United States
Environmental Protection
Agency

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

Pesticide Fact Sheet

Name of Chemical: Flufenacet
Reason for Issuance: Conditional Registration
Date Issued: April 1998

DESCRIPTION OF CHEMICAL

Generic Name:	N-(4-fluorophenyl)-N-(1-methylethyl)-2-[[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]oxy]acetamide
Common Name:	flufenacet [proposed]
Trade Names:	FOE 4053 Technical Herbicide FOE 5043 DF Herbicide Axiom DF Herbicide
EPA Chemical Code:	121903
Chemical Abstracts Service (CAS) Number:	142459-58-3
Year of Initial Registration:	1998
Pesticide Type:	Herbicide
Chemical Family:	thiadiazole
U.S. and Foreign Producers:	Bayer Corporation 8400 Hawthorn Road P.O. Box 4913 Kansas City, MO 64120-0013

USE PATTERNS AND FORMULATIONS

Flufenacet is applied to the soil surface or incorporated preemergence in field corn, corn grown for silage, or soybeans to control certain annual grasses and broadleaf weeds. It will be formulated as a 60% dry flowable [FOE 5043 DF Herbicide] and 54.4% dry flowable with 13.6% metribuzin [Axiom DF Herbicide]. FOE 5043 DF Herbicide will be applied by ground only at 12 to 21 ounces per acre to corn and 7 to 12 ounces per acre to soybeans. Axiom DF Herbicide will be applied by ground only at 13 to 23 ounces per acre to corn and 7 to 13 ounces per acre to soybeans. The maximum use rate is 0.78 lb flufenacet per acre per year.

FOE 5043 Technical is a 95% manufacturing use product.

SCIENCE FINDINGS

SUMMARY SCIENCE STATEMENTS

Adequate chemistry, toxicological, ecological effects, and environmental fate data have been submitted and reviewed to support the conditional registration of FOE 5043 DF Herbicide and Axiom DF Herbicide on corn and soybeans and FOE 5043 Technical as manufacturing use pesticide until April 30, 2003.

The technical FOE 5043 product is classified in toxicity category III [CAUTION] based on acute dermal toxicity and acute dermal toxicity studies. The FOE 5043 DF formulated end use product is classified in toxicity category III [CAUTION] based on the acute oral toxicity and is a skin sensitizer. The Axiom DF formulated end use product is classified in toxicity category III [CAUTION] based on the acute oral toxicity, acute dermal toxicity and acute inhalation toxicity, and is a skin sensitizer.

Flufenacet was shown to be negative in assays for gene mutation in bacteria and mammalian cells, for cytogenetics in mammalian cells and in a mouse micronucleus assay, and for unscheduled DNA synthesis.

Developmental toxicity studies in the rat and rabbit demonstrated developmental effects at or above the maternal

effects level. In the rat the No Observed Effect Level (NOEL) for maternal and developmental toxicity was 25 milligrams/kilogram(mg/kg)/day. In the rabbit, the NOEL for maternal toxicity was 5 mg/kg/day and the NOEL for developmental toxicity was 25 mg/kg/day. In a two-generation rat reproduction study, the parental systemic NOEL was 1.4 mg/kg/day in males and 1.5 mg/kg/day in female and the reproductive NOEL was 1.3 mg/kg/day.

In a 84-day rat feeding study the NOEL was less than 6.0 mg/kg/day for males and was 7.2 mg/kg/day for females. In a 13-week mouse feeding study the NOEL was 18.2 mg/kg/day for males and was 24.5 mg/kg/day for females. In a 13-week dog dietary study the NOEL was 1.70 mg/kg/day for males and 1.67 mg/kg/day for females. In a 21-day rat dermal study the dermal irritation NOEL was 1000 mg/kg/day for males and females and the Systemic NOEL was 20 mg/kg/day for males and 150 mg/kg/day for females. In a 1-year dog chronic feeding study the NOEL was 1.29 mg/kg/day in males and 1.14 mg/kg/day in females and the Lowest Observed Effect Level (LOEL) was 27.75 mg/kg/day in males and 26.82 mg/kg/day in females based on increased alkaline phosphatase, kidney, and liver weight in both sexes, increased cholesterol in males, decreased T3, T4 and ALT in both sexes, and increased incidence of microscopic lesions in the brain, eye, kidney, spinal cord, sciatic nerve and liver.

In the rat chronic feeding / carcinogenicity study the NOEL was less than 1.2 mg/kg/day in males and less than 1.5 mg/kg/day in females and the LOEL was 1.2 mg/kg/day in males and 1.5 mg/kg/day in females based on methemoglobinemia and multi-organ effects in blood, kidney, spleen, heart, and uterus. Under experimental conditions the treatment did not alter the spontaneous tumor profile. In the mouse carcinogenicity study the NOEL was less than 7.4 mg/kg/day in males and was 9.4 mg/kg/day for females and the LOEL was 7.4 mg/kg/day for males and was 38.4 mg/kg/day for females based on cataract incidence and severity. There was no evidence of carcinogenicity for

flufenacet in this study.

Flufenacet is classified as a "Not Likely" carcinogen based on the lack of carcinogenicity in rats and mice.

