UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

Date: March 15, 2007

MEMORANDUM

SUBJECT: Flufenacet: HED Human Health Risk Assessment for Uses on Wheat, Perennial Grasses Grown for Seed and Sweet Corn**.** (Petitions: 6F04631, 0F6095; PC: 121903, DP318555)

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THRU: Paula Deschamp, Chief
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Bayer CropScience has submitted a petition to replace the temporary tolerances (Section 18) on livestock commodities and wheat commodities with permanent tolerances and to expand the uses of the herbicide to include pre-emergence and early season post-emergence applications to sweet corn, wheat, and perennial grasses grown for seed. The Registration Division of the Office of Pesticide Programs (OPP) has requested that HED evaluate hazard and exposure data and conduct dietary, occupational, residential, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from the requested uses of flufenacet.

A summary of the findings and an assessment of human risk resulting from the uses of flufenacet are provided in this document. The residue chemistry assessment was provided by Amelia Acierto (RAB3), the dietary exposure assessment by Susan Stanton (RRB3), the hazard characterization by Kathleen Raffaele (Toxicology Branch), the drinking water assessment by Ron Parker of the Environmental Fate and Effects Division (EFED), percent crop treated assessment by Arthur Grube of the Biological and Economic Analysis Division (BEAD), and the risk assessment and occupational/residential exposure assessment by Jack Arthur (RAB3).

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1.0 EXECUTIVE SUMMARY

Bayer CropScience has submitted a petition (PP#0F6095) to establish permanent tolerances for the use of flufenacet on winter wheat, perennial grasses grown for seed and sweet corn. In addition, Bayer CropScience requests that the temporary tolerances for flufenacet in meat and meat byproducts currently associated with the Section 18 uses of flufenacet (Axiom) in wheat be made permanent in support of the proposed crop uses.

Hazard Assessment

Since completion of the previous risk assessment for flufenacet (ref: *Flufenacet in/on Corn and Soybeans. HED Human Health Risk Assessment***.** J. Arthur**.** May 14, 2003. DP#: 288185), no new toxicity data have been submitted that would change the endpoint selection or FQPA findings upon which the previous assessment was based.

Flufenacet has low-moderate acute toxicity by the oral route and low acute toxicity by the dermal route. It is not irritating to the skin, slightly irritating to the eyes, and is a dermal sensitizer according to the guinea pig maximization test, but not the Buehler test. Several target tissues have been identified, including the liver and nervous systems across several species; changes in thyroid hormones were also reliably seen in several species. No increase in susceptibility was seen in rat and rabbit developmental studies, but qualitative and/or quantitative increases in susceptibility were seen in the rat reproduction study and in the rat developmental neurotoxicity studies. Review of acceptable carcinogenicity and mutagenicity studies provide no indication that flufenacet is carcinogenic or mutagenic.

Dose Response Assessment and Food Quality Protection Act (FQPA) Decision

On April 23, 2003, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for flufenacet with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. In addition, the HIARC evaluated the FQPA Safety Factor in accordance with the 2002 OPP 10X guidance document. While the endpoints and uncertainty factors (UF) selected by the HIARC in 2003 remain unchanged, this current flufenacet risk assessment reflects HED's new guidance on the categorization of the FQPA Safety Factors. Specifically, in this assessment the 10X FQPA Safety Factor has been retained; attributable to the lack of a NOAEL in the DNT study (UF_L) and the lack of comparative susceptibility data for thyroid hormone levels (UF_{DB}). The new policy guidance has been adopted to help clarify the appropriate use of the FQPA Safety and Uncertainty Factors by including all safety factors typically used in HED risk assessments (except inter- and intra-species factors) under a single value identified only as the "FQPA Safety Factor." This avoids the confusion of parsing out the uncertainty factors under "FQPA" and "Special FQPA," as was done in the previous flufenacet risk assessment.

For dietary assessments, the acute RfD (aRfD) was calculated by dividing the Lowest-Observed-Adverse-Effect-Level (LOAEL) by 1000 [i.e., the standard 10X UF for interspecies

extrapolation and 10X UF for intraspecies variation; and a 10X FQPA Safety Factor attributable to the lack of a No-Observed-Adverse-Effect-Level (NOAEL) in the developmental neurotoxicity study (UF_L) and the unfulfilled requirement for a comparative thyroid study (UF_{DB})]. For the aRfD, the LOAEL of 1.7 mg/kg was based on decreased body weight/body weight gain, and missing brain morphometric measurements in caudate/putamen, in pups in the DNT study. The chronic RfD (cRfD) was calculated in the same manner as the aRfD. For the cRfD, the LOAEL of 1.7 mg/kg/day is based on decreased body weight/body weight gain in pups in the DNT study.

