



Pesticide Fact Sheet

Name of Chemical: Fluazinam
Reason for Issuance: New Chemical
Date Issued: August 10, 2001

Description of Chemical

Chemical Name: 3-chloro-N-[3-chloro-2,6-dinitro-4-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-2-pyridinamine

Common Name: Fluazinam

Trade Name: Omega 500F Agricultural Fungicide

Chemical Class: Phenyl-pyridinamine

EPA Chemical Code: 129098

Chemical Abstracts
Service (CAS) Number: 79622-59-61

Year of Initial Registration: 2001

Pesticide Type: Fungicide

U.S. Producer: ISK Biosciences Corporation
5970 Heisley Road
Mentor, Ohio 44060

Use Pattern and Formulations

Omega 500F is a flowable liquid containing 40% (4.17 pounds/gal) of the active ingredient (ai) fluazinam. Omega 500F is used for the control of Sclerotinia blight on peanuts and late blight and white mold on potatoes. The products can be applied with ground equipment including chemigation. For peanuts, the product is applied at the rate of 1-1 ½ pints/acre for a maximum of three applications, applying a yearly total of no more than 4 pts/acre (2.08 lbs ai) with the last application at least 30 days before harvest. On potatoes, the product is applied at the rate of 5 ½ fluid ounces/acre. Under conditions favorable for moderate to high disease pressure from white mold, the rate may be increased to 8 fl.oz/acre. Repeat applications are on a 7 -10 day schedule. The last application must be at least 14 days before harvest and the maximum yearly rate may not exceed 3 ½ pints (1.82 lb ai).

Science Findings

Summary Science Statement

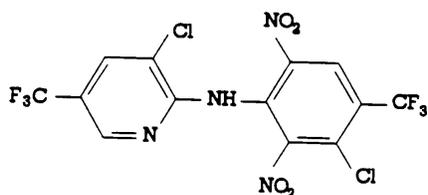
EPA has concluded from the review of the supporting data that there are no risks of concern from the use of fluazinam. The end-use product is in Toxicity Category II because of severe skin irritation and positive dermal sensitization. It was calculated that the acute and chronic risks due to exposure to residues in food and water were below the Agency's level of concern for all population subgroups, including infants and children. Risk from exposure of workers (applicators and other handlers) was also below the Agency's level of concern. There are no residential uses of fluazinam either registered or pending. The Agency also concluded that the use of fluazinam for the labeled uses on peanuts and potatoes is unlikely to present a significant threat to non-target organisms or the environment.

Physical/Chemical Properties

Physical and Chemical Properties for Technical Grade Active Ingredient	
Requirement	Result or Deficiency
Color	Yellow at 23°C (ASTM D 1535-89)
Physical State	Suspension at 23°C
Odor	Pungent at 23°C
Stability	Stable in plastic bottles for 90 days at 50°C. Stable under UV light for 2 hours. Stable to acid and alkali overnight.
Oxidation/Reduction	No visible changes over 6 hours contact with ammonium phosphate, zinc metal, 1% KMnO ₄ , or water. No significant (>5°C) temperature changes over 24 hours contact with ammonium phosphate, zinc metal, 1% KmnO ₄ , or water. Stable to oxygen purge over 2 hours.

Physical and Chemical Properties for Technical Grade Active Ingredient			
Requirement	Result or Deficiency		
Flammability	No data submitted.		
Explosibility	Nonexplosive (Association of American Railroads 17-1F)		
Storage Stability	Stable in plastic containers for 12 months at 25°C and 50% humidity. No physical changes in the containers. Stable in HDPE containers for 36 months at or near 25°C.		
Miscibility	Stable in diluent (Sunspray 11E) at 95% and 50% v/v after 30 minutes at 25°C		
Corrosion Characteristics	No visible changes in the commercial packaging (polyethylene jugs) following storage at 50°C for 91 days. No physical changes in plastic containers after 12 months at 25°C.		
Dielectric Breakdown Voltage	No data submitted. Applicant did not indicate whether product is for use around electrical equipment.		
pH	5.8 at 25°C (1% aqueous solution) (Fisher meter)		
Viscosity	1040 cP at 20 rpm, 572 cP at 50 rpm, 375 cP at 100 rpm (Brookfield viscometer at 25°C)		
Melting Point/ Melting Range	Product is a liquid		
Density/ Relative Density/ Bulk Density	1.259 g/mL at 25°C (CIPAC 3.3.2)		
Dissociation Constant in Water	pKa = 7.22 in 50% C ₂ H ₅ OH-H ₂ O		
Partition Coefficient (Octanol/Water)	log Pow = 3.56		
Solubility	<table border="0"> <tr> <td>Water: 0.025ppm pH 5.5 0.071ppm pH 7.0 350ppm pH 11.0</td> <td>Organics g/L: n-Hexane 6.7 MeOH 162 Ethylether 168 Dichloroethane 485 Toluene 512 Ethylacetate 624 Acetone 645</td> </tr> </table>	Water: 0.025ppm pH 5.5 0.071ppm pH 7.0 350ppm pH 11.0	Organics g/L: n-Hexane 6.7 MeOH 162 Ethylether 168 Dichloroethane 485 Toluene 512 Ethylacetate 624 Acetone 645
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Vapor Pressure	8.25 x 10 ⁻⁶ torr		

Structure:



Toxicological Characteristics:

Acute effects.

