United States Environmental Protection Agency

Office of Prevention, Pesticide and Toxic Substance (7501C)

Pesticide Fact Sheet

Name of Chemical: **Fluopicolide**
Reason for Issuance: **Import Tolerance**
Date Issued: **March 2007**

Description of Chemical

Generic Name:	2,6-dichloro-*N*-[[3-chloro-5-(trifluoromethyl)-2-pyridinyl]methyl] benzamide
Common Name:	Fluopicolide
EPA Chemical Code:	027412
Chemical Class:	benzamide Pyridine
Chemical Abstracts Service (CAS) Number:	239110-15-7
Registration Status:	Not registered, Import Tolerance Established
Pesticide Type:	Fungicide
U.S. Producer:	Valent U.S. Corporation

Use Pattern and Formulations

Fluopicolide is a fungicide to be used on imported grapes. Three foliar applications are to be made to grapes in Europe at the maximum seasonal application rate of 0.36 lb ai/A. Minimum retreatment intervals of 10 days and a preharvest interval of 21 days are to be observed.

Fluopicolide controls a wide range of *Oomycete* (Phycomycete) diseases including downy mildews (*Plasmopara*, *Pseudoperonospara*, *Peronospora*, *Bremia*), late blight (*Phytophthora*), and some *Pythium* species.

The mode of action of fluopicolide has not been determined; however, it is a mode of action unlike the known modes of action of other registered fungicides.

Fluopicolide is a mesosystemic fungicide; it translocates toward the stem tips via the xylem but it does not translocate toward the roots.

2,6-Dichlorobenzamide (BAM) is a metabolite and/or environmental degradate of both fluopicolide and dichlobenil. For use on imported grapes BAM was not included in the risk assessment however, both parent fluopicolide and BAM will be included in risk assessments for future uses of fluopicolide on domestic crops since more exposure to BAM is expected with domestic uses.

There are currently no registered uses of fluopicolide in the U.S., although another petition for fluopicolide domestic uses, including grapes and raisins, is currently pending with the Agency. No Codex, Canadian, or Mexican MRLs have been established for fluopicolide.

Science Findings

Structure and Nomenclature

Table 2 Fluopicolide Nomenclature.

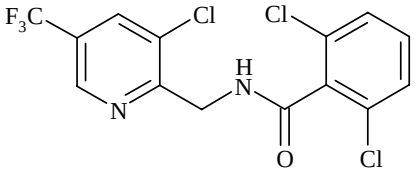
Chemical structure	
Empirical Formula	$C_{14}H_8Cl_3F_3N_2O$
Common name	Fluopicolide
Company experimental name	AE C638206
IUPAC name	2,6-dichloro-*N*-[3-chloro-5-(trifluoromethyl)-2-pyridylmethyl]benzamide
CAS name	2,6-dichloro-*N*-[[3-chloro-5-(trifluoromethyl)-2-pyridinyl]methyl]benzamide
CAS Registry Number	239110-15-7
End-use products (EPs)	1. WG71 Formulation (4.44% AE C638206 + 66.7% fosetyl-aluminum) 2. SE10 (Suspo-Emulsion; similar to an emulsifiable concentrate; 95 g/L)

Table 2 Fluopicolide Nomenclature.	
Chemical Class	Fungicide
Known Impurities of Concern	None

Physical and Chemical Properties

The physical/chemical properties of fluopicolide as they affect inhalation or dermal exposure are not relevant for an imported crop**.**