For occupational assessments, the same developmental neurotoxicity endpoint and LOAEL was used as above. Since the endpoint from the DNT oral study was selected for all durations of dermal and inhalation exposure, a 4% dermal absorption factor and a 100 % inhalation absorption factor are used in the route-to-route extrapolation. The level of concern for occupational dermal and inhalation exposures is for MOEs <300 [10X for interspecies extrapolation, 10X for intraspecies variation; and 3X uncertainty factor (UF_L) due to the lack of a NOAEL in the developmental neurotoxicity study]. For the occupational exposure assessment, dermal and inhalation exposure estimates can be combined because oral equivalent doses and the same endpoint were used for these routes of exposure.

Residential Exposure Estimates

There are no currently existing or proposed uses for flufenacet in residential or public sites and therefore no residential risk assessments were performed.

Dietary (Food plus Drinking Water) Exposure/Risk Estimates

Refined, Tier 3 acute probabilistic and chronic dietary (food + drinking water) exposure assessments were conducted for all existing and proposed food uses of flufenacet. Anticipated residues for many crops (field corn, soybean, sweet corn and wheat) were developed using field trial data. Anticipated residues for livestock commodities were derived using available feeding and metabolism studies in conjunction with the anticipated dietary burden to ruminants, swine and poultry. Tolerance level residues were used to assess flufenacet exposure from the remaining commodities (i.e., cereal grains). Pesticide Data Program (PDP) monitoring data are available for wheat flour (2003, 2004), wheat grain (2005) and pork fat/muscle (2005). The PDP data were not used to develop anticipated residues for wheat commodities, since they reflect the historical, regional section 18 use of flufenacet on wheat in the Pacific Northwest, rather than the proposed section 3 national use. Since wheat makes up 80% of the theoretical swine diet, the PDP data for pork commodities are also considered inappropriate for estimating anticipated residues in these commodities.

Acute and chronic exposure estimates for all commodities were further refined using percent crop treated (%CT) data, following the guidance provided in HED SOP 99.6 (*Classification of Food Forms with Respect to level of Blending*; 8/20/99). Projected %CT data were used to refine anticipated residues for the new food uses (sweet corn and wheat). Available processing data were used to refine anticipated residues for cereal grains and corn. For all other processed

commodities, DEEM (ver. 7.81) default processing factors were assumed.

Estimated drinking water concentrations (EDWCs) were provided by EFED (R. Parker; DP Num: 318616, 318629; 10/04/06) and incorporated directly into the DEEM analyses. For the acute assessment, the entire 30-year distribution of estimated daily surface water concentrations for the Ohio corn crop scenario was used in a probabilistic analysis. For the chronic assessment, the estimated 1-in-10 year annual mean residue in surface water was used as a point estimate in a deterministic analysis.

Short- and intermediate-term aggregate risk assessments were not performed because flufenacet is not registered or proposed for residential uses. A cancer aggregate risk assessment was not performed because flufenacet is not carcinogenic. Aggregate risk assessments for acute and chronic exposure (food + drinking water) are summarized as follows:

Acute Dietary (Food plus Drinking Water) Exposure/Risk

Estimated acute dietary exposure is below HED's level of concern for the U.S. population and all population subgroups. Combined dietary exposure from food and drinking water at the 99.9th percentile of exposure is estimated to be 0.000514 mg/kg/day for the general U.S. population, equivalent to 30% of the acute Population Adjusted Dose (aPAD). The population subgroup with the highest estimated acute dietary exposure is infants, less than 1 year old, with an estimated exposure at the 99.9th percentile of 0.001514 mg/kg/day, equivalent to 89% of the aPAD. The major contributor to dietary exposure for all population subgroups is drinking water. Estimated acute dietary exposure from food alone is less than or equal to 13% of the aPAD for the general U.S. population and all subgroups.

Chronic Dietary (Food plus Drinking Water) Exposure/Risk

Chronic dietary exposure estimates for food and drinking water combined are well below HED's level of concern. Using the DEEM-FCID software, chronic dietary exposure is estimated at 0.000049 mg/kg/day for the general U.S. population (2.9% of the chronic Population Adjusted Dose (cPAD)) and 0.000156 mg/kg/day (9.2% of the cPAD) for infants <1 year old, the population subgroup with the highest estimated chronic dietary exposure to flufenacet. As with the acute assessment, the major contributor to estimated chronic dietary exposure is drinking water. Estimated chronic dietary exposure from food alone represents less than 1% of the aPAD for the general U.S. population and all subgroups.

Characterization of Inputs/Outputs

Both the acute and chronic dietary analyses may be considered partially refined. A characterization of the inputs/outputs and uncertainties regarding the assessment is provided below.

