United States
Environmental Protection
Agency

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

Pesticide Fact Sheet

Name of Chemical: **Famoxadone**
Reason for Issuance: **New Chemical**
Date Issued: **July, 2003**

Description of Chemical

Chemical Name:	3-anilino-5-methyl−5-(4-phenoxyphenyl)-1,3-oxazolidine-2,4-dione (IUPAC)
Common Name:	Famoxadone
Trade Name:	Famoxate™ Technical
Chemical Class:	Oxazolidinedione
EPA Chemical Code:	113202
Chemical Abstracts Service (CAS) Number:	131807-57-3
Year of Initial Registration:	2003
Pesticide Type:	Fungicide
U.S. Producer:	E.I. DuPont Nemours and Company DuPont Agricultural Products P.O. Box 30 Newark, DE 19711-3507

Use Pattern and Formulations

Famoxadone is used in the U.S. in combination with cymoxanil in the formulated product Tanos DF (water dispersible granules with 25% Famoxadone/25% cymoxanil) for the control of

various fungal diseases on fruiting vegetables, tomatoes, potatoes, curcurbits, head lettuce and imported grapes, including raisins. For example, the uses of Tanos 50DF include treating downy mildew on curcurbits and head lettuce and early and late blight on potatoes and fruiting vegetables.

Famoxadone belongs to the oxazolidinedione class of chemicals and is highly active against spore germination and mycelial growth of sensitive fungi. The biochemical mechanism of action of famoxadone is inhibition of the fungal mitochondrial respiratory chain at Complex III, resulting in a decreased production of ATP by the fungal cell.

SUMMARY OF SCIENCE FINDINGS

Acute Toxicity: Technical grade famoxadone has minimal to moderate acute toxicity in acute oral, dermal and inhalation tests, it is moderately irritating to the eyes and skin, and is not a dermal sensitizer.

Subchronic Toxicity: In subchronic feeding studies in rats, mice, and dogs, famoxadone generally caused decreased body weights and body weight gains that were often accompanied by decreased food consumption and food efficiency. A mild regenerative hemolytic anemia was regularly observed. Secondary effects of the anemia were frequently observed in the spleen, bone marrow and liver. Famoxadone frequently induced a mild hepatotoxicity in treated animals characterized by elevated levels of clinical chemistry enzymes indicative of liver damage and/or by histopathological lesions in the liver. Adaptive hepatocellular responses indicating stimulation of the liver microsomal/peroxisomal enzyme system were also regularly observed, but were not considered to be adverse effects. Both the anemia and the hepatotoxicity were mild and did not significantly compromise the overall health status of the treated animals. In a subchronic dermal study in rats, the systemic effects were similar to those observed in oral studies in rats. No dermal irritation was observed. Additional treatment-related effects were observed in dogs, but were not observed in other species. In a subchronic feeding study, myotonic twitches were noted in male and female dogs at the highest dose tested starting on day 21 and continuing throughout the remainder of the study. Lens lesions (cataracts) were observed in dogs at the end of the 90-day study.

Chronic Toxicity: In chronic feeding studies in rats, dogs, Cynomolgus monkeys (gavage study) and mice, famoxadone generally caused decreased body weights and body weight gains that were often accompanied by decreased food consumption and food efficiency. A mild regenerative hemolytic anemia was regularly observed. Secondary effects of the anemia were frequently observed in the spleen, bone marrow and liver. Famoxadone frequently induced a mild hepatotoxicity in treated animals characterized by elevated levels of clinical chemistry enzymes indicative of liver damage and/or by histopathological lesions in the liver. Adaptive hepatocellular responses indicating stimulation of the liver microsomal/peroxisomal enzyme system were also regularly observed, but were not considered to be adverse effects. In a 1-year chronic feeding study in dogs, famoxadone induced treatment-related cataracts in the lens in male and female dogs. Treatment-related cataracts in the lens of the eye were not observed in

the chronic feeding study in rats or in the 1-year gavage study in Cynomolgus monkeys or in the carcinogenicity study in mice. Both the anemia and the hepatotoxicity were mild and did not significantly compromise the overall health status of the treated animals.

Carcinogenicity: In carcinogenicity studies in rats and mice, famoxadone did not demonstrate evidence of carcinogenic potential. Famoxadone is classified as "not likely to be carcinogenic to humans."