Acute Toxicity Data on Fluazinam			
Study Type	Test Substance	Results	Toxicity Category
Acute oral toxicity rats	Technical grade fluazinam (lot #109; 95.3%)	M: LD ₅₀ = 4500 mg/kg F: LD ₅₀ = 4100 mg/kg	III
	Technical grade fluazinam (lot #8412-20; 95.3%)	M: LD ₅₀ >5000 mg/kg F: LD ₅₀ >5000 mg/kg	IV
	Technical grade fluazinam (lot #1/87; 97.9%)	M: LD ₅₀ >5000 mg/kg F: LD ₅₀ >5000 mg/kg	IV
	Omega 500F (40% fluazinam)	M: LD ₅₀ >5000 mg/kg F: LD ₅₀ >5000 mg/kg	IV
Acute dermal toxicity rats, rabbits	Technical grade fluazinam (lot #8303-2; 98.5%)	M: LD ₅₀ >2000 mg/kg F: LD ₅₀ >2000 mg/kg	III
	Omega 500F (40% fluazinam)	M: LD ₅₀ >2000 mg/kg F: LD ₅₀ >2000 mg/kg	III
Acute inhalation toxicity rats	Technical grade fluazinam (lot #109; 95.3%)	M: LC ₅₀ = 0.463 mg/L F: LD ₅₀ = 0.476 mg/L	II
	Fluazinam 50% WP (51.3% fluazinam)	M: LC ₅₀ = 3.0 mg/L F: LD ₅₀ = 3.4 mg/L	IV
Acute eye irritation rabbits	Technical grade fluazinam (lot # SNPE B-1216, No. 1006; 97.9%)	Extremely irritating. Corneal opacity did NOT reverse in 21 days.	I
	Omega 500F (40% fluazinam)	Slightly irritating	III

Acute dermal irritation rabbits	Technical grade fluazinam (lot # SNPE B-1216, No. 1006; 97.9%)	Slightly irritating	IV
	Omega 500F (40% fluazinam)	Moderately irritating	II
Dermal sensitization guinea pigs	Technical grade fluazinam (lot # 1030/91; 96.7%)	Positive	NA
	Ultra-purified fluazinam (lot #Y910401; 100%)	Negative	NA
	Omega 500F (40% fluazinam)	Positive	NA

Toxicity profile:

Toxicity Profile of Fluazinam Technical		
Guideline No.	Study Type	Results
870.3100	90-Day oral toxicity rats	NOAEL: Males = 3.8 mg/kg/day; Females = 4.3 mg/kg/day LOAEL Males = 38 mg/kg/day; Females = 44 mg/kg/day based on increased liver weights and liver histopathology in males, and increased lung and uterus weights in females.
870.3150	90-Day oral toxicity dogs	NOAEL = 10 mg/kg/day LOAEL = 100 mg/kg/day based on retinal effects, increased relative liver weight, liver histopathology and possible increased serum alkaline phosphatase in females and possible marginal vacuolation of the cerebral white matter (equivocal)
870.3200	21-Day dermal toxicity rats	Systemic NOAEL = 10 mg/kg/day LOAEL = 100 mg/kg/day based on increased AST and cholesterol levels in males (liver target) Dermal NOAEL = not identified LOAEL = 10 mg/kg/day based on erythema, acanthosis, and dermatitis
870.3250	90-Day dermal toxicity	NA
870.3465	90-Day inhalation toxicity	NA
870.3700a	Prenatal developmental toxicity rats	Maternal NOAEL = 50 mg/kg/day LOAEL = 250 mg/kg/day based on decreased body weight gain and food consumption and increased water consumption and urogenital staining Developmental NOAEL = 50 mg/kg/day LOAEL = 250 mg/kg/day based on decreased fetal body weights and placental weights, increased facial/cleft palates, diaphragmatic hernia, and delayed ossification in several bone types, greenish amniotic fluid and possible increased late resorptions and postimplantation loss

Toxicity Profile of Fluazinam Technical		
Guideline No.	Study Type	Results
870.3700b	Prenatal developmental toxicity rabbits	Maternal NOAEL = 4 mg/kg/day LOAEL = 7 mg/kg/day based on decreased food consumption and increased liver histopathology. Developmental NOAEL = 7 mg/kg/day LOAEL = 12 mg/kg/day based on an increase in total litter resorptions and possible fetal skeletal abnormalities
870.3700b	Prenatal developmental toxicity rabbits	Maternal NOAEL = 3 mg/kg/day LOAEL = not identified (>3 mg/kg/day) Developmental NOAEL = 3 mg/kg/day LOAEL = not identified (>3 mg/kg/day)
870.3800	Reproduction and fertility effects rats	Parental/Systemic NOAEL = 1.9 mg/kg/day LOAEL = 9.7 mg/kg/day based on liver pathology in F ₁ males Reproductive NOAEL = 10.6 mg/kg/day LOAEL = 53.6 mg/kg/day based on decreased number of implantation sites and decreased litter sizes to day 4 post-partum for F ₁ females (F ₂ litters). Offspring NOAEL = 8.4 mg/kg/day LOAEL = 42.1 mg/kg/day based on reduced F ₁ and F ₂ pup body weight gains during lactation.
870.4100a	Chronic toxicity rats	NOAEL = Males: 1.9 mg/kg/day; Females: 4.9 mg/kg/day LOAEL = Males: 3.9 mg/kg/day; Females: not identified (>4.9 mg/kg/day) based on increased testicular atrophy in males and no effects in females
870.4100b	Chronic toxicity dogs	NOAEL = 1 mg/kg/day LOAEL = 10 mg/kg/day based on gastric lymphoid hyperplasia in both sexes and nasal dryness in females
870.4300	Combined chronic toxicity/carcino-genicity rats	NOAEL = Males: 0.38 mg/kg/day; Females: 0.47 mg/kg/day LOAEL = Males: 3.8 mg/kg/day; Females: 4.9 mg/kg/day based on liver toxicity in both sexes, pancreatic exocrine atrophy in females and testicular atrophy in males. Some evidence of carcinogenicity (thyroid gland follicular cell tumors) in male rats, but not in females.
870.4200b	Carcinogenicity mice	NOAEL = Males: 1.1 mg/kg/day; Females: 1.2 mg/kg/day LOAEL = Males: 10.7 mg/kg/day; Females: 11.7 mg/kg/day based on increased incidences of brown macrophages in the liver of both sexes, eosinophilic vacuolated hepatocytes in males, and increased liver weight in females Clear evidence of carcinogenicity (hepatocellular tumors) in male mice, but not in females
870.4200b	Carcinogenicity mice	NOAEL = Males: <126 mg/kg/day, Females: <162 mg/kg/day LOAEL = Males: 126 mg/kg/day; Females: 162 mg/kg/day based on increased liver weights and liver and brain histopathology in both sexes Equivocal/some evidence of carcinogenicity (hepatocellular tumors) in male mice, but not in females

