United States
Environmental Protection
Agency

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

Pesticide Fact Sheet

Name of Chemical: Cyprodinil
Reason for Issuance: Registration
Date Issued: April 6, 1998

DESCRIPTION OF CHEMICAL

Generic Name: 4-cycloproplyl-6-methyl-N-phenyl-pyrimidinamine

Common Name: Cyprodinil

Trade Names: Cyprodinil Technical, Vangard WP Fungicide, Vangard WG Fungicide

EPA Chemical Code: 288202

Chemical Abstracts Service (CAS) Number: 121552-61-2

Year of Initial Registration: 1998

Pesticide Type: Fungicide

Chemical Family: Anilino-pyrimidine

Ag Company: Novartis Crop Protection, Inc.
P.O. Box 18300
Greensboro, NC 27419

USE PATTERNS AND FORMULATIONS

Cyprodinil is applied to the foliage of almonds, grapes, stone fruit crops, and pome fruit crops to control plant diseases. It will be formulated as a 75% water dispersable granules. Vangard WG and Vangard WP will be applied by foliar sprays at 3 to 5 ounces per acre. The maximum use rate of 30 ounces per acre per season, a relatively low use rate.
Cyprodinil Technical is concentrated cyprodinil used as an ingredient to manufacture individual cyprodinil commercial products.

TARGET PESTS

Target fungi for cyprodinil include scab and brown rot blossom in almonds, grapes, stone fruits and pome fruits.

SCIENCE FINDINGS

SUMMARY SCIENCE STATEMENTS

Cyprodinil appears to pose relatively little human toxicity risk due to low use rate, low risk to groundwater, low dietary risk and low worker exposure.

The technical cyprodinil product is classified in toxicity categories III & IV [CAUTION] based on acute oral, dermal, inhalation toxicity and eye/skin irritation studies. The formulated end use products are also classified in toxicity categories III & IV [CAUTION] based on similar studies.

Mutagenicity: Cyprodinil was shown to be negative in studies for point mutation, for chromosome aberration, and for DNA repair. These results indicate that cyprodinil is unlikely to initiate cancer or cause inheritable genetic defects.

Developmental Toxicity: Cyprodinil is not teratogenic. In the rabbit developmental toxicity study, no developmental toxicity was noted even at the highest dose tested (HDT) of 400 mg/k. In the rat developmental toxicity study , the developmental and maternal NOELs were both 200 mg/kg based on reduced ossification and body weight in pups and decreased food consumption/weight gain in dams at 1000 mg/kg (HDT).

Reproductive Toxicity: In a two-generation reproduction study in rats, the NOEL for maternal systemic toxicity is 1000 ppm and the NOEL for reproductive toxicity is 1000 ppm.

Subchronic Oral Toxicity: In subchronic studies, the lowest NOEL is 50 ppm based on a rat study.

Subchronic Dermal Toxicity: For female rats receiving dermal applications of cyprodinil; NOEL was 5 mg/kg/.day; the NOEL for the male rats in this study is 125 mg/kg/day.

Chronic Oral Toxicity: Two chronic studies found NOELs of 75 ppm in a 24-month rat study and 2500 ppm in a one-year Beagle study. Neither study found evidence of carcinogenicity for cyprodinil.

Carcinogenicity: Cyprodinil is classified as a "Not Likely" (E) carcinogen based on the lack of oncogenic effects in all tested species.

The Reference Dose (RfD) for cyprodinil is 0.0375 mg/kg/day. This value is based on the systemic NOEL of 3.75 mg/kg/day in the rat chronic feeding study with a 100-fold safety factor to account for interspecies extrapolation and intraspecies variability.

A chronic exposure analysis was conducted using tolerance level residues and 100 percent crop treated information to estimate the Theoretical Maximum Residue Contribution (TMRC) for the general population and 22 subgroups. The chronic analysis showed that exposure from the tolerances in or on almonds, grapes, pome fruit crops, and stone fruit crops for non-nursing infants (the subgroup with the highest exposure) would be 27.0 % of the Reference Dose (RfD). The exposure for the general U.S. population would be 5.8% of the RfD.