Developmental Toxicity: In a developmental toxicity study in rats, no developmental toxicity was observed. In a developmental toxicity study in rabbits, an increased incidence of abortions was observed. The does which aborted also had markedly decreased body weight, body weight gain and food consumption. Since it could not be determined whether the abortions were due to maternal toxicity or due to an effect on reproductive/developmental mechanisms, the does and fetuses were considered to be equally sensitive to the test material. There was also an equivocal increase in % postimplantation loss and mean number of resorptions per doe in this study. The results in the two developmental toxicity studies demonstrated no quantitative or qualitative evidence of increased susceptibility of fetuses or pups as compared to adults.

Reproductive Toxicity: In a 2-generation reproduction study in rats, decreased body weights for F_1 and F_2 pups were observed throughout lactation, but no reproductive toxicity was observed. The LOAEL for offspring toxicity was determined to be 800 ppm (44.7 mg/kg/day for males and 53.3 mg/kg/day for females), while a LOAEL for reproductive performance was not observed. The NOAEL for reproductive performance is 800 ppm. The results in the reproduction study demonstrated no quantitative or qualitative evidence of increased susceptibility of fetuses or pups as compared to adults.

Neurotoxicity: In an acute neurotoxicity study in rats, equivocal evidence of a possible slight neurotoxic effect at the limit dose of 2000 mg/kg was observed. In this study, an increased incidence of palpebral (eyelid) closure in the 13-week feeding study in dogs of myotonic twitching in the high dose level male and female animals. In none of the other toxicity studies with famoxadone, including a subchronic neurotoxicity study in rats, were there any toxicologically significant evidence of treatment-related neurotoxicity.

Mutagenicity: Famoxadone may have a weak mutagenic potential, but this is not considered to be toxicologically significant. In three gene mutation studies, results were negative. In three chromosome aberration studies, a weak clastogenic effect was observed in two *in vitro* chromosome aberration studies in human lymphocytes, but in an *in vivo* micronucleus study in mice using bone marrow cells, the results were negative. In four unscheduled DNA synthesis (UDS) studies, although a positive response was observed in an *in vitro* unscheduled DNA synthesis (UDS) assay in primary rat hepatocyte cultures, results in two repeat studies were negative. Also, results in an *in vivo/in vitro* UDS assay in primary rat hepatocyte cultures derived from male rats given oral doses of famoxadone were negative.

Chronic Reference Dose (cRfD) In a 13-week subchronic oral study famoxadone was administered by diet to 4 beagle dogs/sex/group at doses of 0, 40, 300, or 1000 ppm (equal to 0,

1.3/1.4, 10.0/10.1, or 23.8/23.3 mg/kg/day in males/females). The dose and endpoint for establishing the cRfD is based on a LOAEL of 1.4 mg/kg/day, based on treatment-related microscopic lens lesions (cataracts) in eyes of female dogs. A NOAEL could not be determined.

Uncertainty Factor(s): 1000 (10X for inter-species extrapolation, 10X for intra-species variation; and an additional 10X for the use of a LOAEL and the use of a subchronic study. This endpoint is based on an oral study, which is the route of interest for a dietary risk estimate. This study and endpoint were selected because they would address the concerns for toxic effects observed in all the other available studies for this chronic risk assessment.

Chronic RfD = 1.4 mg/kg/day (LOAEL) = **0.0014 mg/kg/day**

1000 (UF)

Physical/Chemical Properties

TABLE 1. Physicochemical Properties of Famoxadone

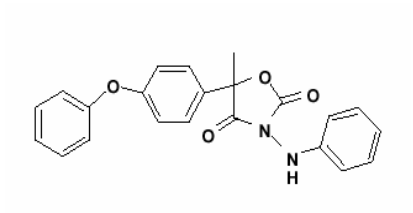
Parameter	**Value**
Color/Physical state	Pale cream powder
Molecular Structure	
Melting point/range	140.3- 141.8°C
pH of 1% aqueous suspension	6.56 at 20°C
Density or specific gravity	D^{20}_4 = 1.310 g/mL
Water solubility (20°C)	pH µg/L unbuffered 52 2 143

TABLE 1. Physicochemical Properties of Famoxadone	
Parameter	**Value**
	3 191 5 243 7 111 9 38
Solvent solubility (20°C)	Solvent g/L acetone 274 acetonitrile 125 dichloromethane 239 ethyl acetate 125 hexane 0.0476 methanol 10.0 1-octanol 1.87 toluene 13.3
Octanol/water partition coefficient (K_{ow})	pH Log K_{ow} " SD 3.0 4.59 " 0.06 5.0 4.80 " 0.13 7.0 4.65 " 0.40 9.0 5.55 " 0.26
Vapor pressure at 20°C	6.4H10^{-4} mPa (4.8H10^{-9} mm Hg)
Henry's Law Constant	4.6H10^{-3} Pa m^3 mol^{-1}, pH 7
Dissociation constant (pK_a)	Expected to be weakly basic. The dissociation constant could not be measured or inferred from solubility or octanol water partition coefficient.