Toxicity Profile of Fluazinam Technical		
Guideline No.	Study Type	Results
870.5100	Bacterial reverse mutation assay (Ames test)	Negative with and without S9 up to cytotoxic concentrations.
870.5100	Bacterial reverse mutation assay (Ames test)	Negative with and without S9 up to cytotoxic concentrations.
870.5300	<i>In vitro</i> mammalian gene mutation assay	Negative with S9 activation up to 9 : g/ml. Negative without S9 activation up to 0.3 : g/ml. Compound tested to cytotoxic concentrations.
870.5300	<i>In vitro</i> mammalian gene mutation assay	Negative with and without S9 activation up to 5 : g/ml. Compound tested to cytotoxic concentrations.
870.5375	<i>In vitro</i> mammalian chromosome aberration (CHL cells)	Negative with and without S9 up to cytotoxic concentrations. Cells harvested at 24 and 48 hours in nonactivated studies and at 24 hours in activated studies.
870.5395	Mammalian erythrocyte micronucleus test	Negative at 24 hour sacrifice (500, 1000, 2000 mg/kg). Negative at 24, 48, and 72 hour sacrifices (2000 mg/kg).
870.5550	UDS in primary rat hepatocytes	Negative; however there were several serious study deficiencies: treatment time shorter than recommended, no data supporting the claim of cytotoxicity, data variability for major endpoints.
870.5550	Differential killing/growth inhibition in <i>B. subtilis</i>	Negative, however only one replicate plate/dose was used.
870.6200a	Acute neurotoxicity screening battery rats	Systemic NOAEL = 50 mg/kg LOAEL = 1000 mg/kg based on soft stools and decreased motor activity on day of dosing. Neurotoxicity NOAEL = 2000 mg/kg LOAEL = not identified (>2000 mg/kg)
870.6200b	Subchronic neurotoxicity screening battery rats	Neurotoxicity NOAEL = Males: 233 mg/kg/day; Females: 280 mg/kg/day LOAEL = not identified (Males: >233 mg/kg/day; Females: > 280 mg/kg/day)
870.6300	Developmental neurotoxicity	NA
870.7485	Metabolism and pharmacokinetics rats	Only 33-40% of the administered dose was absorbed. Most of the administered dose was recovered in the feces (>89%). Excretion via the urine was minor (<4%). Total biliary radioactivity, however, represented 25-34% of the administered dose, indicating considerable enterohepatic circulation.
870.7600	Dermal penetration	NA
<u>Special studies:</u>	4-Week dietary (Range-finding) rats	NOAEL = M: 5.1 mg/kg/day; F: 5.3 mg/kg/day LOAEL = M: 26.4 mg/kg/day; F: 25.9 mg/kg/day based on decreased body weight gain and food consumption, increased serum phospholipids, increased total cholesterol, increased relative liver weights, and liver histopathology.

Toxicity Profile of Fluazinam Technical		
Guideline No.	Study Type	Results
	4-Week dietary (Range-finding) mice	NOAEL = M: 7.6 mg/kg/day; F: 8.2 mg/kg/day LOAEL = M: 36 mg/kg/day; F: 43 mg/kg/day based on decreased body weight gain, increased serum glucose, increased kidney weights.
	4-Week dietary (Range-finding) mice	NOAEL = not identified (M ;<555 mg/kg/day; F: <658 mg/kg/day) LOAEL = M: 555 mg/kg/day; F: 658 mg/kg/day based on vacuolation of white matter in brain, increased liver weights, histopathology in liver.
	90-Day dietary (Special liver study) rats	NOAEL = not determined (M:<37.6 mg/kg/day, F:<44.7 mg/kg/day) LOAEL = M: 37.6 mg/kg/day, F: 44.7 mg/kg/day based on increased relative liver weights and liver histopathology.
	11-Week oral toxicity (Special retinal study) dogs	NOAEL/LOAEL not determined.
	7-Day inhalation toxicity rats Test Material: Frowncide WP (51.9% a.i.)	NOAEL = M: 1.38 mg/kg/day; F: 1.49 mg/kg/day LOAEL = M: 3.97 mg/kg/day; F: 4.25 mg/kg/day based on increased testes weight (males) and increased liver weight (females).
	Developmental toxicity (range-finding) rats	Maternal and developmental NOAELS and LOAELS were not assigned.
	Eight special mechanistic studies to assess the CNS white matter vacuolation	White matter vacuolation in the CNS of mice, rats, and dogs was found to be due to Impurity-5.

Summary of Toxicology Findings.