The maximum estimated concentrations of cyprodinil in surface water and in ground water are less than EPA's levels of concern for cyprodinil in drinking water as a contribution to acute aggregate exposure. Therefore, EPA concluded with reasonable certainty that residues of cyprodinil in drinking water, when considered alons with other sources of exposure for which EPA has reliable data, would not result in unacceptable levels of aggregate human health risk.

Tolerances are established for the for residues of the fungicide cyprodinil, 4-cyclopropyl-6-methyl-N-phenyl-2-pyrimidinamine, in or on:

- almond nutmeat at 0.02 parts per million (ppm),
- almond hulls at 0.05 ppm,
- grapes at 2.0 ppm,
- raisins at 3.0 ppm,
- pome fruit crop grouping at 0.1 ppm,
- stone fruit crop grouping at 2.0 ppm
- wet apple pomace at 0.15 ppm.

<u>CHEMICAL CHARACTERISTICS</u>

Empirical Formula: $C_{14}H_{15}N_3$
Molecular Weight: 225.3
Color: beige
Physical State: powder with agglomerates at 20C
Odor: weak
Melting Point: 75.9°C
Density at (20C): 1.21 g/cm^3
Solubility in g/100 ml: distilled water - 0.0016 (16 ppm) (parts per million)

buffered pH 5 - 0.0020 (20 ppm)
buffered pH 7 - 0.0013 (13 ppm)
buffered pH 9 - 0.0015 (15 ppm)

Vapor Pressure: 3.8 x 10-6 mm Hg at 25 C
Dissociation Constant: pKa = 4.44 at 25 C
Octanol/Water partition coefficient: Log Kow = 3.9 at pH 5
4.0 at pH 7
4.0 at pH 9
pH: 9.5 at 25 C (1% aqueous dispersion)

Stability:
Stable in the presence of steel, tin and aluminum.
Stable in the presence of Zn(II), Cu(II) and Al(VI) ions.
Unstable in the presence of Fe(II) ions.
Stable in sunlight and elevated temperatures.

TOXICOLOGY CHARACTERISTICS

Vangard WG Fungicide and Vangard WP Fungicide
(End-Use Product)

Acute Oral Toxicity (rat): LD50 > 5000 mg/kg
Toxicity Category: IV

Acute Dermal Toxicity (rabbit): LD50 > 2000 mg/kg
Toxicity Category: III

Inhalation (rat): LD50 > 2.89 mg/liter
Toxicity Category: IV

Primary Eye Irritation: Minimally irritating
Toxicity Category: III

Primary Skin Irritation: Slightly irritating
Toxicity Category: IV

Dermal Sensitization: Negative

Cyprodinil Technical
(manufacturing use product)

Acute Oral Toxicity (rat): LD50 = 2796 mg/kg
Toxicity Category: III

Acute Dermal Toxicity (rat): LD50 > 2000 mg/kg
Toxicity Category: III

Acute Inhalation Toxicity (rat): LC50 > 1.2 mg/liter

Toxicity Category: III

Primary Eye Irritation): Minimally irritating
Toxicity Category: IV

Primary Skin Irritation): Slightly irritating
Toxicity Category: IV

Dermal Sensitization: Weak to moderate.

Acute Toxicity.
The acute toxicity data of cyprodinil show that this chemical is not acutely toxic by the oral, inhalation and dermal routes of exposure. Technical cyprodinil, however, is a dermal sensitizer.