In an acute rat neurotoxicity study the NOEL was less than 75 mg/kg and the LOEL was 75 mg/kg/day based on decreased motor activity in males. In a rat subchronic neurotoxicity study the NOEL was 7.3 mg/kg/day in males and 8.4 mg/kg/day in females and the LOEL was 38.1 mg/kg/day in males and 42.6 mg/kg/day in females based on microscopic lesions in the cerebellum/medulla and spinal cords.

A rat metabolism study showed that radio-labeled flufenacet was rapidly absorbed and metabolized by both sexes. Urine was the major route of excretion at all dose levels and smaller amounts were excreted via the feces.

A 55-day dog study subcutaneous via mini-pump with Thiadone [flufenacet metabolite] supports the hypothesis that limitations in glutathione interdependent pathways and antioxidant stress result in metabolic lesions in the brain and heart following flufenacet exposure. Non-guideline studies provide evidence supporting the hypothesis of an extra thyroidal mechanism to explain alterations in circulating thyroid hormone concentrations.

The Reference Dose (RfD) for flufenacet is 0.004 mg/kg/day. This value is based on the systemic LOEL of 1.2 mg/kg/day in the rat chronic feeding / carcinogenicity study with a 300-fold safety factor to account for interspecies extrapolation (10 x), for intraspecies variability (10 x), and because of the lack of a NOEL in the rat chronic feeding / carcinogenicity study (3 x).

A DRES chronic exposure analysis was conducted using tolerance levels and percent crop treated information based on maximum possible acres treated by this new herbicide to estimate the Anticipated Maximum Residue Contribution (ARC) for the general population and 22 subgroups. The chronic analysis showed that

exposure from the tolerances in or on corn and soybeans for non-nursing infants less than 1 year old (the subgroup with the highest exposure) would be 6.5% of the Reference Dose (RfD). The exposure for the general U.S. population would be 2.6% of the RfD.

An acute dietary risk assessment is required for flufenacet and its metabolites containing the 4-fluoro-N-methylethyl benzenamine moiety based on the LOEL of 75.0 mg/kg/day from the acute neurotoxicity study. The calculated MOE's for acute risk of flufenacet and its metabolites for the General U. S. population was 50,000 and for the most exposed subgroups, infants (< 1 year) and Children (1-6 years), the MOE was 37,500. These figures are well are above 900 or below which would be EPA's level of concern based on interspecies extrapolation (10 x) and intraspecies variability (10 x), to protect infants and children (3x), and because of the lack of a NOEL in the acute neurotoxicity study (3 x).

The drinking water level of concerns (DWLOCs) for acute exposure to flufenacet in drinking water calculated for U.S population was 2.87 ppm and for children (1 - 6 years old) was 813 ppb. The acute drinking water estimated concentration based on ground water monitoring data is 0.18 ppb and based on surface water model data is 17.0 ppb. The calculated acute aggregate exposures for flufenacet in food and water are well below EPA's level of concern.

The drinking water level of concerns (DWLOCs) for chronic exposure to flufenacet in drinking water calculated for U.S. population was 136 ppb and for children (1 - 6 years old) was 37.7 ppb. The chronic drinking water estimated concentration based on ground water monitoring data is 0.03 ppb and based on surface water model data it is 14.2 ppb.

Tolerances are established for the combined residues of the herbicide, N-(4-fluorophenyl)-N-(1-methylethyl)-2-[[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]oxy]acetamide and its

metabolites containing the 4-fluoro-N-methylethyl benzenamine moiety in or on field corn grain at 0.05 parts per million (ppm), field corn forage at 0.4 ppm, field corn stover at 0.4 ppm, and soybean seed at 0.1 ppm.

EPA is currently developing an screening, testing program and a priority setting scheme for endocrine disrupters. Based on the toxicity findings, flufenacet should be considered as a candidate for evaluation as an endocrine disrupter when the criteria are established.

Flufenacet is stable to hydrolysis. In laboratory and on soil surfaces flufenacet did not photolyze during 10.5 continuous days of irradiation. The calculated half-lives were 248 days for the irradiated samples and 167 days for the dark control samples.

Flufenacet is moderately stable in the aerobic soil environment tested. Flufenacet was relatively stable in the anaerobic soil environment tested. Flufenacet was stable in a pond water/soil system incubated under anaerobic conditions for approximately 90 days.

Flufenacet is very mobile to mobile in sand, loamy sand, clay loam, silt loam, and sandy loam soils. Flufenacet degradates are very mobile to mobile in sand, sandy loam, silty loam, and clay loam soils. In column leaching study aged flufenacet was shown to be moderately to very mobile in sand, sandy loam, silt loam and clay loam soils.

Flufenacet residues did not accumulate in Bluegill Sunfish exposed in a flow-through system for 28 days.

In field dissipation studies in North Carolina and Wisconsin, there was no evidence that parent flufenacet leached below 5 inches. The last detection of parent compound was at 135 and 369 days after application. In the North Carolina study, at day 5, the thiadone degradate was recovered at 0.06 and 0.02 ppm in the 6 to 12 and the 12 to 18 inch depths, respectively.