Technical grade fluazinam was in Toxicity Category III for acute oral toxicity for one lot, whereas two other lots were in Toxicity Category IV. For acute dermal toxicity, technical grade fluazinam was in Toxicity Category III and for acute inhalation in Toxicity Category II. Technical grade fluazinam was extremely irritating in a primary eye irritation study (Toxicity Category I) and slightly irritating in a primary skin irritation study (Toxicity Category IV). In dermal sensitization studies, technical grade fluazinam (96.7% purity) was positive, but ultra-purified fluazinam (100% purity) was negative for dermal sensitization.

In a battery of acute toxicity studies of the end-use product, Omega 500F, a flowable liquid concentrate of fluazinam containing 40% active ingredient), the acute oral toxicity was Toxicity Category IV, the acute dermal toxicity was Toxicity Category III and the acute inhalation toxicity was Toxicity Category IV. In a primary eye irritation study, the formulation was slightly irritating (Toxicity Category III); in a primary skin irritation study, it was moderately irritating (Toxicity Category II) and in a dermal sensitization study, it was positive for dermal sensitization.

In subchronic and chronic oral, dermal and inhalation studies in rats, dogs and mice, the liver was a major target organ and signs of liver toxicity were regularly observed in many studies. These signs included changes in clinical chemistries indicative of liver toxicity, increased absolute and/or relative liver weights, increased incidences of macroscopic liver lesions and increased incidences of a variety of microscopic liver lesions. Treatment-related effects were also observed in other organs in subchronic and chronic oral, dermal and inhalation studies in rats, dogs and mice, but these effects were not regularly noted in all three species or in all studies in a given species.

Of particular concern was a neurotoxic lesion described as vacuolation of the white matter of the brain and sometimes cervical spinal cord which was initially observed in long-term (1-2 year) chronic studies in mice and dogs and later, upon careful re-examination of the central nervous system (CNS), also in shorter-term (4-week to 90-day) subchronic studies. Although this lesion was also observed in control animals, the increased incidence and/or severity of the lesion in test animals was clearly treatment-related and dose-related. Further investigation of this finding in a series of special studies demonstrated the same lesion could also be induced in rats. In the special studies, the following were also determined.

- Fluazinam, *per se*, was not responsible for the induction of this lesion. Evaluation of the effects of impurities present in technical grade fluazinam revealed that one single impurity, Impurity-5, was solely responsible for the induction of this lesion.
- No significant differences in susceptibility or in incidence or severity of vacuolation of the white matter of the CNS were observed between species (mice, dogs, or rats). Similarly, no significant differences were attributed to sex.
- Electron microscopy of the white matter (cerebellum) of mice treated with technical grade fluazinam indicated that treatment-related effects were confined to the myelin sheaths.

Large vacuoles were observed in the intramyelin sheaths due to the accumulation of fluid between the sheaths. The nucleus and mitochondria in the oligodendroglia were observed to remain intact, suggesting no damage to these cells.

- White matter vacuolation in the CNS was reversible. The myelin sheaths appeared to recover completely during a recovery period of up to 56 days.
- There appears to be a non-linear dose-response with a clear threshold below which no effect occurs. It was concluded that a LOAEL of 0.1 mg/kg/day and a NOAEL of 0.02 mg/kg/day for CNS effects could be established for Impurity-5.

At the current maximum concentration of Impurity-5 in technical grade fluazinam of 0.1%, the NOAEL for CNS effects of 0.02 mg/kg/day for Impurity-5 is equivalent to a NOAEL for CNS effects of 20 mg/kg/day for technical grade fluazinam. The NOAEL of 20 mg/kg/day for CNS effects for technical grade fluazinam is comparable to the NOAEL for chronic effects for technical grade fluazinam of 1.1 mg/kg/day used to establish the chronic RfD for fluazinam. Therefore, based on a consideration of all the available data and information relating to this treatment-related neurotoxic lesion, it was concluded that the chronic dietary RfD of 0.011 mg/kg/day for “all populations”, including infants and children, is protective of the CNS effects caused by the presence of Impurity-5 in technical-grade fluazinam.

In a carcinogenicity study in rats, an increased incidence of thyroid gland follicular cell tumors was observed in males. In this study, there were statistically significant positive trends for thyroid gland follicular cell adenocarcinomas and combined follicular cell adenomas/adenocarcinomas. There was also a statistically significant increase by pair-wise comparison of the high dose group (40 mg/kg/day) with the control group for combined follicular cell adenomas/adenocarcinomas. There was no treatment-related increase in tumor incidence in female rats. The highest dose level tested in this study was considered to be adequate but not excessive. It was concluded that there was some evidence that the thyroid tumors observed in the male rats in this study were treatment-related. There were insufficient data to determine whether the thyroid gland tumors may have been due to disruption of thyroid-pituitary homeostasis.

In two carcinogenicity studies in mice, increased incidences of liver (hepatocellular) tumors were observed in male mice. In one study, there were statistically significant positive trends for hepatocellular adenomas, carcinomas and combined adenomas/carcinomas. There were also statistically significant increases by pair-wise comparison of the high dose group (107 mg/kg/day) with the control group for hepatocellular adenomas, carcinomas and for combined adenomas/carcinomas. There were no treatment-related tumors observed in the female mice. The highest dose level tested in this study was considered to be adequate but not excessive. It was concluded that there was clear evidence of treatment-related increases in both benign and malignant liver tumors in the male mice in this study. In the other study, there were no statistically significant positive trends for hepatocellular adenomas, carcinomas or combined adenomas/carcinomas for the male mice. However, there was a statistically significant increase by pair-wise comparison with the control group for hepatocellular adenomas at the mid dose (377 mg/kg/day) and for combined adenomas/carcinomas at the mid dose and high dose (964 mg/kg/day). The tumorigenic response in this study did not occur in a dose-related manner. The

highest dose level tested for male mice in this study was considered to be adequate but not excessive and it was concluded that there was equivocal/some evidence for hepatocarcinogenicity in the male mice in this study because the data suggested a possible treatment-related increase in benign liver tumors. Although a statistically significant positive trend was observed for combined hepatocellular adenomas/carcinomas for the female mice in this same study, the highest dose for the female mice (1185 mg/kg/day) was considered to be excessive because there was a treatment-related increase in mortality for the female mice at this dose level. It was determined that the hepatocellular tumors observed in female mice at the high-dose level in this study occurred at an excessively toxic dose which may have resulted in indirect effects that may not have been present at lower doses.