Subchronic Toxicity.
a. In a 28 day range-finding study in rats, the LOEL is 3000 ppm (316 and 299 mg/kg/day for males and females respectively) based on lower bodyweight gains, microcytosis, increased cholesterol and phospholipid levels and hepatocyte hypertrophy. The NOEL is 600 ppm (64.8 and 62.2 mg/kg/day for males and females respectively).

b. In a 28 day gavage study in rats, the LOEL is 100 mg/kg body weight/day for rats, based on increased liver weights and abnormalities in liver morphology. The NOEL is 10 mg/kg body weight/day.

c. In a 90 day rat study, the LOEL is 300 ppm (19 mg/kg body weight/day) for rats, based on increased chronic tubular kidney lesions in males. The NOEL is 50 ppm (3.14 mg/kg/day).

d. In a 3-month range-finding study in mice, the LOEL is 2000 ppm based on histopathological changes in the liver. The NOEL is 500 ppm (males - 73.3; females - 103 mg/kg/day).

e. In a 3-month study in Beagle dogs, the LOEL is 20,000 ppm (males - 560, females - 581 mg/kg/day) based on lower bodyweight gains and decreased food consumption in both sexes. The NOEL is 7000 ppm (males - 210, females - 232 mg/kg/day).

f. Groups of rats received repeated dermal applications of cyprodinil over a 28-day period. In this study, the LOEL is 25 mg/kg/day for female rats and 1000 mg/kg/day for male rats, based on alterations in clinical signs (piloerection). The NOEL is 5 mg/kg/day for females and 125 mg/kg/day for males.

Chronic Toxicity.
a. In a 24-month chronic toxicity/carcinogenicity study in rats, the LOEL is 1000 ppm (35.6 mg/kg/day) based on the degenerative liver lesions (spongiosis hepatis) in males. The NOEL for chronic toxicity is set at 75 ppm (2.7 mg/kg /day).

b. In a chronic toxicity study in Beagle dogs, the NOEL is 2500 ppm (males - 65.63, females - 67.99 mg/kg/day).

4. Carcinogenicity
a. In the 24-month chronic toxicity/carcinogenicity rat study, discussed in above under chronic toxicity, there was no indication of carcinogenic potential at any dose level up to 2000 ppm in males and 5000 ppm in females.

b. In an 18-month carcinogenicity study in mice, the LOEL is 2000 ppm (males - 212.4 mg/kg/day) based on a dose-related increase in the incidence of focal and multifocal hyperplasia of the exocrine pancreas in males. The NOEL is 150 ppm (males - 16.1 mg/kg/day). This study was tested to adequate levels based on signs of toxicity in males at 2000 ppm and females at 5000 ppm. There was no indication of carcinogenic potential at any dose level.

5. Developmental Toxicity.
a. In a gavage study in female rats, the LOEL for maternal toxicity is 1000 mg/kg/day based on lower bodyweight/bodyweight gain and reduced food consumption. The NOEL for maternal toxicity was 200 mg/kg/day. The LOEL for developmental toxicity is 1000 mg/kg/day based on lower mean fetal weights and an increased incidence of delayed ossification. The NOEL for developmental toxicity is 200 mg/kg/day.

b. In a gavage study in female rabbits, the maternal LOEL is 400 mg/kg/day, based on decreased body weight gain. The maternal NOEL is 150 mg/kg/day. The fetal developmental LOEL is 400 mg/kg/day based on a slight increase of litters showing extra (13th) ribs. The fetal developmental NOEL is 150 mg/kg/day.

6. Reproductive Toxicity.
In a two-generation reproduction study in rats, the LOEL for maternal systemic toxicity is 4000 (about 326 mg/kg/day) based on lower body weights in the F_0 females during the pre-mating period. The NOEL for maternal systemic toxicity is 1000 ppm (about 81 mg/kg/day). The LOEL for reproductive/developmental toxicity is 4000 ppm (about 326 mg/kg/day) based on decreased pup weights (F_1 and F_2). The NOEL for reproductive toxicity is 1000 ppm (about 81 mg/kg/day).