Toxicological Characteristics:

Table 2. Acute Toxicity of Famoxadone Technical (Selected Studies)			
Guideline No./Study Type	MRID No.	Results	Toxicity Category
870.1100 Acute oral, rats	44302407	M: LD_{50} = >5000 mg/kg F: LD_{50} = >5000 mg/kg	IV
870.1200 Acute dermal, rabbits	44302409	M: LD_{50} = >2000 mg/kg F: LD_{50} = >2000 mg/kg	III
870.1300 Acute inhalation, rats	44302410	M: LC_{50} = >5.3 mg/L F: LC_{50} = >5.3 mg/L	IV
870.2400 Primary eye irritation, rabbits	44302411	Moderately irritating	III

870.2500 Primary skin irritation, rabbits	44946205	Moderately irritating	III
870.2600 Dermal sensitization, guinea pig	44302413	Non-sensitizer	NA

Table 3 Toxicity Profile of Famoxadone Technical (Selected Studies)

Guideline No./Study Type	Results
870.3100 90-Day oral toxicity, rats	NOAEL = M: 3.3 mg/kg/day. F: 4.2 mg/kg/day. LOAEL = M: 13.0 mg/kg/day based on mild hemolytic anemia and decreased glucose. F: 16.6 mg/kg/day based on decreased body weight gain, food consumption, and food efficiency; mild hemolytic anemia and decreased globulin.
870.3100 90-Day oral toxicity, mice	NOAEL = M: 62.4 mg/kg/day. F: 79.7 mg/kg/day. LOAEL = M: 534 mg/kg/day based on mild hemolytic anemia with secondary responses in spleen and mild hepatotoxicity in the liver. F: 757 mg/kg/day based on mild hemolytic anemia with secondary responses in spleen and mild hepatotoxicity in the liver.
870.3150 90-Day oral toxicity, dogs	NOAEL = M: 1.3 mg/kg/day. F: <1.4 mg/kg/day. LOAEL = M: 10.0 mg/kg/day based on lens cataracts in eyes. At 23.8/21.2 mg/kg/day, also myotonic twitches (starting on day 21); decreased body weight, body weight gain, food consumption, and food efficiency; slight anemia and hyperkalemia. F: 1.4 mg/kg/day based on lens cataracts in eyes. At 10.1 mg/kg/day, no additional effects. At 23.3/20.1 mg/kg/day, same effects as for males at 23.8/21.2 mg/kg/day.
870.3200 28-Day dermal toxicity, rats	NOAEL = M: 250 mg/kg/day. F: 1000 mg/kg/day. LOAEL = M: 500 mg/kg/day based on increased alkaline phosphatase, alanine aminotransferase and sorbitol dehydrogenase; and mild hepatotoxicity in the liver. F: none (>1000 mg/kg/day). No dermal irritation in M or F.
870.3700a Prenatal developmental toxicity, rats	**Maternal** NOAEL = 250 mg/kg/day. LOAEL = 500 mg/kg/day based on transient decreased body weight gain and food consumption. **Developmental** NOAEL = 1000 mg/kg/day. LOAEL = none (>1000 mg/kg/day).
870.3700b	**Materna**l NOAEL = 350 mg/kg/day.