A battery of mutagenicity assays indicated that fluazinam was not genotoxic.

Qualitative evidence of increased susceptibility of fetuses to fluazinam was demonstrated in a developmental toxicity study in rats. Increased incidences of facial/palate clefts and other rare deformities in the fetuses were observed in the presence of minimal maternal toxicity. In a developmental toxicity study in rabbits and in a 2-generation reproduction study in rats, neither quantitative nor qualitative evidence of increased susceptibility of fetuses or pups to fluazinam was observed.

In a metabolism study in rats, only 33-40% of the administered dose of radio labeled fluazinam was absorbed. Most of the administered dose was recovered in the feces (>89%). Unabsorbed parent compound represented most of the identified radioactivity in the feces. Excretion via the urine was minor (<4%). Total biliary radioactivity, however, represented 25-34% of the administered dose, indicating considerable enterohepatic circulation. Analysis of chromatograms indicated that numerous metabolites were present in the bile.

Occupational and Residential Exposure and Risk Characterization.

The product label limits use to ground application so there is a potential for exposure to fluazinam during mixing, loading, and application activities. A short-/intermediate-term exposure/risk assessment using applicable endpoints was performed. Exposure and risk for the mixer/loaders and applicators were estimated separately.

The following handler scenarios were identified for the proposed uses: (1a) open mixing/loading all liquid formulation for ground application on peanuts; (1b) open mixing/ loading all liquid formulation for ground application on potatoes; (2a) applying sprays on peanuts using a groundboom sprayer; and (2b) applying sprays on potatoes using a groundboom sprayer.

No chemical-specific handler exposure data were submitted in support of this registration. Data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 as presented in PHED Surrogate Exposure Guide (8/98) is used to assess handler exposures for regulatory actions when chemical-specific monitoring data are not available.

The handler exposure and risk were evaluated at baseline level (handlers wearing long pants, a long-sleeved shirt, no gloves, and no respirator) and mitigation controls (i.e. PPE and engineering controls) were added until the target MOE of 100 (for dermal risk), 300 (for short-term inhalation risk) or 1000 (for intermediate-term inhalation risk) was reached.

The dermal MOEs calculated for the applicator are above the target MOE of 100 at the baseline level (range from 800 to 2,400). All inhalation MOEs are above the target MOE of 1,000 at the baseline level (range from 1,300 to 6,900). However, the dermal MOEs calculated for the mixer/loader are below the target MOE of 100 at the baseline level (range from 4 to 12). Hence, an additional PPE (using “single layer with gloves” as additional control) level exposure/risk assessment for this scenario was performed. The mixer/loader MOEs evaluated at the PPE level are above the target MOE of 100 (range from 490 to 1,500). Based on the use pattern, chronic or long-term exposures are not expected for occupational handlers.

Postapplication exposures are expected. Postapplication daily exposures (mg/kg/day) were calculated using transfer coefficients (Tc), standard assumptions of 0.2 for the fraction of ai retained on foliage (F) and 0.1 for the fraction of residue that dissipates daily (D). The short-/intermediate-term dermal MOEs for post-application activities on day 0 range from 33 (for irrigation & scouting of peanuts) to 500 (for hand weeding of both crops). The MOE for irrigation and scouting of peanuts reaches to the target MOE of 100 on day 11 (MOE = 106). These MOEs could be refined if dislodgeable foliar residue (DFR) data were available. Harvest activities are conducted by fully mechanized equipment. A quantitative risk assessment was not performed.

There are no residential uses for fluazinam at this time; therefore, a risk assessment for non-occupational/residential handler and postapplication exposures was not performed.

Aggregate Exposure and Risk Characterization.

1. General Considerations.

The Agency evaluated the hazard and exposure data for fluazinam to determine the appropriate FQPA safety factors for protection of infants and children. Because of the lack of a developmental neurotoxicity study and the qualitative evidence of increased susceptibility of rat fetuses to fluazinam, it was determined that the FQPA safety factor should be retained at 10X when assessing acute dietary exposure for “females 13-50 years of age” since, in addition to the need for a developmental neurotoxicity study, increased susceptibility of rat fetuses was observed following *in utero* exposure in the rat developmental toxicity study resulting in concern for the developing fetus. It was also determined that the FQPA safety factor should be reduced to 3X when assessing exposure for “all populations” for all exposure durations (acute and chronic) since there was uncertainty due to the lack of a developmental neurotoxicity study. This study will further characterize the toxicity of fluazinam and may provide endpoints and NOAELs that could be used in risk assessments for any subpopulation/exposure duration.