7. Neurotoxicity.
Neurotoxicity studies were not required for this chemical.

8. Mutagenicity.

Mutagenicity studies with cyprodinil included gene mutation assays in bacterial and mammalian cells, a mouse micronucleus assay and in vivo unscheduled DNA synthesis (UDS) assays. The results were negative for mutagenicity in all studies.

Mutagenicity: All results were negative in the mutagenicity test battery, with or without metabolic activation. The potential for point mutation was assessed in both prokaryotic and eukaryotic systems (*Salmonella typhimurium*, *Escherichia coli*, and Chinese hamster lung V79 cells). Tests for chromosome aberrations, both numerical and structural, were conducted using Chinese hamster ovary cells (*in-vitro)* and mouse bone marrow (*in-vivo)*. A special test designed for evaluating DNA repair in rat hepatocyte was also negative. These results indicate that cyprodinil is unlikely to initiate cancer or cause heritable genetic defects.

Metabolism: The metabolism of cyprodinil has been characterized in plants and animals. No toxicologically significant metabolites have been identified. The metabolism profile supports the use of an analytical enforcement method that accounts for only parent cyprodinil.

ECOLOGICAL CHARACTERISTICS

Avian Acute Toxicity:
Bobwhite: LD50 > 2000 mg/kg bw
Mallard: LD50 > 500 mg/kg bw

Avian Dietary Toxicity:
Bobwhite: 5-day LC50 > 5200 ppm
Mallard: 5-day LC50 > 5200 ppm

Avian Chronic Toxicity - Reproduction:
Bobwhite: NOEL = 600 ppm
Mallard : NOEL = 500 ppm

Freshwater Fish Acute Toxicity:
Bluegill Sunfish 96-hr LC50 = 3.2 ppm
Rainbow Trout: 96-hr LC50 = 2.41 ppm

Freshwater Fish Early Life Toxicity:
Fathead Minnow NOEC = 0.23 ppm

Freshwater Invertebrate Toxicity:
Daphnia magna acute LC50 = 32.8 ppb
Mysidopsis acute LC50 = 8 ppb
Daphnia magna Life Cycle: NOEC = 8 ppb

Estuarine and Marine Organisms Toxicity:
Sheepshead Minnow - acute: LC50 = 1.25

Acute Eastern Oyster Shell Deposition: EC50 = 0.433 ppm,
Acute Mysid: LC50 = 8.14 ppb,

Aquatic Plant Growth and Reproduction:
Skeltonema costatum: EC50 1.97 ppm, NOEC 1.05 ppm
Anabaena flos-aquae: EC50 2.25 ppm, NOEC 0.538 pp.

Non-Target Insects Toxicity: Honey Bee Acute Contact LD50 > 784 μg ai/bee
Invertebrate Toxicity: Earthworm Acute LD50 > 111 μg ai/kg soil

Cyprodinil was shown to be practically non-toxic to birds, practically non-toxic to small mammals, and practically non-toxic to bees and earthworms. Cyprodinil is moderately toxic to fish and very highly toxic to freshwater and marine invertebrates.

ECOTOXICITY PRECAUTIONS

To further reduce the risk to non-target aquatic organisms the following precautionary statement must appear on the label:

Observe the following precautions when spraying in the vicinity of aquatic areas such as lakes; reservoirs; rivers; permanent streams; marshes or natural ponds; estuaries and commercial fish ponds.

- Do not apply within 75 feet of bodies of water such as lakes, reservoirs, rivers, permanent streams, natural ponds, marshes or estuaries.
- For all plantings within 150 feet of bodies of water as described above, spray crops from outside the planting away from the bodies of water.
- Shut off the sprayer when at row ends.
- Spray last three rows windward of aquatic areas using nozzles on one side only, with spray directed away from aquatic areas. Avoid spray going over the tops of trees by adjusting or turning off top nozzles. Shut off nozzles on the side away from the grove/orchard when spraying the outside row. Shut off nozzles when turning at ends of row or passing tree gaps in the rows.
- Do not cultivate within 10 feet of aquatic areas as to allow a vegetative filter strip.
- Do not apply when weather conditions favor drift to aquatic areas. Do not apply when gusts or sustained winds exceed 10 mph.
- Do not apply during a temperature inversion. Mist or fog may indicate the presence of an inversion in humid areas.