Prenatal developmental toxicity, rabbits	LOAEL = 1000 mg/kg/day based on abortions; decreased body weight, body weight gain, and food consumption; and abnormal stools. **Developmenta**l NOAEL = 350 mg/kg/day. LOAEL = 1000 mg/kg/day based on abortions and equivocal increases in postimplantation loss and mean resorptions per doe.
870.3800 Reproduction and fertility effects, rats	**Parental/Systemic** NOAEL = M/F: 11.3/14.2 mg/kg/day. LOAEL = M/F: 44.7/53.3 mg/kg/day based on decreased body weight, body weight gain, and food consumption; and hepatotoxicity in the liver. **Reproductive** NOAEL = M/F: 44.7/53.3 mg/kg/day. LOAEL = M/F: none (>44.7/53.3 mg/kg/day). **Offspring** NOAEL = M/F: 11.3/14.2 mg/kg/day. LOAEL = M/F: 44.7/53.3 mg/kg/day based on decreased body weights for F_1 and F_2 pups throughout lactation.
870.4100b Chronic toxicity, dogs	NOAEL = M: 1.2 mg/kg/day. F: 1.2 mg/kg/day. LOAEL = M: 8.8 mg/kg/day based on lens cataracts in eyes. F: 9.3 mg/kg/day based on lens cataracts in eyes. No other adverse effects were observed in M or F.
870.4100 Chronic toxicity, Cynomolgus monkeys (1-year gavage study)	NOAEL = M: 100 mg/kg/day. F: 100 mg/kg/day. LOAEL = M: 1000 mg/kg/day based on mild hemolytic anemia with secondary responses in spleen, liver and kidney; and sinus dilatation in spleen. F: 1000 mg/kg/day based on mild hemolytic anemia with secondary responses in spleen, liver and kidney; and sinus dilatation in spleen. No evidence of lens cataracts in eyes of M or F.
870.4200b Carcinogenicity, mice	NOAEL = M: 96 mg/kg/day. F: 130 mg/kg/day. LOAEL = M: 274 mg/kg/day based on slight hepatotoxicity in the liver; no anemia. F: 392 mg/kg/day based on amyloidosis and slight hepatotoxicity in the liver; no anemia. **No evidence of carcinogenicity in M or F.**
870.4300 Combined chronic toxicity/carcinogenicity, rats	NOAEL = M: 8.4 mg/kg/day. F: 2.2 mg/kg/day. LOAEL = M: 16.8 mg/kg/day based on slight hemolytic anemia with compensatory erythropoiesis and secondary responses in spleen and bone marrow; and mild hepatotoxicity in the liver. F: 10.7 mg/kg/day based on decreased body weight gain and slight hemolytic anemia. At 23.0 mg/kg/day, also secondary responses to anemia in spleen, bone marrow and/or liver; and mild hepatotoxicity in the liver. **No evidence of carcinogenicity in M or F**.
870.5100	Negative without and with S-9 activation up to limit dose of 5000

Reverse gene mutation (*S. typhi./E. coli)*	µg/plate.
870.5300 Forward gene mutation (CHO/HGPRT locus)	Negative without and with S-9 activation up to the limit of solubility (in DMSO) of 30 µg/mL.
870.5300 Forward gene mutation (CHO/HGPRT locus)	Negative without and with S-9 activation up to cytotoxic concentrations (≥200 µg/mL without S-9 and ≥150 µg/mL with S-9).
870.5375 Chromosome aberration (human lymphocytes)	Positive (weak clastogenic effect) without S-9 activation. Statistically significant increases in percentage of aberrant cells at several dose levels ranging from 5-15 µg/mL. Cytotoxicity was observed at 10-18 µg/mL. Negative with S-9 activation.
870.5375 Chromosome aberration (human lymphocytes)	Positive (weak clastogenic effect) without S-9 activation. Statistically significant increases in percentage of aberrant cells at several dose levels ranging from 15-30 µg/mL. Cytotoxicity was observed at 20-30 µg/mL. Negative with S-9 activation.
870.5395 Micronucleus assay (mouse bone marrow)	Negative at single oral doses of up to limit dose of 5000 mg/kg.
870.5550 Unsched. DNA synthesis (prim. rat hepatocytes)	Positive response (increased net nuclear grain counts) observed at several treatment levels ranging from 0.05-10 µg/mL. Cytotoxicity was observed at 10 µg/mL.
870.5550 Unsched. DNA synthesis (prim. rat hepatocytes)	Negative at treatment levels up to 10 µg/mL. Cytotoxicity was observed at 10 µg/mL.
870.5550 Unsched. DNA synthesis (prim. rat hepatocytes)	Negative at treatment levels up to 5.0 µg/mL. Cytotoxicity was observed at 2.5 and 5.0 µg/mL.
870.5550 Unsched. DNA synthesis (hepatocytes derived from male rats given Famoxadone)	Negative at single oral doses of up to 2000 mg/kg. No marked increases in net nuclear grain counts or percentage of cells in repair in hepatocyte cultures.
870.6200a Acute neurotoxicity screening battery,	NOAEL = M: 1000 mg/kg. F: 2000 mg/kg. LOAEL = M: 2000 mg/kg based on decreased body weight gain and food consumption (on days 1-2); and palpebral (eyelid) closure (on

rats	day 1 only). F: none (>2000 mg/kg).
870.6200b Subchronic neurotoxicity screening battery, rats	NOAEL = M: 11.7 mg/kg/day. F: 14.4 mg/kg/day. LOAEL = M: 47 mg/kg/day based on decreased body weight, body weight gain, food consumption and food efficiency. F: 59 mg/kg/day based on decreased body weight, body weight gain, food consumption and food efficiency. No evidence of neurotoxicity in M or F.