For acute dietary exposure scenarios, two toxicology endpoints were selected. For “females 13-50 years of age”, the toxicology endpoint was from a developmental toxicity study in rabbits in which the developmental NOAEL was 7 mg/kg/day and the LOAEL was 12 mg/kg/day, based on increased incidence of total litter resorptions and possibly increased incidence of fetal skeletal abnormalities. Application of an Uncertainty Factor (UF) of 100 results in an acute RfD of 0.07 mg/kg/day and application of the FQPA SF of 10X to the acute RfD results in an aPAD of 0.007 mg/kg/day. For acute dietary “general population, including infants and children”, the toxicology endpoint was from an acute neurotoxicity study in rats in which the NOAEL was 50 mg/kg/day and the LOAEL was 1000 mg/kg/day, based on decreased motor activity and soft stools on the day of dosing. Application of an UF of 100 results in an acute RfD of 0.50 mg/kg/day and application of the FQPA SF of 3X to the acute RfD results in an aPAD of 0.167 mg/kg/day. For chronic dietary exposure for “all populations”, the toxicology endpoint was from a carcinogenicity study in mice in which the NOAEL was 1.1 mg/kg/day and the LOAEL was 10.7 mg/kg/day, based on liver histopathology and increased liver weight. Application of a UF of 100 results in a chronic RfD of 0.011 mg/kg/day and application of the FQPA SF of 3X to the chronic RfD results in a cPAD of 0.00367 mg/kg/day.

2. Food.

Acute and chronic dietary exposure analyses were performed using tolerance residue levels, 100% crop treated (CT) data for all commodities (Tier 1), and DEEM defaults for all processing factors. The FQPA Safety Factor has been retained for acute exposure for females 13-50 yrs old and reduced to 3X for all other population subgroups and exposures. In the acute dietary exposure analysis for females 13-50 years old, for which the FQPA safety factor was retained at 10x, the acute dietary exposure was 2% of the acute population adjusted dose (aPAD). In the acute dietary exposure analysis for the rest of the general population, for which the FQPA safety factor was reduced to 3X, the exposure occupied <1% of the aPAD. In the chronic dietary exposure analysis, for which the FQPA safety factor was reduced to 3X, the exposure occupied up to 11% of the chronic PAD, with the most highly exposed population subgroup being females 13-50 years old. These results should be viewed as conservative exposure estimates since additional refinements are possible.

3. Water.

Fluazinam appears to be relatively persistent and have low mobility. Despite the fact that fluazinam appears to undergo rapid degradation in various media, a closer inspection of the transformation products formed shows that the transformation product is structurally very similar to the parent. It was noted that the major degradates in the aerobic aquatic metabolism were structurally very similar to the parent fluazinam, and that when the amounts of such compounds are added, the trend of dissipation of total fluazinam residues is much slower than that observed taking into consideration only parent fluazinam. Since the environmental fate studies indicated that the parent compound forms transformation compounds which are similar in structure to the parent under most conditions, in addition to the EECs for fluazinam, EECs were estimated for total fluazinam residues. The models SCIGROW and GENECC were used to generate

conservative estimates of fluazinam and its degradates of concern in ground and surface waters, respectively.

For total fluazinam residues, the surface water acute (peak) value is 18.0 ppb and the chronic (average 56-day) value is 3.15 ppb. The groundwater screening concentration is 0.10 ppb. These values represent upper-bound estimates of the concentrations of total residues of fluazinam that might be found in surface water and groundwater due to the use of fluazinam at the maximum application rate.

Aggregate Risk Assessments and Risk Characterization.

The acute aggregate assessment for all population subgroups includes only food and water exposures. The acute dietary (food only) exposure to fluazinam will utilize <1 % of the aPAD for the U.S. population and 2% of the aPAD for the most highly exposed population subgroup, females 13-50 years old. Residues of fluazinam degradates are persistent with low mobility and could be found in ground and surface water. The acute exposures to fluazinam in drinking water as determined by modeling data are below the calculated acute DWLOC for all population subgroups of concern. It is concluded that exposure from fluazinam residues in food and water is not likely to exceed 100% of the acute PAD and therefore does not exceed the Agency's level of concern.

The chronic aggregate assessment for all population subgroups includes only food and water exposures, as there are no registered residential uses of fluazinam. The chronic dietary (food only) exposure to fluazinam will utilize 8% of the cPAD for the U.S. population and 11% of the cPAD for the most highly exposed population subgroup, females 13-50 years old. Residues of fluazinam degradates are persistent with low mobility and could be found in ground and surface water. There are no residential or other non-occupational uses of fluazinam, so no exposure is expected from these routes. The chronic exposures to fluazinam in drinking water as determined by modeling data are below the calculated chronic DWLOC for all population subgroups of concern. EPA does not expect the aggregate exposure to exceed 100% of the cPAD and therefore does not exceed the Agency's level of concern.

Since there are no residential uses of fluazinam, short- and intermediate-term risk assessments were not performed.

Since fluazinam has been classified as "Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential", based upon the Agency's 1999 Cancer Risk Assessment Guidelines, a cancer risk assessment was not performed.

Additional Toxicity Data Requirements:

The toxicological data base for fluazinam is adequate at this time to support the requested registration and tolerances according to Subdivision F Guideline requirements and 40 CFR § 158.690. There is high confidence in the hazard endpoints and dose-response assessments

conducted for this chemical. However, the following additional toxicology studies are being required to be performed and submitted within a reasonable period of time in order to more clearly and fully characterize the toxicity of this chemical.

- Guideline 870.3465: 28-day inhalation toxicity in rats.
- Guideline 870.6300: Developmental neurotoxicity study in rats. Test material to be technical grade fluazinam containing the maximum level of Impurity-5 permitted in the current specification for technical grade fluazinam. The protocol should be submitted to EPA for comment before the start of the study and should include full neurohistopathological examination of dams.
- Guideline 870.6200: Subchronic neurotoxicity screening battery in rats (conditional requirement). Based on a consideration of the results in the developmental neurotoxicity study in rats required above, the Agency will subsequently recommend whether a repeat of the subchronic neurotoxicity study in rats (870.6200) should also be required to support the registration of fluazinam.
- Potato processed commodity study at a higher treatment level, 5X (conditional requirement).
- Dislodgeable Foliar Residue (DFR) data to address the “11-days” for reaching the target MOE of 100 (conditional requirement).