The following statement must appear in the Environmental Hazards section of the label: "Do not apply directly to water, or to

areas where surface water is present or to intertidal areas below the mean high water mark. Do not contaminate water by disposal of equipment washwaters."

ENVIRONMENTAL CHARACTERISTICS

Cyprodinil is soluble in water (13 mg/l at 25 C and pH 7.9) but does not volatilize readily from moist soil or water surfaces. Although a high octanol:water partition coefficient suggests potential for cyprodinil bioconcentration or bioaccumulation, a fish bioaccumulation study shows rapid depuration.

Cyprodinil does not hydrolyze readily. Photolysis will not account for significant transformation of cyprodinil in soil or in water.

The major source of cyprodinil dissipation in the environment was determined to be aerobic soil biotransformation. Cyprodinil is characterized as "slightly persistent" to "persistent" in soil, "persistent" in sediments and "moderately persistent" to "persistent" in water/sediment systems. Anaerobic soil and water/sediment biotransformation studies indicated no biotransformation under anaerobic conditions.

Cyprodinil shows strong sorption to soil and low mobility.

TOLERANCE ASSESSMENT

Tolerances are established for the residues of the fungicide cyprodinil in or on almond nutmeat at 0.02 parts per million (ppm), almond hulls at 0.05 ppm, grapes at 2.0 ppm, raisins at 3.0 ppm, pome fruit crops at 0.1 ppm, wet apple pomace at 0.15 ppm, and stone fruit crops at 2.0 ppm.

HUMAN AGGREGATE EXPOSURES

In examining aggregate exposure, Food Quality Protection Act (FQPA) directs EPA to consider available information concerning exposures from the pesticide residue in food and all other non-occupational exposures. The primary non-food sources of exposure the Agency looks at include drinking water (whether from groundwater or surface water), and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor uses).

1. From Food and Feed Uses

The Reference Dose (RfD) for cyprodinil is 0.0375 mg/kg/day. This value is based on the systemic NOEL of 3.75 mg/kg/day in the rat chronic feeding study with a 100-fold safety factor to account for interspecies extrapolation and intraspecies variability.

EPA estimates that exposure from the tolerances for non-nursing infants (the subgroup with the highest exposure) will be 27.0% of the Reference Dose (RfD). The exposure for the general U.S. population would be 5.8% of the RfD. This analysis of chronic exposure analysis was conducted using tolerance level residues and 100 percent crop treated information to estimate the Theoretical Maximum Residue Contribution (TMRC) for the general population and 22 subgroups. This analysis used a worst case estimate of dietary exposure with all residues at tolerance levels and 100 percent of the commodities assumed to be treated with cyprodinil. Even without refinements, the chronic dietary exposure to cyprodinil appears to be minimal.

2. From Drinking Water

Taking into account the proposed uses in this action, EPA concludes with reasonable certainty that residues of cyprodinil in drinking water (when considered along with other sources of exposure for which EPA has reliable data) would not result in unacceptable levels of aggregate human health risk.

EPA bases this determination on a comparison of estimated concentrations of cyprodinil in surface water and groundwater to back-calculated "levels of concern" for cyprodinil in drinking water. These levels of concern in drinking water were determined after EPA had considered all other non-occupational exposures for which it has reliable data, including all uses considered in this action. The estimates of cyprodinil in surface water are derived from water quality models that use conservative assumptions (health-protective) regarding the pesticide transport from the point of application to surface and ground water.

3. From Non-Dietary Uses

There are no non-food uses of cyprodinil registered. No non-dietary exposures are expected for the general population.