Two voluntary small-scale prospective monitoring studies were conducted for FOE 5043 Herbicide in Nebraska and Iowa. No flufenacet residues (parent or degradates) were detected in groundwater in the Iowa study. In the Nebraska studies flufenacet degradates were detected in groundwater at a maximum concentration of 0.90 ppb (0.66 ppm sulfonic acid, 0.18 ppb thiadone, 0.06 ppb oxalate). Analytical results indicate that the maximum pesticide residues were decreasing after day 480 in shallow wells, In the deep wells, no significant change has been seen in total residue concentrations since day 479 (analysis are available up to Day 692). Considering that flufenacet residues are not likely to degrade under anaerobic conditions, it is likely that these residue will increase in deep wells in the future. A label Groundwater and Surface Water Application Advisories are required. Two prospective groundwater monitoring studies in vulnerable sites and surface water monitoring studies are a condition of registration. Automatic cancellation triggers are a condition of registration if monitoring detects water residue levels at the DWLOC.

Flufenacet was shown to be slightly toxic to birds, slightly toxic to small mammals, practically non-toxic to bees and other beneficial insects, and moderately toxic to fresh water, estuarine, and marine fish and invertebrates. Flufenacet is highly toxic to terrestrial, semi-aquatic, and aquatic plants. Adverse effects to surrounding plant communities may occur if flufenacet moves off the treatment site. Endangered mammals and plants also may be affected. Environmental hazard precautionary statements are required. Bayer Corporation will conduct a product stewardship program to assist growers in reducing the herbicide's impact on non-target organisms.

CHEMICAL CHARACTERISTICS

Empirical Formula:	$C_{14}H_{12}O_2N_3SF_4$
Molecular Weight:	362
Color:	tan
Physical State:	solid

Odor:	mercaptan-like odor
Melting Point:	75.5 - 77.0°C
Density at (20°C):	1.312 g/mL
Solubility g/liter:	water - 56 mg/L acetone - >200 g/L acetonitrile - >200 g/L dichloromethane - >200 g/L dimethylformamide - >200 g/ml dimethylsulfoxide - >200 g/L 2-propanol - 170 g/L n-hexane - 8.7 g/L 1-octanol - 88 g/L polyethylene glycol - 74 g/L toluene - >200 g/L
Vapor Pressure:	2×10^{-6} h Pa at 25° C
Dissociation Constant:	Does not dissociate in water
Octanol/Water partition coefficient:	P_{ow} = 1600 at 24° C Log P_{ow} = 3.20
pH:	4.49 (approx 1% aqueous slurry)
Stability:	Stable at normal warehouse temperatures. Corroded tinplate, steel and brass. Did not corrode aluminum and stainless steel.

TOXICOLOGY CHARACTERISTICS

FOE 5043 DF Herbicide
(End-Use Product)

Acute Oral Toxicity (rats):	LD50 Males 1365 mg/kg LD50 Females 371 mg/kg
Toxicity Category:	III (Males) II (Females)
Acute Dermal Toxicity (rabbits):	LD50 > 5000 mg/kg
Toxicity Category:	IV
Acute Inhalation Toxicity (rats):	LC50 > 3.12 mg/l
Toxicity Category:	IV
Primary Eye Irritation (rabbits):	Irritation of iris and conjunctiva resolved in 48 hours
Toxicity Category:	IV
Primary Skin Irritation (rabbits):	Non-irritant
Toxicity Category:	IV

Dermal Sensitization (guinea pigs):	Weak Dermal Sensitizer

Axiom DF Herbicide
(End-Use Product)

Acute Oral Toxicity (rats):	LD50 Males 2347 mg/kg LD50 Females 2072 mg/kg
Toxicity Category:	III
Acute Dermal Toxicity (rabbits):	LD50 > 2000 mg/kg
Toxicity Category:	III
Acute Inhalation Toxicity (rats):	LC50 > 0.977 mg/l
Toxicity Category:	III
Primary Eye Irritation (rabbits):	Mild irritation of conjunctiva resolved by 72 hours
Toxicity Category:	IV
Primary Skin Irritation (rabbits):	Non-irritant
Toxicity	

Category:	IV
Dermal Sensitization (guinea pigs):	Weak Dermal Sensitizer

FOE 5043 Technical
(manufacturing use product)

Acute Oral Toxicity (rats):	LD50 Males 1617 mg/kg LD50 Females 589 mg/kg
Toxicity Category:	III
Acute Oral Toxicity (mice):	LD50 Males 1331 mg/kg LD50 Females 1756 mg/kg
Toxicity Category:	III

Acute Dermal Toxicity (rabbits):	LD50 > 2000 mg/kg
Toxicity Category:	III
Acute Inhalation Toxicity (rats):	LC50 > 3.74 mg/L
Toxicity Category:	IV
Primary Eye Irritation (rabbits):	Non-irritant
Toxicity Category:	IV
Primary Skin Irritation (rabbits):	Non-irritant
Toxicity Category:	IV
Dermal Sensitization (Buehler test) (guinea pigs):	Non-sensitizer
Dermal Sensitization (Maximization test) (guinea pigs):	Skin Sensitizer
84-day dietary (rats):	NOEL < 100 ppm [<6.0 mg/kg/day males] NOEL = 100 ppm [7.2 mg/kg/day females]