Occupational and Residential Exposure and Risk Characterization.

Chemical-specific data for assessing human exposures during pesticide handling activities were not submitted for famoxadone. Therefore, the Agency used Pesticide Handlers Exposure Database (PHED V 1.1) to assess handler exposure. Based on the application rates and uses, exposures are expected to be short- and intermediate-term in duration. Since both dermal and inhalation endpoints were based on the same toxicological effects for short- and intermediate-term exposures, the route-specific MOEs were combined into a total MOE. All MOEs for handlers were greater then the target MOEs of 100 (short term) and 300 (intermediate-term) and therefore do not exceed the Agency's level of concern. The Agency is imposing a re-entry interval of 12 hours for the Tanos 50DF product. The Agency will also be requiring on product labels personal protective equipment (PPE) required by the Worker Protection Standard (WPS).

For short-term (1-30 days) occupational dermal and inhalation exposures, the toxicology endpoint was selected from the subchronic feeding study in dogs in which myotonic twitches were observed in male and female dogs at the highest dose tested (23 mg/kg/day) starting on day 21. The next lower dose in this study (10 mg/kg/day) was the dose selected for the short-term risk assessments. The cataracts observed in the eyes of dogs in this study and in the chronic feeding study in dogs did not occur until after 8 weeks (56 days) of exposure and therefore were not an appropriate endpoint on which to base a short-term (1-30 days) risk assessment. For short-term exposures, the target Margin of Exposure (MOE) is 100. For intermediate-term (1-6 months) and long-term (>6 months) occupational dermal and inhalation exposures, the toxicology endpoint was selected from the same subchronic feeding study in dogs, but was based on microscopic lens lesions (cataracts) observed in the eyes of female dogs at the LOAEL of 1.4 mg/kg/day. This dose/endpoint/study was also selected for long-term dietary risk assessment. For intermediate-term exposures, the target MOE is 300. This MOE includes the conventional factor of 100 and an additional factor of 3 since a LOAEL, rather than a NOAEL, was selected for risk assessments. For long-term exposures, the target MOE is 1000. This MOE includes the conventional factor of 100 and an additional factor of 10 for the use of the LOAEL and dose from a subchronic study for long-term risk assessment. For dermal exposures, a 5% dermal absorption factor was used. For inhalation exposures, a 100% inhalation absorption factor (default value) was used.

At this time, only agricultural uses have been proposed for famoxadone. There are no uses that would result in residential or recreational exposures. Assessments addressing residential

and recreational risks are not warranted at this time.

Aggregate Exposure and Risk Characterization.

The currently proposed uses for famoxadone encompass only agricultural use sites. Therefore, when addressing aggregate exposures, only the dietary pathways of food and drinking water were considered. No appropriate endpoint attributable to a single oral dose was identified in the available toxicology studies on famoxadone. Therefore, an acute aggregate risk assessment for famoxadone is not warranted.

Dietary exposure and risk estimates were evaluated using Dietary Evaluation Model, Version 1.3 (DEEM-FCID). These exposure estimates are based on average field trial residues but retain the conservative assumption of 100% crop treated and should be considered moderately refined.

For considering exposure to residues of famoxadone in drinking water, the Agency has calculated Drinking Water Levels of Comparison (DWLOCs). These values are the maximum concentration of a chemical that occur in drinking water after taking into account exposures to residues from other pathways and sources. The DWLOCs are compared against the modeled estimated environmental concentrations (EECs). DWLOC values that are greater than the EECs indicate that aggregate exposures are unlikely to exceed the Agency's level of concern.

As shown in Table 4, the DWLOCs for the general U.S. population and all of the representative population subgroups modeled by DEEM-FCID are greater than both the surface water and ground water EECs.

Famoxadone has been classified as not likely to be carcinogenic to humans. As such, a cancer aggregate risk assessment is not warranted.

Table 4. Chronic DWLOC Calculations.