Food:

- The assessment for food incorporates anticipated residue estimates for most crops and livestock commodities that were derived using field trial data. Although field trial data provide more refined exposure estimates than tolerances, the results may still be considered somewhat conservative, since field trials are conducted under maximum use conditions (maximum allowed application rate, minimum PHI, etc.). In actual practice, flufenacet is likely to be applied using a range of rates and PHIs, and treated commodities may be stored for various time periods (beyond the minimum PHI) prior to consumption by humans or livestock.

- Anticipated residues for food commodities were adjusted for %CT, using screening level usage estimates for the existing crops (field corn and soybeans) and projected %CT estimates for new uses (sweet corn and wheat), both of which are intended to provide protective exposure estimates.

Drinking Water:

- Drinking water is the risk "driver" in both the acute and chronic dietary analyses. PRZM-EXAMS surface water modeling data were used probabilistically in the acute analysis and deterministically in the chronic analysis. The modeling estimates were partially refined in that they took into consideration crop-specific percent cropped area (PCA). PRZM/EXAMS data represent the range of concentrations that are estimated to result from the annual use of flufenacet over a 30 year period at the maximum application rate. Although the PRZM/EXAMS models provide more refined estimates of surface water residues than the Tier 1 FIRST model, the drinking water inputs may be considered conservative, since they assume that applications will be made at maximum application rates to the entire crop within the watershed every year for 30 years.

- The PRZM/EXAMS results for the Ohio corn scenario were used in this assessment and in the previous 2003 dietary assessment for flufenacet. Although the Illinois corn scenario returned a slightly higher 1-in-10 year peak concentration in EFED's current analysis, the difference is so small (10 ppb vs. 8.6 ppb) that it would not be expected to significantly impact the risk assessment results. The results for the Ohio corn scenario are considered to provide a reasonable, high-end estimate of drinking water exposure to residues of flufenacet.

Occupational Exposure Estimates

Based on the proposed use patterns, there is a potential for short- and intermediate-term dermal and inhalation exposure to flufenacet during mixing, loading, and application. Handler's exposure and risk were estimated for: (1) mixer/loader: open mixing dry flowable for groundboom, and (2) ground-boom application: open cab. No chemical-specific handler exposure data were submitted in support of this Section 3 registration request. In accordance with HED's Exposure Science Advisory Council (SAC) policy, exposure data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 as presented in PHED Surrogate Exposure Guide (8/98) were used.

For handlers, daily short- and intermediate-term dermal exposures were compared to a LOAEL = 1.7 mg/kg/day from an oral rat developmental neurotoxicity study, using a 4 % dermal absorption factor for route-to-route extrapolation and a 60 kg standard female body weight. Daily inhalation exposures also were compared to the 1.7 mg/kg/day LOAEL from the oral rat developmental neurotoxicity study, using a 100% absorption factor (for an oral equivalent dose). Dermal and inhalation exposure estimates, as described above, were then combined to obtain a total dose and compared to the 1.7 mg/kg/day LOAEL from the oral rat developmental neurotoxicity study, because the same endpoint is applicable to both routes of exposure. The level of concern (LOC) for both short- and intermediate-term dermal and inhalation exposure is for an MOE of 300 or less. The MOEs for the combined dermal and inhalation exposures for most scenarios are not of concern when handlers are wearing baseline clothing, plus gloves. However, mixing/loading dry flowable to support groundboom applications on corn requires gloves, coveralls and a dust/mist respirator (combined MOE = 330), or packaging of the product in water-soluble packets (combined MOE = 1000) in order to not be of concern to HED.

Negligible postapplication dermal exposure is expected because most flufenacet applications are made preplant and preemergence. Because a limited post-emergence use (i.e. on wheat, to the 3rd leaf stage, and sweet corn, to the 5th leaf stage) is proposed, a postapplication exposure assessment was performed for scouting and irrigation activities, using the same dermal toxicity endpoint and dose described for occupational handlers. The resulting MOEs of 460 to 4000 on the day of application (i.e., day zero) are not of concern. Technical flufenacet has a Toxicity Category III for Acute Oral and Acute Dermal (all other acute categories are IV). Per the Worker Protection Standard (WPS), a 12-hr REI is required for chemicals classified under Toxicity Category III, and therefore, an REI of 12 hours should appear on all flufenacet labels.