	LOEL = 100 ppm [6.8 mg/kg/day] for males based on suppression of thyroxine (T4) level. LOEL = 400 ppm [28.8 mg/kg/day] for females based on hematology and clinical chemistry findings.
13-week dietary (mice):	NOEL = 100 ppm [18.2 mg/kg/day males and 24.5 mg/kg/day females] LOEL = 200 ppm [64.2 mg/kg/day for males and 91.3 mg/kg/day for females] based on histopathology of the liver, spleen and thyroid.
13-week dietary (dog):	NOEL = 50 ppm [1.70 mg/kg/day males and 1.67 mg/kg/day females] LOEL = 200 ppm [6.90 mg/kg/day for males and 7.20 mg/kg/day for females] based on evidence that the biotransformation capacity of the liver has been exceeded, (as indicated by increases in LDH, liver weight, ALK and hepatomegaly), globulin and spleen pigment in females, decreased T4 and ALT values in both sexes, decreased albumin in males, and decreased serum glucose in females.
21-day dermal (rats):	Dermal Irritation NOEL = 1000 mg/kg/day (males and females) Systemic NOEL = 20 mg/kg/day (males) Systemic NOEL = 150 mg/kg/day (females) Systemic LOEL = 150 mg/kg/day for males and 1000 mg/kg/day for females based on clinical chemistry data (decreased T4 and FT4 levels in both sexes) and centrilobular hepatocytomegaly in females.
Developmental	

Toxicity (rabbit):	Maternal NOEL = 5 mg/kg/day Maternal LOEL = 25 mg/kg/day based on histopathological finds in the liver. Developmental NOEL = 25 mg/kg/day Developmental LOEL = 125 mg/kg/day based on increased skeletal variations.
Developmental Toxicity (rat):	Maternal NOEL = 25 mg/kg/day Maternal LOEL = 125 mg/kg/day based on decreased body weight gain initially. Developmental NOEL = 25 mg/kg/day Developmental LOEL = 125 mg/kg/day based on decreased fetal body weight, delayed development [mainly delays in ossification in the skull, vertebrae, sternebrae, and appendages], and an increase in the incidence of extra ribs.
Two Generation Reproduction (rat):	Parental Systemic NOEL = 20 ppm [1.4 mg/kg/day in males and 1.5 mg/kg/day in females] Parental Systemic LOEL = 100 ppm [7.4 mg/kg/day in males and 8.2 mg/kg/day in females] based on increased liver weight in F1 females and hepatocytomegaly in F1 males. Reproductive NOEL = 20 ppm [1.3 mg/kg/day] Reproductive LOEL = 100 ppm [6.9 mg/kg/day] based on increased pup death in early lactation (including cannibalism) for F1 litters and the same effects in both F1 and F2 pups at the high dose level of 500 ppm [37.2 mg/kg/day in F1 males and 41.5 mg/kg/day in F1 females, respectively].
1 Year Chronic	

Feeding (dog):	NOEL = 40 ppm [1.29 mg/kg/day in males and 1.14 mg/kg/day in females] LOEL = 800 ppm [27.75 mg/kg/day in males and 26.82 mg/kg/day in females] based on increased alkaline phosphatase, kidney, and liver weight in both sexes, increased cholesterol in males, decreased T3, T4 and ALT values in both sexes, and increased incidence of microscopic lesions in the brain [axonal degeneration], eye [vacuolization of the ciliary body epithelium], kidney [hyperplasia of the epithelial cells], spinal cord [axonal degeneration], sciatic nerve [axonal degeneration] and liver [hepatocytomegaly].
Chronic Feeding/ Carcinogenicity (rat):	NOEL < 25 ppm [1.2 mg/kg/day in males and 1.5 mg/kg/day in females]. LOEL = 25 ppm [1.2 mg/kg/day in males and 1.5 mg/kg/day in females] based on methemoglobinemia and multi-organ effects in blood, kidney, spleen, heart, and uterus. Under experimental conditions the treatment did not alter the spontaneous tumor profile.
Carcinogenicity (mouse):	NOEL < 50 ppm [7.4 mg/kg/day] in males NOEL = 50 ppm [9.4 mg/kg/day] for females LOEL = 50 ppm [7.4 mg/kg/day] for males, and LOEL = 200 [38.4 mg/kg/day] for females based on cataract incidence and severity. There was no evidence of carcinogenicity for flufenacet in this study.
Carcinogenicity:	According to the new proposed guidelines for Carcinogen Risk Assessment (April, 1996), the appropriate descriptor for human carcinogenic

potential of flufenacet is "Not Likely" based on the lack of carcinogenicity in rats and mice.

Acute Neurotoxicity (rat): NOEL < 75 mg/kg
LOEL = 75 mg/kg/day based on decreased motor activity in males

Subchronic Neurotoxicity (rat): NOEL = 120 ppm [7.30 mg/kg/day in males and 8.4 mg/kg/day in females]
LOEL = 600 ppm [38.1 mg/kg/day in males and 42.6 mg/kg/day in females] based on microscopic lesions (axonal swelling in the cerebellum / medulla and spinal cords).