Population Subgroup	cPAD mg/kg/day	Food Exp mg/kg/day	Max Water Exp mg/kg/day[a]	Ground Water EEC (µg/L)	Surface Water EEC (µg/L)	DWLOC (Fg/L)[b]
General U.S. Population	0.0014	0.000505	0.000895	0.23	0.47	31
All Infants, (< 1 year old)	0.0014	0.000175	0.001225	0.23	0.47	12

Table 4. Chronic DWLOC Calculations.						
Population Subgroup	cPAD mg/kg/day	Food Exp mg/kg/day	Max Water Exp mg/kg/day[a]	Ground Water EEC (µg/L)	Surface Water EEC (µg/L)	DWLOC (Fg/L)[b]
Children, 1-2 years old	0.0014	0.001057	0.000343	0.23	0.47	3.4

[a] Maximum water exposure (mg/kg/day) = [(chronic PAD (mg/kg/day) - food exposure (mg/kg/day)]

[b] DWLOC(Fg/L) = [maximum water exposure (mg/kg/day) x body weight (kg)]) [water consumption (L) x 10^{-3} mg/Fg]. Consumption = 1 L/day for populations <13 years old and 2 L/day for populations $ 13 years old. Default body weights = 70 kg for males $ 13 years old and general U.S. population, 60 kg for females $ 13 years old, and 10 kg for all others. Values are rounded to 2 significant figures.

Human health aggregate risk assessments have been conducted for acute aggregate exposure (food + drinking water) and chronic aggregate exposure (food + drinking water). Short-, intermediate-, and long-term aggregate assessments were not performed, since there are no registered or proposed residential uses. A cancer risk assessment was not performed, because the Agency classified famoxadone as "not likely to be carcinogenic to humans." All aggregate exposure and risk estimates are below the Agency's level of concern for the scenarios listed above.

<u>Ecological Effects/Environmental Fate Characteristics</u>:

Hydrolysis

The half-life for famoxadone is 31 - 41 days in pH 5 solution, 2 - 2.7 days in pH 7 solution, and 1.55 - 1.8 hours in pH 9 solution (in the dark at 25°C, sterile aqueous buffered solutions). Hydrolysis of the parent compound is pH dependent and the rate of degradation increases with increasing pH. Under neutral to basic conditions hydrolysis would likely be a significant route of degradation.

Aqueous Photolysis

The half-life for famoxadone in irradiated solution (pH 5) is 1.1 - 1.9 days (equivalent to 2.6 - 4.6 days of natural sunlight) and in the dark control is 41 days.

Soil Photolysis

The half-life for famoxadone in irradiated soil is 3.3 - 4.9 days (after correction for dark

controls, equivalent to 9.5 - 16.2 days of natural sunlight).

Mobility

Famoxadone is of slight mobility using the general classification scheme of McCall. The mobility of famoxadone, at nominal concentrations of 5.0, 10.0, and 25.0 ng/mL, was investigated in three soils (sand, sandy loam, and sandy clay loam). K_d values ranged from 71.3 - 109.8 for the sand soil (2.29% o.c.); 33.9 - 51.9 for the sandy loam soil (1.34% o.c.), and 16.5 - 29.4 for the sandy clay loam soil (0.58% o.c.); 1/n values ranged from 0.737 to 0.831. Following adsorption, K_{oc} values were 3890 for the sand soil, 3300 for the sandy loam soil, and 4030 for the sandy clay loam soil.

Field Dissipation

In four different Terrestrial Field Dissipation Studies (three U.S. studies, one Canadian study), famoxadone had dissipation half-lives ranging from 6.5 - 32.9 days. Famoxadone was not detected (detection limit - 0.007 ppm) below the 15-cm soil depth at any of the sites.

Bioaccumulation

The accumulation of famoxadone in two different (^{14}C labeled in different ring positions) juvenile bluegill sunfish indicated bioconcentration factors of 971X - 1286X for the edible tissue, 3327X - 3608X for the nonedible tissue, and 2434X - 3425X for the whole fish tissues. Depuration was rapid with 50% of the total residues accumulated by exposure day 28 eliminated by day 2 of the depuration period. Because of the rapid depuration of famoxadone, bioaccumulation is not expected to be a significant concern.

Spray Drift

No famoxadone-specific studies were reviewed. Droplet size spectrum (201-1) and drift field evaluation (201-2) studies are required since famoxadone may be applied aerially. The registrant, E.I. DuPont de Nemours is a member of the Spray Drift Task Force (SDTF), a membership of U.S. pesticide registrants. The Agency has been working with the SDTF, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency has completed its evaluation of the data base submitted by the SDTF and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessment for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in the spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate. Due to risks associated with exposures via spray drift, product labels should include a strong enforceable statement to avoid off-target spray drift.