Table 3. Physicochemical Properties of Fluopicolide.		
Parameter	Value	Reference
Molecular Weight	383.59	
Melting point/range	149 °C	MRID 46474015
pH	6.5 at 22.0 °C	MRID 46474013
Density	1.65 g/cc	MRID 46474016
Water solubility (20 °C)	2.86 mg/L at pH 4 2.80 mg/L at pH 7 2.80 mg/L at pH 9	MRID 46474021
Solvent solubility (g/L at 20 °C)	n-Hexane: 0.20 Ethanol: 19.2 Toluene: 20.5 Ethyl acetate: 37.7 Acetone: 74.7 Dichloromethane: 126 Dimethyl sulfoxide: 183	MRID 46474022
Vapor pressure at 25 °C	8.03×10^{-7} Pa	MRID 46474023
Dissociation constant (pKa)	No evidence of ionization in the pH range of 1.9 to 9.8	MRID 46474017
Octanol/water partition coefficient $Log(K_{OW})$	Log P_{OW} = 3.26 at pH 7.8 and 22 ± 1 °C	MRID 46474018
	Log P_{OW} = 2.9 at pH 4.0, 7.3 and 9.1 and 40 °C	MRID 46474019
UV/visible absorption spectrum	Absorption maxima wavelengths (nm): In methanol: 203 and 271 In methanol/HCl: 202 and 270 In methanol/NaOH: 219 and 271	MRID 46474014

Hazard Characterizations

An appropriate endpoint was identified for the chronic dietary exposure scenario based on a NOAEL in a developmental toxicity study in rabbits and uncertainty factors of 10x for extrapolation from animals to humans (interspecies variation) and 10x for potential variation in sensitivity among members of the human population (intraspecies variation). A LOAEL in that study was based on death, abortions/premature deliveries, decreased food consumption, and decreased body weight gain. No appropriate endpoint was identified for an acute dietary assessment. Incidental oral, dermal, and inhalation endpoints were selected but are not applicable to this risk assessment because residential and occupational exposures are not anticipated for an imported crop. Fluopicolide is not likely to be carcinogenic to humans.

A dietary exposure assessment was conducted using the Dietary Exposure Evaluation Model DEEM-FCID™, Version 2.03, which uses food consumption data from the U.S. Department of Agriculture's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The dietary exposure assessment was conducted for residues of fluopicolide (parent only) in food (only). Since U.S. registration is not required for an imported crop and there are no existing U.S. registrations for fluopicolide, no fluopicolide residues are expected to occur in drinking water.

The chronic dietary (food only) exposure assessment for fluopicolide on imported grapes was a conservative assessment using the recommended tolerance levels and assuming that 100% of the crop was treated and 100% of the crop was imported. An adequate processing study was conducted on grapes indicating no concentration in grape juice but concentration in raisins. No default processing factors were used since an adequate processing study was available; tolerance levels of 2.0 ppm and 6.0 ppm were used for grapes and raisins, respectively. Since grapes are imported, no fluopicolide residues are expected to occur in rotational crops. Since no livestock feed items are associated with grapes, no fluopicolide residues are expected to occur in livestock commodities.

The chronic dietary (food only) exposure to fluopicolide is below the Agency's level of concern for the general U.S. population and all population subgroups. The chronic dietary exposure estimates are <1% cPAD for the general U.S. population and 3% cPAD for children 1-2 years old, the most highly exposed subgroup.

Toxicology

Acute Toxicity: Fluopicolide has moderate toxicity with no deaths noted in male or female rats at doses of > 2000 mg/kg when given orally, and > 4000 mg/kg dermally. Following inhalation exposure, an LC_{50} of >1.789 to < 5.16 mg/L was calculated. Toxicity was observed primarily in the inhalation studies and included a decrease in body weight, decrease in mean body temperature and signs of irritation (piloerection, hunched posture, reddened nostrils). Moderate eye irritation occurred in the form of chemosis and corneal opacities, but all effects were gone by 72 hours. Slight dermal irritation occurred, but the test substance was not a skin sensitizer.

Subchronic Toxicity: The most common effect observed in the 90 day studies was a decrease in body weight gain. Weight gain was markedly decreased in male and female rats in a subchronic study at doses that exceeded the limit dose (1668-1673 mg/kg/day), and male and female rats in a subchronic neurotoxicity study had reduced body weight gain at doses of 780.6 and 125.2 mg/kg/day, respectively. There was no effect on weight gain in dogs or mice in subchronic studies. Besides effects on body weight and body weight gain, no definitive cross-species target organ was identified in subchronic studies with fluopicolide. No organ lesions were found in dogs administered up to 1000

mg/kg/day for 90 days. Male rats had hypertrophy of the zona glomerulosa in the adrenal gland, trabecular hyperostosis of the bone joint, and decreased bone marrow cellularity after exposure to 1668 mg/kg/day for 90 days. Similar lesions in the adrenal gland and bone marrow were found in female rats administered 119 mg/kg/day for 90 days. In mice, females administered 965 mg/kg/day showed an increased incidence of hepatic oval cell proliferation.