Mutagenicity: Gene mutation/*In vitro* assay in bacteria flufenacet was negative with and without activation. Gene mutation/*In vitro* assay in mammalian cells chinese hamster lung fibroblasts cells flufenacet was negative with and without activation. Cytogenetics/*In vitro* assay in mammalian cells chinese hamster ovary cells flufenacet was negative with and without activation. Cytogenetics/*In vivo* mouse micronucleus assay there was no evidence of either a clastogenic or mutagenic effect. *In vitro* unscheduled DNA synthesis assay in primary rat hepatocytes flufenacet was negative for inducing genotoxic effects.

Metabolism: A rat metabolism study showed that radio-labeled flufenacet was rapidly absorbed and metabolized by both sexes. Urine was the major route of excretion at all dose levels and smaller amounts were excreted via the feces. A maximum of 7% of administered dose

was found in the tissue and residual carcass. 39 metabolites were detected in excreta and 23 were positively identified.

Special Studies: In a 55-day dog study subcutaneous via mini-pump with Thiadone [flufenacet metabolite] support the hypothesis that limitations in glutathione interdependent pathways and antioxidant stress result in metabolic lesions in the brain and heart following flufenacet exposure. Non guideline studies provide evidence supporting hypothesis of an extra thyroidal mechanism to explain alterations in circulating thyroid hormone concentrations.

ECOLOGICAL CHARACTERISTICS

Avian Acute Toxicity:

Bobwhite Quail: LD_{50} = 1608 mg/kg

Avian Dietary Toxicity:

Bobwhite Quail: 5-day LC_{50} > 5317 ppm
Mallard Duck: 5-day LC_{50} > 4970 ppm

Avian Reproduction:

Bobwhite Quail NOEL = 441 ppm
LOEL = 1890 ppm based on number of 14-day hatchlings, eggs cracked, hatchling weight
Mallard Duck: NOEL = 89 ppm
LOEL = 211 ppm based on number of 14-day hatchlings

Freshwater Fish Acute Toxicity:

Bluegill Sunfish LC_{50} = 2.4 ppm
(second study) LC_{50} = 2.26 ppm
Rainbow Trout: LC_{50} = 3.49 ppm
(second study) LC_{50} = 5.84 ppm

Fish Early Life-Stage Toxicity under Flow-through Conditions:

Rainbow Trout	NOEC* = 0.179 ppm *No Observed Effect Concentration LOEC* = 0.334 ppm based on length at post hatch days 33 and 64 *Lowest Observed Effect Concentration MATC* = 0.245 ppm *Maximum Allowable Toxicant Concentration

Freshwater Invertebrate Toxicity:

Daphnia magna	EC50 = 30.9 ppm (A supplemental study)
Hyalella azteca	EC50 = 2.80 ppm

Freshwater Invertebrate Life-Cycle Toxicity:

Daphnia magna	NOEC = 6.3 ppm LOEC = 12.8 ppm based on number of neonate/reproductive day and time to first brood MATC = 9.0 ppm

Estuarine and Marine Organisms Acute Toxicity:

Eastern Oyster Shell deposition	EC50 = 12.6 ppm
Sheepshead Minnow	LC50 = 3.38 ppm
Mysid Shrimp	LC50 = 2.72 ppm

Estuarine / Marine Invertebrate Life-Cycle Toxicity:

Mysid Shrimp	NOEC = 0.012 ppm LOEC = 0.022 ppm based on growth, larval survival and young/female/reproductive day MATC = 0.016 ppm (Supplemental Study)

Mysid Shrimp	NOEC = 0.05 ppm LOEC = 0.10 ppm based on growth, larval survival and young/female/reproductive day MATC = 0.07 ppm (Supplemental Study)

Non-Target Insects Toxicity:

Honey Bee Acute Contact	LD50 > 25 µg ai/bee

Seedling Emergence and Vegetative Vigor for Flufenacet Technical (Tier II)

Seedling Emergence:

Monocot - Corn	EC_{25} = 0.20 (lb ai/acre) - shoot dry weight
Monocot - Onion	EC_{25} = 0.27 (lb ai/acre) - shoot dry weight
Monocot - Sorghum	EC_{25} = 0.006 (lb ai/acre) - shoot dry weight
Monocot - wheat	EC_{25} = 0.015 (lb ai/acre) - shoot dry weight
Dicot - Turnip	EC_{25} = 0.082 (lb ai/acre) - shoot dry weight
Dicot - Soybean	EC_{25} = 0.075 (lb ai/acre) - shoot dry weight
Dicot - Cotton	EC_{25} = 0.260 (lb ai/acre) - shoot dry weight
Dicot - Cucumber	EC_{25} = 0.132 (lb ai/acre) - shoot dry weight
Dicot - Sunflower	EC_{25} = 0.41 (lb ai/acre) - shoot height
Dicot - Tomato	EC_{25} = 0.022 (lb ai/acre) - shoot dry weight