ECOLOGICAL CHARACTERISTICS

Acute Freshwater Fish

Bluegill	96-hr LC_{50} = 13 (9.3, 21) Fg/L	NOAEC = 9.3 Fg/L
Rainbow trout	96-hr LC_{50} = 12 (5.2, 72) Fg/L	NOAEC = 5.2 Fg/L

Acute Estuarine/Marine Fish

Sheepshead minnow	96-hr LC_{50} = 49.4 (44.1, 56.1) Fg/L	NOAEC = 27.7 Fg/L

Chronic (Early-Life) Freshwater Fish

Rainbow trout	NOAEC 1.4 Fg/L	LOAEC = 4.1 Fg/L

Chronic (Early-Life) Estuarine/Marine Fish

Sheepshead minnow	NOAEC 5.6 Fg/L	LOAEC = 11.2 Fg/L

Acute Freshwater Invertebrates

Daphnia magna	48-hr EC_{50} = 11.8 (10.1, 14.5) Fg/L	NOAEC = 3.5 Fg/L
Chironomus riparius	Pore water concentrations:	
	28-day EC_{50} = 15 (12.7, 18.2) mg/L	NOAEC < 0.55 mg/L
	Sediment concentrations.	
	28-day EC_{50} = 2.4 (2.0, 2.8) mg/kg	NOAEC <0.07 mg/kg

Acute Estuarine/Marine Invertebrates

Eastern oyster (Shell deposition)	96-hr EC_{50} = 1.6 (1.0, 2.7) Fg/L	NOAEC < 1.10 Fg/L
Mysid shrimp	96-hr EC_{50} = 3.8 (2.2, 4.9) Fg/L	NOAEC = 2.2 Fg/L

Chronic (Life-Cycle) Freshwater Invertebrate

Daphnia magna	NOAEC = 0.085 Fg/L	LOAEC = 0.29 Fg/L

Chronic (Life-Cycle) Estuarine/Marine Invertebrate

Mysid shrimp	NOAEC = 0.83 Fg/L	LOAEC = 1.72 Fg/L

Aquatic Plants

Lemna gibba	14-day EC_{50} >81 Fg/L	NOAEC = 81Fg/L
Skeletonema costatum	120-hr EC_{50} >75 Fg/L	NOAEC = 75 Fg/L
Selenastrum capricornutum	120-hr EC_{50} = 23 (12, 29) Fg/L	NOAEC = 3.9Fg/L
Navicula pelliculosa	120-hr EC_{50} =13 (9.6, 19.0) Fg/L	NOAEC <9.87Fg/L
Anabaena flos-aquae	120-hr EC_{50} >84.3 Fg/L	NOAEC =42.6 Fg/L

Avian Acute Single Oral Dose

Bobwhite quail	LD_{50} > 2250 mg/kg-bw	NOAEC = 2250 mg/kg-bw
Bobwhite quail	LD_{50} > 511 mg/kg-bw	NOAEC = 66 mg/kg-bw

Avian Acute Dietary

Bobwhite quail	LC_{50} > 5620 mg/kg-diet	NOAEC = 5620 mg/kg-diet
Mallard duck	LC_{50} > 5620 mg/kg-diet	NOAEC = 5620 mg/kg-diet

Avian Chronic

Bobwhite quail	NOAEC = 46 mg /kg-diet	LOAEC = 252 mg/kg-diet
Mallard duck	NOAEC = 46 mg/kg-diet	LOAEC = 252 mg/kg-diet

Earthworm

Eisenia fetida andrei 14-day LC_{50} = 470 mg/kg-soil NOAEC < 62.5 mg/kg-soil

Terrestrial Plants

Species studied were: common onion, corn, winter wheat, sorghum, sugar beat, soybean, pea, tomato, rape, cucumber. For all endpoints in the emergence study and the vegetative vigor study, the EC_{25} > 0.187 lb/acre and the NOAEC = 0.187 lb/acre.

Environmental Risk Summary:

Agency analysis indicates that famoxadone presents the greatest risks to fish and aquatic invertebrates through spray drift and runoff in the dissolved phase as compared to the other taxonomic groups evaluated in this assessment.

For aquatic and terrestrial plants, LOCs are not exceeded for the proposed uses of famoxadone. In this risk assessment, modeling results did not indicate potential concerns for aquatic or terrestrial plants.