Chronic Toxicity: As in the subchronic studies, the main effect in the chronic studies was a decrease in body weight gain with no definitive cross-species target organ identified. Male dogs had reduced weight gain after exposure to 1000 mg/kg/day for one year; body weight of females was not affected. Mice had severely decreased body weight and body weight gain with administration of 551.0 and 772.3 mg/kg/day to males and females, respectively, for 18 months. Male and female rats had decreased weight gain after exposure to 109.4 and 142.2 mg/kg/day for 2 years, respectively. No organ lesions were found in dogs administered up to 1000 mg/kg/day for 52 weeks. Thyroid cystic follicular hyperplasia was seen in male rats after 109.4 mg/kg/day for two years. In mice, altered liver cell foci were seen in males and females given 551.0 or 772.3 mg/kg/day, respectively, for 18 months.

Carcinogenicity: No evidence for carcinogenicity was seen in rats administered fluopicolide in food for 24 months. Treatment of rats did not result in an increase in overall tumor incidence or an increase in the incidence of any specific type of tumor. In contrast, mice had an increased incidence of hepatocellular adenoma following administration of 3200 ppm in the diet for 18 months (551.0 and 772.3 mg/kg/day for males and females, respectively).

Neurotoxicity: No evidence of neurotoxicity was seen in acute or subchronic oral rat neurotoxicity studies with fluopicolide. A transient decrease in body temperature was the only finding in male and female rats given a single dose of 2000 mg/kg. Brain weight, brain morphometry, and neuropathology were not affected by treatment.

Developmental Toxicity: In developmental toxicity studies, maternal toxicity was clearly evident only in rabbits as increased mortality, abortion, and decreased body weight gain at 60 mg/kg/day, the highest dose tested. Minimal maternal toxicity was observed in rats dosed with 700 mg/kg/day; slightly reduced body weight gain did not result in lower absolute body weight. At the same dose affecting the dam, 700 mg/kg in rats and 60 mg/kg in rabbits, fetal growth was affected in both species and observed as decreases in body weight and crown-rump length. Also, at 700 mg/kg, delays in fetal ossification and increased incidence of skeletal malformations were observed in rat fetuses, with neither of these effects seen in rabbit fetuses. No external or visceral abnormalities were observed in either species. In rats the adverse effect was judged to be greater in the fetus than in the dam, suggesting a greater susceptibility in the fetus compared to that of the dam.

Reproductive Toxicity: Reproductive performance was not affected in a two-generation reproduction toxicity study in which fluopicolide was administered to male and female rats at nominal dietary concentrations of 0, 100, 500, or 2000 ppm (0, 7.4-8.8, 36.4-43.7, 144.6-179.9 mg/kg/day, respectively, for males and 0, 8.1-9.4, 41.0-46.9, 159.7-193.9 mg/kg/day, respectively, for females). Evidence of parental toxicity in the high-dose groups included decreased body weight gain in F_0 females and kidney toxicity in F_0 and F_1 males and females. Kidney lesions consisted of cortical tubular basophilia or dilation, medullary granular casts, cortical scarring, interstitial inflammation, and/or corticomedullary mineralization. Body weight of the high-dose F_1 and F_2 pups was significantly less than that of the controls beginning on lactation day 14. The high-dose pups had decreased weight gain throughout the 28-day lactation interval. Overall weight gain during lactation was decreased by 8-9% of the control level in the high-dose F_1 male and female pups and by 11-14% in the high-dose F_2 male and female pups. No other effects on offspring growth or survival were noted in either generation.

Dermal toxicity: Acute dermal toxicity studies showed that fluopicolide was only a slight dermal irritant (Tox. Category IV). A dermal subchronic toxicity study showed no systemic or local effects at the limit dose.