Vegetative Vigor

Monocot - Corn	EC_{25} = 0.30 (lb ai/acre) - shoot height

Monocot - Onion	EC_{25} = 0.30 (lb ai/acre) - shoot dry weight
Monocot - Sorghum	EC_{25} = 0.017 (lb ai/acre) - shoot dry weight
Monocot - wheat	EC_{25} = 0.034 (lb ai/acre) - shoot dry weight
Dicot - Turnip	EC_{25} = 0.082 (lb ai/acre) - shoot dry weight
Dicot - Soybean	EC_{25} = 0.074 (lb ai/acre) - shoot dry weight
Dicot - Cotton	EC_{25} = 0.18 (lb ai/acre) - shoot dry weight
Dicot - Cucumber	EC_{25} = 0.052 (lb ai/acre) - shoot dry weight
Dicot - Sunflower	EC_{25} = 0.22 (lb ai/acre) - shoot height
Dicot - Tomato	EC_{25} = 0.16 (lb ai/acre) - shoot dry weight

Nontarget Aquatic Plant Toxicity (Tier II):

Vascular Plants	
Duckweed	
Lemna gibba	EC_{50} = 0.00245 ppm
Nonvascular Plants	
Green algae	
Kirchneria subcapitata	EC_{50} = 0.00454 ppm
(Second study)	EC_{50} = 0.0029 ppm
Marine diatom	
Skeletonema costatum	EC_{50} = 0.0144 ppm
(Second study)	EC_{50} = 0.005 ppm
Freshwater diatom	
Navicula pelliculosa	EC_{50} = 6.08 ppm
(Second study)	EC_{50} = 3.8 ppm

Blue-green algae
Anabaena
flos-aquae EC_{50} = 34 ppm

Flufenacet was shown to be slightly toxic to birds, slightly toxic to small mammals, practically non-toxic to bees and other beneficial insects, and moderately toxic to fresh water, estuarine, and marine fish and invertebrates. For terrestrial plants, tomato is the most sensitive dicot and wheat and sorghum are the most sensitive monocots and cucumber the most sensitive and sorghum the most sensitive monocot in the vegetative vigor tests. For aquatic plants, green algae was the most sensitive nonvascular species and duckweed the most sensitive vascular species.

The primary risk resulting from the application of flufenacet on corn and soybean growing areas is bird, mammal, reptile and terrestrial-phase amphibian reproductive and chronic toxic effects. Terrestrial vertebrate chronic levels of concern are exceeded for the registered single maximum broadcast-sprayed, soil-incorporated and band-applied application rates of flufenacet. Wild mammal acute restricted use and endangered species levels of concern are also exceeded at the proposed maximum single broadcast and soil-incorporated registered application rates. Therefore, endangered herbivores and insectivores may be acutely affected. Because flufenacet is highly toxic to terrestrial, semi-aquatic and aquatic plants, endangered plants and plant communities surrounding the treatment site may be acutely affected at registered application rates. As a result, Bayer Corporation will employ an educational program to instruct growers, certified crop advisors and applicators, on best management practices to minimize the impact of flufenacet to endangered species, terrestrial vertebrates, and surrounding plant communities. In addition, Bayer is participating in the Endangered Species Task Force that is gathering information on the locations of all endangered species relative to areas used for agriculture.

To reduce the risk to non-target plants the following label statements are required on the label:

Do not apply when environmental conditions may favor drift to non-target sites. Do not apply aerially.

The following statement must appear in the Environmental Hazards section of the label:

> Do not apply directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. Do not contaminate water by disposal of waste waters.

ENVIRONMENTAL CHARACTERISTICS

Flufenacet is stable to hydrolysis at pH 5, 7 and 9. Flufenacet did not photolyze during 10.5 continuous days of irradiation. On soil surfaces, flufenacet did not photolyze during 10.5 continuous day of irradiation. Calculated half-lives were 248 days for the irradiated samples and 167 days for the dark control samples.

Flufenacet is moderately stable in the aerobic soil environment. The initial half-life was calculated 33.8 days. The second degradation half-life was calculated as greater than or equal to one year. Flufenacet was relatively stable in the anaerobic soil environment tested. The initial half-life was calculated as 62.4 days from the aerobic incubation phase while the anaerobic half-life was 240 days. Flufenacet was stable in a pond water/soil system incubated under anaerobic conditions for approximately 90 days; the calculated half-life was 492 days.

Flufenacet is very mobile to mobile in sand, loamy sand, clay loam, silt loam, and sandy loam soils. Flufenacet degradates are very mobile to mobile in sand, sandy loam, silty loam, and clay loam soils. In column leaching study aged flufenacet was shown to be moderately to very mobile in sand, sandy loam, silt loam and clay loam soils.

Flufenacet residues did not accumulate in Bluegill Sunfish exposed in a flow-through system for 28 days.

In field dissipations studies in North Carolina and Wisconsin, there was no evidence that parent flufenacet leached below 5 inches. The last detection of parent compound was at 135 and 369 days after application. In the North Carolina study, at day 5, the thiadone degradate was recovered at 0.06 and 0.02 ppm in the

6 to 12 and the 12 to 18 inch depths, respectively.