Ecological Effects/Environmental Fate Characteristics:

1. Environmental Fate Summary:

It was concluded that fluazinam appears to degrade at moderate to low rates in aerobic soils, but it is more rapidly transformed into other compounds of similar backbone structure in high pH solutions or in aerobic or anaerobic aquatic media. The transformation products of fluazinam appear to be relatively persistent under most conditions. Fluazinam may be photolysed relatively rapidly in water, resulting in a tricyclic compound. While the parent and two transformation products, HYP A and CAP A, have relatively low mobility, indicating low potential for ground water contamination, further information on the other degradates is required in a new Terrestrial Field Dissipation Study.

a. Hydrolysis

The hydrolysis of fluazinam is pH dependent. It was relatively stable at pH 5, and hydrolyzed with half-lives of 42 and 6 days at pH's of 7 and 9, respectively. The major degradate was CAP A.

b. Photolysis

Fluazinam photolyses in aqueous solutions mainly to G-504, a tricyclic compound, and possibly one or more other unidentified products. The half-life obtained in the study was 2.5 days. The soil photolysis, on the other hand, the half-life was 22 days (compared to 69 days for

the dark control). The available data has been deemed supplemental at this time.

c. Metabolism

The metabolism of fluazinam appears to be moderate in soils (DT_{50} # 30 days) in a sandy loam soil. The calculated half-life was about 132 days, which is in agreement with the fact that after 361 days, 6.8 and 9.5% of the applied fluazinam remained intact for the ^{14}C -Pyridyl and ^{14}C -Phenyl labels, respectively. No major degradation products were observed in this study, but a major fraction (- 41%) was bound material at the end of the study (day 361).

d. Sediment/Water Systems

The aerobic aquatic and the anaerobic aquatic metabolism studies resulted in very short half-lives (#8 hours in both studies). In addition, in such studies, various metabolites were formed. All the major metabolites have structures that resemble the structure of the parent. The sum of the amount of the parent concentration plus the concentrations of the degradates (total fluazinam residues) decreases very slowly in both cases. The major degradates observed in these studies include DAPA, SDS-67200, AMPA, DCPA, and CAPA.

e. Mobility

In batch equilibrium studies, fluazinam shows low mobility in four soils tested. $K_{OC, ads}$ values ranged from 1705-2316. Similarly, an available soil column leaching study of aged fluazinam indicated low mobility of the residues of fluazinam. Less than 1% of the applied radiocarbon was found in the leachates and >80% remained at the top of the soil columns. There is mobility information for two of the metabolites of fluazinam: HYP A and CAPA. Of them, HYP A appeared to be generally more mobile (K_{OC} =620-3100, 6 soils), and CAPA appeared to be generally less mobile than the parent (K_{OC} =1289-3784, 4 soils). These two batch/equilibrium studies were conducted on sterile soils.

f. Field Dissipation

Four terrestrial field dissipation studies were submitted. Such studies were found to provide only limited supplemental information. In particular, the data about the degradates is very questionable due to poor recoveries in a storage stability study. In general, it appeared that parent fluazinam degraded moderately rapidly in studies conducted in Ephrata, Washington, Kempton, North Dakota, Porterville, California, and Monctezuma, Georgia. The dissipation half-lives ranged from 9 to 49 days.

g. Bioaccumulation

Fluazinam demonstrated potential to bioaccumulate in fish. The maximum BCFs were 348X for fillet, 1220 for whole fish, and 1850 for viscera, all of which were obtained with the phenyl label material. Residues (67%) were eliminated from the fillet during the depuration

phase (21 days).

2. Ecological Effects Summary:

a. Aquatic (Acute/Chronic Hazard Summary)

Fluazinam is considered to be very highly toxic to highly toxic to fish (freshwater and estuarine/marine) on an acute basis ($LC_{50} = 0.036 - 0.11$ ppm). Chronic freshwater NOAEC/LOAEC values were calculated at 0.0053 - 0.00069 ppm and 0.010 - 0.014 ppm, respectively, with larval survival, reduced number of spawns, and growth as the endpoints affected. Acute toxicity values for aquatic invertebrates suggest that fluazinam is highly toxic to freshwater invertebrates (*Daphnia* $EC_{50} = 0.18 - 0.22$ ppm) and very highly toxic to estuarine/marine invertebrates (oyster $EC_{50} = 0.0047$ and mysid shrimp $EC_{50} = 0.039$ ppm). Chronic toxicity to invertebrates are only represented through the *Daphnia magna* life cycle where the NOAEC was calculated at 0.068 ppm and the LOAEC at 0.140 ppm. The endpoints affected for this study were reproductive (reduced number of young per female) and growth effects. No acceptable data have been submitted to assess the chronic effects of fluazinam to estuarine/marine fish or invertebrates. An estuarine/marine fish life-stage toxicity test (Guideline 72-4a) and an estuarine/marine invertebrate life-cycle toxicity test (Guideline 72-4b) are required to fulfill these requirements.

b. Risk to Aquatic Organisms (Acute/Chronic)

The risk assessment suggests that exposure of this compound to fish (freshwater and estuarine/marine) through the proposed use patterns (peanuts and potatoes) can result in acute (restricted use and endangered species concern category) and chronic risk. Exposure to aquatic invertebrates (freshwater and estuarine/marine) from peanut use can result in acute risk (restricted use and endangered species concern category). No acute or chronic exceedences are expected for freshwater invertebrates from the potato use. Chronic exposure to estuarine/marine fish and invertebrates could not be calculated at this time because of a lack of appropriate data.

c. Terrestrial Hazard Summary

Fluazinam appears to be practically nontoxic to avian species on a subacute basis (mallard and Bobwhite quail $LC_{50} > 10,500$ ppm). Chronic toxicity data show that fluazinam exposure can result in growth reduction in young (14-day old survivors weight) with a NOAEC = 200 - 350 ppm and LOAEC = 350 - 500 ppm.