Toxicologicol Endpoints

Table 4. Summary of Toxicological Doses and Endpoints for Fluopicolide for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All Populations)	None	None	None	**An endpoint attributable to a single dose was not identified from the available data.**
Chronic Dietary (All Populations)	Maternal NOAEL=20 mg/kg/day	UF_A=10x UF_H=10x FQPA SF = 1X	Chronic RfD = 0.2 mg/kg/day cPAD = 0.2 mg/kg/day	**Developmental Toxicity Study in Rabbits** LOAEL = 60 mg/kg/day based on death, abortions/ premature deliveries, decreased food consumption, decreased body weight gain.
Incidental Oral Intermediate-Term (1 - 6 months)	maternal NOAEL = 20 mg/kg/day	UF_A=10x UF_H=10x FQPA SF = 1X	MOE = 100 (occupational) MOE = 100 (residential)	**Developmental Toxicity Study in Rabbits** LOAEL = 60 mg/kg/day based on death, abortions/ premature deliveries, decreased food

				consumption, decreased body weight gain.
Dermal Short-Intermediate- and Long-Term (1-30 days and 1-6 months)	maternal NOAEL = 20 mg/kg/day	UF_A=10x UF_H=10x FQPA SF = 1X	MOE = 100 (occupational) MOE = 100 (residential)	**Developmental Toxicity Study in Rabbits** LOAEL = 60 mg/kg/day based on death, abortions/ premature deliveries, decreased food consumption, decreased body weight gain.
Inhalation Short-Intermediate- and Long-term (1-30 days and 1-6 months)	maternal NOAEL = 20 mg/kg/day	UF_A=10x UF_H=10x FQPA SF = 1X	MOE = 100 (occupational) MOE = 100 (residential)	**Developmental Toxicity Study in Rabbits** LOAEL = 60 mg/kg/day based on death, abortions/ premature deliveries, decreased food consumption, decreased body weight gain.
Cancer (oral, dermal, inhalation)	Classification: **"Not Likely to be Carcinogenic to Humans"**.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key data (i.e., lack of a critical study). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Food Quality Protection Act Considerations

The toxicology database for fluopicolide is complete and adequate to characterize potential pre- and/or post-natal risk for infants and children. Acceptable/guideline studies for developmental toxicity in rats and rabbits as well as a 2-generation reproduction study in rats are available. Based on the hazard database, the Agency's concludes there are no concerns and no residual uncertainties with regard to pre- and/or post-natal toxicity. After evaluating the toxicological and exposure data, the fluopicolide team recommended that the FQPA safety factor be reduced to 1X because: (1) There is a complete toxicity database for fluopicolide; (2) There are no residual uncertainties concerning pre- and post-natal toxicity and no neurotoxicity concerns; (3) The dietary food exposure

assessment utilizes tolerance level residues and 100% CT; (4) There is no potential for drinking water exposure; and (5) There is no potential for residential exposure.

Dietary exposure and risk estimates

Acute: No acute reference dose was established nor was a dietary endpoint identified in either the general population or for females aged 13-49 years. There were no appropriate studies that demonstrated evidence of toxicity attributable to a single dose for these populations. As a result, an acute dietary exposure assessment is unnecessary.

Chronic: A chronic dietary risk assessment was conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID^{TM}), which incorporates food consumption data as reported by respondents in the USDA 1994-1996 and 1998 Nationwide Continuing Surveys of Food Intake by Individuals (CSFII), and accumulated exposure to the chemical for each commodity. The dietary assessment included grape commodities, as the only source of residues for fluopicolide. It was assumed that 100% of all grape commodities contained tolerance level residues. The chronic dietary (food only) exposure to fluopicolide is below HED's level of concern for the general U.S. population and all population subgroups. The chronic dietary exposure estimates are <1% cPAD for the general U.S. population and 3% cPAD for children 1-2 years old, the most highly exposed subgroup.

Cancer: Fluopicolide was classified as "Not Likely to be Carcinogenic to Humans", therefore, a cancer dietary analysis was not performed.

Occupational and Residential Exposure:

As there are no U.S. registrations or proposed registrations, occupational and residential data deficiencies are not applicable to this tolerance petition.