Two voluntary small-scale prospective monitoring studies were conducted for FOE 5043 Herbicide in Nebraska and Iowa. No flufenacet residues (parent or degradates) were detected in groundwater in the Iowa study. In the Nebraska study flufenacet degradates were detected in groundwater at a maximum concentration of 0.90 ppb (0.66 ppm sulfonic acid, 0.18 ppb thiadone, 0.06 ppb oxalate). Analytical results indicate that the maximum pesticide residues were decreasing after day 480 in shallow wells. In the deep wells, no significant change has been seen in total residue concentrations since day 479 (analysis are available up to Day 692). Considering that flufenacet residues are not likely to degraded under anaerobic conditions, it is likely that these residue will increase in deep wells in the future. The drinking water estimated concentrations (DWECs) for groundwater (parent flufenacet and degradate thiadone) calculated from the monitoring data would be 0.18 ppb for acute and 0.03 ppb for chronic concentrations.

The DWECs for surface water based on the computer models PRZM 2.3 and EXAMS 2.97.5 were calculated to be 17.0 ppb for the acute concentration and 14.2 ppb for chronic concentration (parent flufenacet and degradate thiadone)

Due to concerns about the mobility and persistence of flufenacet and degradate thiadone in the subsurface and ground water, and surface water the following label statements are required:

Groundwater Advisory

> This chemical is known to leach through soil into ground water under certain conditions as result of label use. The use of this chemical in areas where soils are permeable particularly where the water table is shallow, may result in ground-water contamination.

Surface Water Advisory

This chemical has properties that may result in surface water contamination via dissolved runoff and/or erosion.

Under some conditions, this chemical, and/or its transformation products, may have a high potential for runoff into surface water (primarily via dissolution in runoff water) for several weeks post-application. Vulnerable Conditions include poorly draining or wet soils with readily visible slopes toward adjacent surface waters, frequently flooded area, areas over-laying extremely shallow ground water, areas with in-field canals or ditches that drain to surface-water, areas not separated or adjacent surface waters with vegetated filter strips, and areas over-laying tile drainage systems that drain to surface water.

Proper Handling Instructions

This product may not be mixed or loaded within 50 feet of any wells (including abandoned wells and drainage wells), sink holes, perennial or intermittent streams and rivers, and natural or impounded lakes and reservoirs. This setback does not apply to properly capped or plugged abandoned wells and does not apply to impervious pad or properly diked mixing/loading areas.

Operations that involve, mixing, loading, rinsing, or washing this product into or from pesticide handling or application equipment or contained within 50 feet of any well are prohibited unless conducted on an imperious pad constructed to withstand the weight of the heaviest load that may be positioned on or moved across the pad. Such a pad shall be designed and maintained to contain any product spills or equipment leaks, container or equipment rinse or washwater, and rainwater that may fall on the pad. Surface water shall not be allowed either flow over or from the pad, which means the pad must be self contained. The pad shall be sloped to facilitate material removal. An unroofed pad shall be of sufficient capacity to contain at a minimum 110% of the capacity of the largest pesticide container or application equipment on the pad. A pad that is covered by a roof of

sufficient size to completely exclude precipitation from contact with the pad shall have a minimum containment capacity of 100% of the capacity of the largest pesticide container or application equipment on the pad. Containment capacities as described above shall be maintained at all times. The above specific minimum containment capacities do not apply to vehicles when delivering pesticide shipments to the mixing/loading site. States may have in effect additional requirements regarding wellhead setbacks and operational containment.

Do not apply this product through any type of irrigation system.

Do not use flood irrigation to apply or incorporate this product.

Product must be used in a manner which will prevent back siphoning in wells, spills or improper disposal of excess pesticide, spray mixtures or rinsates.

TOLERANCE ASSESSMENT

Tolerances are established for the combined residues of the herbicide, N-(4-fluorophenyl)-N-(1-methylethyl)-2-[[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]oxy]acetamide and its metabolites containing the 4-fluoro-N-methylethyl benzenamine moiety in or on field corn grain at 0.05 parts per million (ppm), field corn forage at 0.4 ppm, field corn stover at 0.4 ppm, and soybean seed at 0.1 ppm.

AGGREGATE EXPOSURES

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

1. From Food and Feed Uses

The Reference Dose (RfD) for flufenacet is 0.004 mg/kg/day. This value is based on the systemic LOEL of 1.2 mg/kg/day in the rat chronic feeding study with a 300-fold safety factor to account for interspecies extrapolation (10 x), for intraspecies variability (10 x), and because of the lack of a NOEL in the rat chronic feeding / carcinogenicity study (3 x).

A DRES chronic exposure analysis was conducted using tolerance levels and percent crop treated information based on maximum possible acres treated by this new herbicide to estimate the Theoretical Maximum Residue Contribution (TMRC) for the general population and 22 subgroups. The chronic analysis showed that exposure from the tolerances in or on corn and soybeans for non-nursing infants less than 1 year old (the subgroup with the highest exposure) would be 64.8% of the Reference Dose (RfD). The exposure for the general U.S. population would be 25.6% of the RfD.

An acute dietary risk assessment is required for flufenacet and its metabolites containing the 4-fluoro-N-methylethyl benzenamine moiety based on the LOEL of 75.0 mg/kg/day from the acute neurotoxicity study. The acute analysis estimates the distribution of single-day exposures for the overall U.S. population and certain subgroups. The Margin of Exposure (MOE) is a measure of how closely the exposure comes to the LOEL and is calculated as a ratio of the LOEL to the exposure. The calculated MOE's for acute risk of flufenacet and its metabolites for the General U. S.population was 50,000 and for the most exposed subgroups, infants (< 1 year) and Children (1-6 years), the MOE was 37,500. These figures are above the MOE of 900 or below which is the level of concern based on interspecies extrapolation (10 x), intraspecies variability (10 x), lack of a NOEL in the acute neurotoxicity study (3 x), and to protect infants and children (3 x).

