 30 ppm (2.54 mg/kg/day for males and 2.74 mg/kg/day for females) based on systemic signs including increase in the absolute and relative weights of the thyroid glands and liver in males and females of the F_0 and F_1 generations; decrease in the absolute weight of the pituitary gland in females in the F_1 parental animals; and increase incidence of follicular epithelial hypertrophy of the thyroid glands in females of the F_1 generation. The NOEL for reproductive toxicity was 30 ppm (2.54 and 2.74 mg/kg/day for males and females respectively). The LOEL for reproductive toxicity was 300 ppm (26.03 mg/kg/day for males and 28.40 mg/kg/day for females based on clinical signs of toxicity in the F_1 and F_2 offspring; decreased litter size in the F_1 and F_2 litters; decreased body weights in the F_1 and F_2 litters; decrease in the percentage of F_1 parental animals

mating; reduction in fertility index in F_1 parental animals; reduced post-implantation survival and offspring postnatal survivability in the F_2 litters; and delay in physical development in the F_1 and F_2 litters.

Mutagenicity. Several mutagenicity tests were negative. These include an Ames (salmonella) test in the presence and absence of S9 activation; an in vitro gene mutation (Chinese hamster V79 cells)/HGPRT assay both with and without S9 activation; a cytogenic assay (Human lymphocytes) test of clastogenic effects with and without S9 activation; and a mouse micronucleus assay.

Metabolism (Rat): ^{14}C fipronil was administered orally in aqueous methylcellulose to male and female rats at doses of 4 and 150 mg/kg (single dose) and 4 mg/kg for 14 days (repeated dose). The rate and extent of absorption appeared similar among all dose groups, but may have been decreased at the high dose. Distribution data showed significant amounts of residual radioactivity in the carcass, G.I. tract, liver, adrenals, and abdominal fat at 168 hours post dose for all rats in all dose groups. Repeated low oral dosing or a single high oral dose resulted in an overall decrease in the amount of residual radioactivity found but an increase in the amount in abdominal fat, carcass, and adrenals. Feces appeared to be the major route of excretion where 45-75% of an administered dose was excreted. Excretion in urine was 5-25%. Increases in the percentages excreted in urine and feces were observed with repeated low oral dosing or a single high dose, while the percentage found in all tissues combined decreased. There were no significant sex-related differences in excretion. Major metabolites in urine included ring opened products of the metabolite MB 45897, two oxidation products, MB 46136 and RPA 200766, and the parent chemical fipronil. In feces, the parent was detected as a significant fraction of the sample radioactivity a well as the oxidation products MB 46136 and MB 45950. Whole blood half life ranged from 149.4 to 200.2 hours at 4 mg/kg. At 150 mg/kg, whole blood half-life was noticeably decreased to 54.4 hours in male rats and 51.2 hours in female rats.

<u>Toxicology Characteristics</u>: End-use product (Chipco Choice Insecticide)

Acute oral (Rat): Estimated LD50> 5000mg/kg; Tox Category IV

Acute dermal (Rabbit): Estimated LD50> 2000mg/kg; Tox Category III

Acute inhalation (Rat): Estimated LC50> 5.06mg/L; Tox Category IV

Primary eye irritation (Rabbit): Irritation clearing by 3rd day;

Tox Category III

Primary Dermal Irritation (Rabbit): Slight irritation, clearing by 72 hours; Tox Category IV

Dermal Sensitization (Guinea Pig): Not a sensitizer

ENVIRONMENTAL FATE CHARACTERISTICS: Technical Grade Fipronil

HYDROLYSIS DATA. Fipronil is stable to hydrolysis at mildly acid to neutral pH, but degrades with a half-life of 28 days in more basic solutions (pH 9). The major degradation product from alkaline hydrolysis is the amide (RPA 200766).

PHOTODEGRADATION IN WATER. Fipronil has a half-life of 3.63 hours when exposed to a xenon light source in the laboratory. The major degradates were MB 46513 and RPA 104615 at 43% and 8% of applied radioactivity. No volatile compounds were found.

PHOTODEGRADATION ON SOIL. Fipronil degrades slowly on loamy soil when exposed to light. The half-life is 34 days. Three major degradates were identified as RPA 200766, at a concentration of 10.86% of applied radioactivity. Two other degradates were identified as MB 46513, and RPA 104615 and measured at 8.65% and 8.87% of interest regions. There was no evidence of volatility of fipronil or its metabolites.

AEROBIC SOIL METABOLISM. Under aerobic conditions, soil organisms slowly break down fipronil. The half life in sandy loam soil is 122 (TLC data) - 128 (HPLC data) days. Several metabolites were identified. Two of these (RPA 200766 and MB 46136) account for 27%-38% and 14-24% of the total applied radioactivity, respectively.