Data Gaps

Toxicology: None

Residue Chemistry: The Agency has examined the residue chemistry database for the new active ingredient fluopicolide and has identified issues that need to be resolved: (1) the submission of Storage and Stability Data; and (2) submission of additional specific Process Food and Feed data.

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DISCLAIMER: The information presented in this Pesticide Fact Sheet is for informational purposes only and may not be used to fulfill data requirements for pesticide registration and reregistration.

APPENDIX I:

GLOSSARY OF TERMS AND ABBREVIATIONS

ADNT	**Acute delayed neurotoxicity**
a.i.	**Active Ingredient**
aPAD	**Acute Population Adjusted Dose**
ARI	**Aggregate Risk Index**
BCF	**Bioconcentration Factor**
CAS	**Chemical Abstracts Service**
ChE	**Cholinesterase**
ChEI	**Cholinesterase inhibition**
cPAD	**Chronic Population Adjusted Dose**
%CT	**Percent crop treated**
DAT	**Days after treatment**
DEEM-FCID	**Dietary Exposure Evaluation Model - Food Consumption Intake Database**
DNA	**Deoxyribonucleic acid**
DNT	**Developmental neurotoxicity**
DIT	**Developmental immunotoxicity**
DWLOC	**Drinking Water Level of Comparison.**
EC	**Emulsifiable Concentrate Formulation**
EEC	**Estimated Environmental Concentration. The estimated pesticide concentration in an environment, such as a terrestrial ecosystem.**
EPA	**U.S. Environmental Protection Agency**
FQPA	**Food Quality Protection Act**
GLC	**Gas Liquid Chromatography**
GLN	**Guideline Number**
LC_{50}	**Median Lethal Concentration. A statistically derived concentration of a substance that can be expected to cause**

	death in 50% of test animals. It is usually expressed as the weight of substance per weight or volume of water, air or feed, e.g., mg/l, mg/kg or ppm.
LD_{50}	**Median Lethal Dose. A statistically derived single dose that can be expected to cause death in 50% of the test animals when administered by the route indicated (oral, dermal, inhalation). It is expressed as a weight of substance per unit weight of animal, e.g., mg/kg.**
LOAEL	**Lowest Observed Adverse Effect Level**
LOAEC	**Lowest Observed Adverse Effect Concentration**
LOC	**Level of Concern**
LOD	**Limit of Detection**
LOQ	**Limit of quantitation**
mg/kg/day	**Milligram Per Kilogram Per Day**
mg/L	**Milligrams Per Liter**
MOE	**Margin of Exposure**
MRID	**Master Record Identification (number), EPA's system of recording and tracking studies submitted**
MTD	**Maximum tolerated dose**
NA	**Not Applicable**
NOEC	**No Observable Effect Concentration**
NOEL	**No Observed Effect Level**
NOAEL	**No Observed Adverse Effect Level**
NOAEC	**No Observed Adverse Effect Concentration**
NPDES	**National Pollutant Discharge Elimination System**
OP	**Organophosphate**
OPP	**EPA Office of Pesticide Programs**
OPPTS	**EPA Office of Prevention, Pesticides and Toxic Substances**
PAD	**Population Adjusted Dose**
PAG	**Pesticide Assessment Guideline**
PAM	**Pesticide Analytical Method**
PHED	**Pesticide Handler's Exposure Data**
PHI	**Preharvest Interval**
ppb	**Parts Per Billion**
PPE	**Personal Protective Equipment**
ppm	**Parts Per Million**
PRZM/ EXAMS	**Tier II Surface Water Computer Model**
RAC	**Raw Agriculture Commodity**
RBC	**Red Blood Cell**
RED	**Reregistration Eligibility Decision**
REI	**Restricted Entry Interval**
RfD	**Reference Dose**
SCI-GROW	**Tier I Ground Water Computer Model**
SF	**Safety Factor**
TGAI	**Technical Grade Active Ingredient**
UF	**Uncertainty Factor**

µg	**micrograms**
µg/L	**Micrograms Per Liter**
µL/g	**Microliter per gram**
USDA	**United States Department of Agriculture**
WPS	**Worker Protection Standard**

APPENDIX II:
Citations Considered to be Part of the Data Base Supporting the Registration of Fluopicolide