ENVIRONMENTAL RISK MITIGATION

The Agency has conducted a screening level analysis to assess potential ecological risks posed by famoxadone. The exceedance of a RQ does not necessarily indicate "high risk" to a species as the RQ is not an absolute estimate of the likelihood, magnitude, or severity of risk. Inputs into this screening level assessment were designated to overestimate likely exposures and effects of famoxadone. Given the slight exceedences of the RQs and the risk mitigation that will be imposed for famoxadone, the Agency, believes that potential ecological risks are low.

FRESHWATER FISH/INVERTEBRATES: Based on a screening level analysis, the Endangered Species LOC and Acute Restricted Use LOC for freshwater fish and invertebrates are slightly exceeded. Acute Fish RQs and Acute Invertebrate RQs ranged from 0.04 - 0.24. Chronic Fish RQs ranged from 0.08 - 0.24, while Chronic Invertebrates RQs ranged from 2.47 - 8.35.

ESTUARINE/MARINE FISH/INVERTEBRATES: Based on a screening level analysis, the Endangered Species LOC for estuarine/marine fish was exceeded for Florida tomatoes, Florida peppers, and Maine potatoes. The Endangered species LOC and Acute Restricted Use LOC for estuarine/marine invertebrates was exceeded in all scenarios; however, there are currently no

federally listed endangered estuarine invertebrates. RQs ranged from 0.01 - 1.81. Chronic RQs ranged from 0.02 - 0.86.

AVIAN: Based on a screening level analysis, Chronic RQs for herbivorous birds, insectivorous birds and herbivorous mammals exceeded the LOCs from exposure to famoxadone residues in wildlife food items indicating potential for chronic risks. Chronic RQs ranged from 0.3 - 4.7 at the estimated maximum residue levels, and ranged from 0.1 to 1.70 at the predicted mean residue levels. Short grass eating birds had the highest RQs of 1.7 at the estimated mean residues level and 4.7 at the estimated maximum residue level, these are the only exceedances of the Avian Chronic LOC. For chronic exposure the predicted mean residue is the appropriate level for risk assessment. The only Endangered species that feeds exclusively on short grasses is native to Hawaii and the commodities that famoxadone is registered for use on are generally not grown in that area.

MAMMALS: RQs were not calculated to evaluate potential acute risks to mammals because of the low toxicity to mammals (LD_{50} >5000 mg/kg). Acute risk is low at the proposed application rates. Chronic effects are not expected for mammals using anticipated mean residue levels, which is the appropriate level for use in a chronic analysis.

BENEFICIAL INSECTS: Famoxadone may have negative effects on beneficial insects (e.g., hoverfly and green lacewing). The Agency has concerns with the potential for negative impacts on endangered insects.

ENVIRONMENTAL RISK MITIGATION: The Agency believes that famoxadone presents the greatest risk to fish and aquatic invertebrates through spray drift and runoff in the dissolved phase. In order to mitigate this risk the Agency will be requiring use limitations, label warning statements and/or restrictions on the end-use product label:

** Maximum number of use per season - The Agency is restricting the maximum number of applications per season to six and limiting the maximum seasonal use rate.

** The Agency will require spray drift language on all end use products.

** The Agency will also require a beneficial insect warning statement on all end use products.

In addition, the Agency will be requiring a 25-foot vegetative buffer strip around treated fields. While the Agency cannot quantify the reduction in risk to non-target/endangered species resulting from this restriction on the use, it should significantly reduce the potential for spray drift and/or runoff, which are the major concerns. The Agency also notes that this product has a relatively low seasonal maximum use rate compared to current alternatives.

Famoxadone is an alternative to other fungicides some of which may have higher seasonal use rates, a different maximum number of applications, or shorter re-treatment intervals. Thus while the Agency cannot strictly compare the RQs from those various fungicides the Agency does

note that the issues with this fungicide are similar and that the RQ for the same use site are comparable. The Agency believes that by restricting the maximum seasonal use rate and by employing the use of vegetative buffer strips, actual ecological risks are significantly lower than model estimates.

The Agency notes that DuPont is a member in the FIFRA Endangered Species Task Force.

SUMMARY OF DATA GAPS

Environmental Fate and Effects Data Requirements:

835.1220	163-1 Leaching/Adsorption/Desorption (one additional soil type which should be finer-grained than those previously tested - which were sand, sandy/loam, and sandy/clay/loam)
850.1075	72-1 Acute freshwater fish (Rainbow trout) guideline study using the end-use product
850.1735	Whole sediment acute toxicity invertebrates, freshwater (chironomids, the 28-day test
850.3020	Honey-bee acute contact with the end-use product
850.3030	Honey Bee Toxicity of residues on foliage with the end-use product

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