ANAEROBIC AQUATIC METABOLISM. Fipronil degrades slowly in water and sediment under anaerobic conditions. The half life is 116 (HPLC data) - 130 (TLC data) days. Two major metabolites were found, MB 45950 and RPA 200766, at maximum concentrations of about 47% and 18% of applied radioactivity, respectively. MB 45950 was found in the soil extracts and RPA 200766 was found in both soil and water. The **Anaerobic soil metabolism** data requirement was also met by the anaerobic aquatic metabolism data.

LEACHING/ADSORPTION/DESORPTION. The column leaching and adsorption/desorption studies show that fipronil has low mobility in soil. It tends to bind to soil and it is expected not to leach to groundwater.

TERRESTRIAL FIELD DISSIPATION. The terrestrial field dissipation study showed that fipronil dissipates with a half life of 1.1 to

1.5 months for bare soil and 0.4 to 0.5 months for turfed soil. Fipronil residues tend to stay in the upper 6 inches of soil, and thus exhibit low potential to leach to groundwater. Of the major degradates identified in lab studies, only two (MB 46136 and RPA 200766) were found in field studies at amounts greater than the limit of detection.

FISH ACCUMULATION. The fish accumulation study showed that fipronil appears to bioaccumulate in fish when exposed to treated water at a concentration of about 900 nanograms for 35 days. The data indicate that the residues are almost completely eliminated after 14 days depuration. Bioconcentration factors were 321, 164, and 575 for whole fish, edible tissue and non-edible tissue, respectively. The major metabolites found were MB 46136, MB 45897, and MB 45950.

ECOLOGICAL EFFECTS CHARACTERISTICS: Technical Grade Fipronil

BIRDS. Fipronil is highly toxic to upland game birds on an acute oral basis, very highly toxic on a subacute dietary basis, and is practically non-toxic to waterfowl on both an acute and subacute basis. The chronic (avian reproduction) studies show no effects at the highest levels tested in mallards (NOEC) = 1000 ppm) or bobwhite quail (NOEC = 10 ppm). The metabolite MB 46136 is more toxic than the parent to avian species tested (very highly toxic to upland game birds and moderately toxic to waterfowl on an acute oral basis).

MAMMALS. Fipronil is moderately toxic to small mammals on an acute oral basis. The LD50 is 97 mg/kg in rats.

FRESHWATER FISH. 96 hour acute toxicity studies show fipronil is very highly toxic to bluegill sunfish (LC 50 = 0.083 ppm) and highly toxic to rainbow trout (LC50 = 0.246 ppm). The results of a fish early life-stage toxicity study in rainbow trout show that fipronil affects larval growth with an NOEC of 0.0066 ppm and an LOEC of 0.015 ppm. The metabolite MB 46136 is more toxic than the parent to freshwater fish (6.3 times more toxic to rainbow trout and 3.3 times more toxic to bluegill sunfish).

FRESHWATER INVERTEBRATES. A daphnia study using fipronil (EC50 = 190 ppb) shows fipronil is highly toxic to aquatic invertebrates. An invertebrate life-cycle toxicity study using daphnia (freshwater) showed that fipronil affects the length of daphnids at concentrations greater than 9.8 ppb (NOEC). The LOEC = 20 ppb and the maximum allowable toxicant concentration (MATC) = 14 ppb. Metabolites MB 46136 and MB 45950 are more toxic than the parent to freshwater invertebrates (MB 46136 is 6.6 times more toxic and MB 45950 is 1.9 times more toxic to freshwater invertebrates).

ESTUARINE AND MARINE ANIMALS. Three acute studies using oysters, mysids, and sheepshead minnows shows that fipronil is highly acutely toxic to oysters (EC50 = 0.77 ppm) and sheepshead minnows (EC50 = 0.13 ppm), and very highly toxic to mysids (EC50 = 140 pptr). An invertebrate life-cycle toxicity study using mysid shrimp (estuarine) showed that fipronil affects survival, reproduction and growth in mysids at concentrations less than 5.0 pptr (LOEC = 5 pptr; NOEC < 5.0 pptr) and the MATC < 5 pptr.

AQUATIC PLANTS. The data for aquatic plants is summarized below:
Freshwater diatom EC50 > 0.12 ppm
Duckweed EC50 > 0.10 ppm
Freshwater green algae EC50 = 0.14 ppm
Marine Diatom EC50 > 0.14 ppm
Freshwater blue-green algae > 0.17 ppm.

4. **SUMMARY OF DATA GAPS:** There are no data gaps for this use.

5. **CONTACT PERSON**:

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