Mammalian toxicity data suggest that this compound is practically nontoxic to small mammals on an acute basis (rat LD₅₀ = 4,300 mg/kg). Reproductive effects that were based on a decreased number of implantation sites and decreased litter size were noted at an LOAEC = 500 ppm (NOAEC = 100 ppm). Acute toxicity on honeybees show that fluazinam is practically nontoxic to bees (LD₅₀ > 200 ug/bee).

d. Risk to Avian Species (Acute/Chronic)

Although acute exposure should result in minimal toxic effects to birds, the risk assessment suggests that the proposed uses can cause chronic (reduced growth in young) effects in birds. RQ values were calculated for exposure to peanuts (maximum EECs RQ = 1.0 - 1.8 and 56 day average EECs RQ = 1.1 ppm) and potatoes (maximum EECs RQ = 1.0 - 1.5 and 56 day average(RQ = 1).

e. Risk to Mammalians (Acute, Chronic)

The risk assessment suggests that the proposed uses can result in chronic risk to mammalians (herbivores and insectivores). RQ values were calculated for exposure to peanuts (maximum EECs RQ = 1.6 - 3.5 and 56 day average EECs RQ = 1.0 - 2.2) and potatoes (maximum EECs RQ = 1.0 - 1.9 and 56 day average EECs RQ = 1.4 - 3.0). Acute concerns appear to be focused on grass eating endangered mammals (RQ = 0.1)

f. Risk to Plants

The toxicity of fluazinam to terrestrial plants and vascular and nonvascular aquatic plants cannot be assessed because there are no acceptable studies with fluazinam. The assessment for nonvascular plants is incomplete in that the assessment is based on a supplemental study and additional nonvascular plant species testing is being recommended.

3. Environmental Risk Assessment:

Available data on fluazinam suggest that this compound is (parent and degradates) moderately persistent, should not leach substantially to ground water but may present concerns for transport to surface water by runoff (especially in soils with low organic content).

The risk quotient (RQ) values for fluazinam's use patterns indicate that there is minimal acute risk to birds and mammals from fluazinam exposure. However, there is the likelihood of chronic risk to these organisms. Because of this risk, endangered species concerns must also be considered. The risk assessment suggests that exposure of this compound to fish (freshwater and estuarine/marine) through the proposed use patterns can result in acute (restricted use and endangered species concern category) and chronic risk. Exposure to aquatic invertebrates (freshwater and estuarine/marine) from peanut use can result in acute risk (restricted use and

endangered species concern category). No acute or chronic exceedences are expected for freshwater invertebrates from the potato use. Chronic exposure to estuarine/marine fish and invertebrates could not be calculated at this time because of a lack of appropriate data.

The above conclusions likely represent an over estimation of the potential risk to fish and wildlife. The calculations used are based on a Tier I assessment and further refinement of the exposure analysis would result in significantly lower calculated risks. Also, the model used in the calculations is an uncertain but likely conservative predictor of fluazinam concentrations in water. The model does not take into consideration the solubility of the compound. In this case, fluazinam has a very low water solubility. When this is considered, risk concerns for aquatic exposures would be much lower than those calculated.

The estimated environmental risks posed by fluazinam, however, compare favorably with those posed by fungicides currently in the marketplace. When compared to chlorothalonil, triphenyltin hydroxide, iprodione, and captan, currently-registered compounds that have recently completed the reregistration process, fluazinam presents similar or substantially lower risks than the available alternatives. To further mitigate any risk, the registrant has agreed to the following mitigation measures: a prohibition on aerial application, the establishment of a 25-foot vegetative filter strip between aquatic areas and cultivated areas, and a prohibition on applications within 25 feet of aquatic areas. While the mitigatory relief that these measures cannot be quantified, these changes should result in a significant reduction in the estimated environmental risks, further alleviating any potential concerns.

4. Outstanding Environmental Fate and Effects Data Requirements:

- Guidelines 161-2 and 161-3: Additional data has been requested to upgrade the Photolysis in Water and Photodegradation on Soil data requirements. The additional information will refine the information about the quantitation of the parent and degradates.
- Guideline 164-1: EFED believes that the available Terrestrial Field Dissipation studies provide useful information about the parent fluazinam. However, poor recoveries for two of the transformation products upon storage stability cast doubts over the results obtained for them in the field. At this time, only one new study is required. The study should be conducted on a very typical site. The registrant must take all measurements of precaution to assure that the results are reliable. A concurrent storage stability study must be conducted and submitted to the Agency.
- Guidelines 72-4(a,b): Early Life Stage Fish and Invertebrate Life Cycle (Estuarine/Marine)
- Guideline 122-1 or 123-1: Tier I or Tier II - Terrestrial Plant Growth - Seedling Emergence and Vegetative Vigor.
- Guideline 122-2 or 123-2: Tier I or Tier II - Aquatic Plant Growth - duckweed (*Lemna gibba*), freshwater green algae (*Selenastrum capricornutum*), marine diatom (*Skeletonema costatum*), blue-green algae (*Anabaena flos-aquae*), and a freshwater diatom.

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