2. From Potable Water

The drinking water level of concerns (DWLOCs) for acute exposure to flufenacet in drinking water calculated for U.S population was 2.87 ppm and for children (1 - 6 years old) was

813 ppb. These figures are based on the acute dietary food exposures subtracted from the ratio of the acute LOEL to the acceptable MOE for aggregate exposure to obtain the acceptable acute exposure to flufenacet in drinking water. The acute drinking water estimated concentration based on ground water monitoring data is 0.18 ppb and based on surface water model data is 17.0 ppb. The calculated acute aggregate exposures for flufenacet in food and water are well below EPA's level of concern.

The drinking water level of concerns (DWLOCs) for chronic exposure to flufenacet in drinking water calculated for U.S. population was 136 ppb and for children (1 - 6 years old) was 37.7 ppb. These figures are based on the chronic dietary food exposures subtracted from the Reference Dose (RfD) to obtain the acceptable chronic exposure to flufenacet in drinking water. The chronic drinking water estimated concentration based on ground water monitoring data is 0.03 ppb and based on surface water model data it is 14.2 ppb.

EPA concludes that there is a reasonable certainty that no harm will result from aggregate exposure to flufenacet residues. The nature of the residue in plants is adequately understood for the purposes of this time-limited tolerance. Based on the results of animal metabolism studies, it is unlikely that significant residues would occur in secondary animal commodities from this use.

3. From Non-Dietary Uses

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

4. Cumulative Exposure to Substances with Common Mechanism of Toxicity

Flufenacet is structurally a thiadiazole. EPA is not aware of any other pesticides with this structure.

For flufenacet, EPA has not yet conducted a detailed review of common mechanisms to determine whether it is appropriate, or how to include this chemical in a cumulative risk assessment. After EPA develops a methodology to apply common mechanism of toxicity

issues to risk assessments, the Agency will develop a process (either as part of the periodic review of pesticides or otherwise) to reexamine these tolerance decisions. The Agency has determined that there are no metabolites of toxicological concern associated with flufenacet. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, flufenacet does not appear to produce a toxic metabolite produced by other substances. Therefore, EPA has not assumed that flufenacet has a common mechanism of toxicity with other substances.

EPA is required to develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other effect...." The Agency is currently working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists in developing a screening and testing program and a priority setting scheme to implement this program. Congress has allowed 3 years from the passage of FQPA (August 3, 1999) to implement this program. At that time, EPA may require further testing of this active ingredient and end use products for endocrine disrupter effects. Based on the toxicological findings for flufenacet relating to endocrine disruption effects, flufenacet should be considered as a candidate for evaluation as an endocrine disrupter when the criteria are established.

OCCUPATIONAL EXPOSURE

EPA has concluded using the systemic NOEL of 20 mg/kg/day from the 21-day dermal study in rats and that the Margin of Exposure (MOE) for occupational exposure range between 160 and 570. A MOE of 100 or higher is accepted as showing an adequate margin of safety for occupational exposure based on the following: 1) there are no residential uses, thus children are not exposed from the pesticide's application; 2) the end point was seen in male rats only; 3) there is a large spacing between the NOEL and the LOEL; and 4) dermal absorption is low, approximately 4%. The available evidence does not indicate any evidence of significant toxicity

from short-term dermal, intermediate term dermal, or inhalation routes of exposure.

An chronic occupational risk assessment is not appropriate since worker exposure from application to field corn and soybeans once a year does not occur often enough to be considered a chronic exposure i.e. a continuous exposure that occurs for, at least, several months.

SUMMARY OF DATA GAPS

1. Acute Toxicity of the thiadone degradate to Aquatic Species [Guideline #'s 72-1, 72-2, and 72-3]

2. Environmental Fate Data on the thiadone degradate [Guideline #'s 161-1, 161-2, 162-1, 162-2 or 162-3, 162-4, and 163-2]

3. Freshwater Fish Life-Cycle Test conducted with FOE 5043 Technical [Guideline # 72-5]

4. Two Prospective Groundwater Monitoring Studies at vulnerable sites

5. Tier II Terrestrial Plant Test conducted with Axiom DF [Guideline # 123-1]

6. Data regarding the stability of the glucoside conjugate and the malonylalanine conjugate of thiadone and subsequent bioavailability of any release free thiadone

7. Editorial revision of the analytical method

8. Validation of the product chemistry enforcement analytical method [OPPTS 830.1800]

9. Additional Crop Rotation data [Guideline # 165-2]

10. Surface Water Monitoring

11. A Developmental Neurotoxicity Study

PUBLIC INTEREST FINDING

FOE 5043 DF Herbicide and Axiom DF Herbicide are effective at controlling certain grasses and broadleaf weeds that are common through out corn and soybean production areas. Due to lower use rates and the alternative herbicides that will be replaced, the total herbicide volume applied to corn and soybeans could be reduced.

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