4. Cumulative Exposure to Substances with Common Mechanism of Toxicity

For cyprodinil, EPA has not conducted a detailed review of common mechanism yet to determine whether it is appropriate, or how to include this chemical in a cumulative risk assessment. After EPA develops a methodology to apply common mechanism of toxicity issues to risk assessments, the Agency will develop a process (either as part of the periodic review of pesticides or otherwise) to reexamine these tolerance decisions. The Agency has determined that there are no metabolites of toxicological concern associated with cyprodinil. Cyprodinil is a anilino-pyrimidine fungicide. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, cyprodinil does not appear to produce a toxic metabolite produced by other substances. Therefore, EPA has not assumed that cyprodinil has a common mechanism of toxicity with other substances.

5. Aggregate Risk to US Population

EPA has concluded that aggregate exposure to cyprodinil from food will utilize 5.8% of the RfD for the U.S. population. The major identifiable subgroup with the highest aggregate exposure is non-nursing infants (< 1 year old) as discussed below. EPA generally has no concern for exposures below 100% of the RfD because the RfD represents the level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risks to human health. Despite the potential for exposure to cyprodinil in drinking water and from non-dietary, non-occupational exposure, EPA does not expect the aggregate exposure to exceed 100% of the RfD. EPA concludes that there is a reasonable certainty that no harm will result from aggregate exposure to cyprodinil residues

DETERMINATION OF SAFETY FOR INFANTS AND CHILDREN

FQPA provides that EPA shall apply an additional safety factor for infants and children in the case of threshold effects to account for pre- and post-natal toxicity and the completeness of the data base, unless EPA determines that such an additional factor is not necessary to protect the safety of infants and children. An additional Uncertainty Factor to account for possible increased sensitivity of children to cyprodinil was not used because the pre- and post-natal toxicology data base for cyprodinil is complete with respect to current toxicological data requirements. The results of these studies indicate that infants and children are not more sensitive to exposure, based on the results of the oral rat and rabbit developmental toxicity studies

and the 2-generation reproductive toxicity study in rats.

OCCUPATIONAL EXPOSURE

EPA has concluded using the NOEL of 3.75 mg/kg/day from the chronic study in rats that the Margin of Safety (MOS) for occupational exposure between 76 and 3098. A MOS of 1.0 is generally accepted as showing an adequate margin of safety. The available evidence does not indicate any evidence of significant toxicity from intermediate term dermal or inhalation routes of exposure.

SUMMARY OF DATA GAPS

7. Data Requirements
   a. Toxicology - There are currently no data gaps for toxicity data.

   b. Chemistry

      i. Product chemistry data (required from OPPTS Series 830.7050, Product Properties Test Guidelines) pertaining to UV/visible absorption for the PAI.

      ii. Agency validation of analytical method for plants.

      iii. Submission of an analytical reference standard of cyprodinil to the EPA repository.

      iv. Revision of labels to prohibit concentrated spray (50-100 gal/acre) by ground application **or** submission of additional residue data.

      v. Additional residue data for peaches and cherries.

      vi. Storage stability data for ruminant RACs.

      vii. Revised Section F.

c. Occupational and Residential Exposure

      i. Worker exposure for post application tasks associated with grapes and stone fruits should be considered a data gap.

PUBLIC INTEREST FINDING

Vangard WG and Vangard WP are new plant pesticides with activity against a wide array of important plant diseases. Belonging to the novel chemical class known as the anilino-pyrimidines, cyprodinil represents a new mode of action. Due to low use rates and the alternative fungicides that will be replaced, the total fungicide volume applied to almonds, grapes, pome fruits and stone fruits will likely to be reduced. The novel action of this active ingredient shows no cross-insensitivity (cross-resistance) to other currently available classes of fungicides, i.e., benzimidazoles, demethylation inhibitors (DMIs or SIs), or dicarboximides.

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