Recommendation for Tolerances

This human health risk assessment supports conditional registration (see Section 8. Data Needs/Label Requirements) and the establishment of permanent tolerances for the combined residues of flufenacet [*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 the following commodities at the indicated levels:

Recommended Tolerances for Flufenacet	
Commodity	Recommended Tolerance (ppm)
40 CFR §180.527(a). Tolerances 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.	
Corn, field, forage	0.45
Corn, field, grain	0.05
Corn, field, stover	0.30
Corn, sweet, forage	0.45
Corn, sweet, kernel plus cob with husks removed	0.05
Corn, sweet, stover	0.30
Soybean, seed	0.05
Wheat, bran	0.80
Wheat, forage	6.0
Wheat, grain	0.60
Wheat, hay	1.2
Wheat, straw	0.35
Cattle, kidney	0.05
Goat, kidney	0.05
Hog, kidney	0.05
Horse, kidney	0.05
Sheep, kidney	0.05
40CFR §180.527(c). *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, with regional registration.	
Grass, forage	7.0
Grass, hay	0.4
40CFR §180.527(d). *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 for indirect or inadvertent residues (Rotational Crop Tolerances)	
Alfalfa, forage	2.0
Alfalfa, hay	2.0
Alfalfa, seed	0.10
Clover, forage	2.0
Clover, hay	2.0

Recommended Tolerances for Flufenacet	
Cereal, grain, crop group 15, except rice	0.10
Cereal, grain, forage, fodder, and straw, crop group 16, except rice	2.0
Grass, forage, fodder and hay, crop group 17	2.0

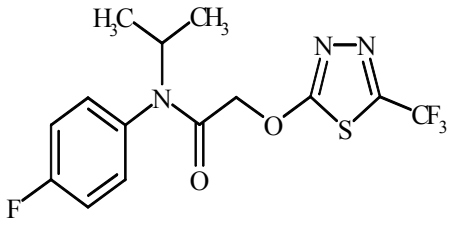
2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

Flufenacet is currently marketed by Bayer CropScience under the trade names Define™ DF Herbicide, 60% flufenacet (EPA Reg. No. 264-765), Define™ SC Herbicide, 41% flufenacet (EPA Reg. No.264-819); and Axiom® DF Herbicide, 54.4% flufenacet and 13.6% metribuzin (EPA Reg. No. 264-766).

2.1 Identification of Active Ingredient

The chemical structure and nomenclature for flufenacet are presented in Table 1.

Table 1. Nomenclature of Flufenacet

Compound	
Common name	Flufenacet
Company experimental name	FOE 5043
IUPAC name	4'-fluoro-*N*-isopropyl-2-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yloxy]acetanilide
CAS name	*N*-(4-fluorophenyl)-*N*-(1-methylethyl)-2-[[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]oxy]acetamide
CAS #	142459-58-3
End-use products/EP	Define™ SC Herbicide, 41% (EPA Reg. No.264-819), Axiom® DF Herbicide, 54.4% + 13.6% metribuzin (EPA Reg No. 264-766), Define™ DF Herbicide, 60% (EPA Reg. No.264-765, originally registered as EPA Reg. No. 3125-487).

2.2Physical and Chemical Properties of Active Ingredient

The physicochemical properties of flufenacet are presented in Table 2.

Table 2. Physicochemical Properties of Technical Grade Flufenacet			
Parameter	Value		Reference
Melting point/range (°C)	75.5-77.0		MRID#: 43441101
pH	4.49 (approx. 1% aqueous slurry)		
Density	1.312 g/mL (at 20°C)		
Water solubility (20°C)	56 mg/L (0.0056 g/100 ml)		
Solvent solubility (g/l at 20°C)	n-hexane: 8.7 2-propanol: 170 acetonitrile: >200 1-octanol: 88 dimethylformamide: >200 polyethylene glycol + ethanol: 160	toluene: >200 dichloromethane: >200 acetone: >200 dimethylsulfoxide: >200 polyethylene glycol: 74	
Vapor pressure at 25°C	2 X 10^{-6} h Pa (N-isomer) (equivalent to 4 X 10^{-6} torr)		
Dissociation constant (pKa)	Does not dissociate in water.		
Octanol/water partition coefficient Log(KOW)	Pow = 1600 at 24°C; log Pow = 3.20		
UV/visible absorption spectrum (λmax, nm)	Not available		

3.0 HAZARD CHARACTERIZATION

Reference: *FLUFENACET - 2nd Report of the Hazard Identification Assessment Review Committee*. (Memo, K. Raffaele, 04/30/03, TXR# 0051853.

The existing toxicological database for flufenacet supports the establishment of permanent tolerances for residues of flufenacet in/on the RACs resulting from the registered and proposed uses.

3.1 Hazard Profile

Flufenacet has low-moderate acute toxicity by the oral route and low acute toxicity by the dermal route. It is not irritating to the skin, slightly irritating to the eyes, and is a dermal sensitizer according to the guinea pig maximization test, but not the Buehler test. Several target tissues have been identified, including liver and nervous system across several species; changes in thyroid hormones were also reliably seen in several species. No increase in susceptibility was seen in rat and rabbit developmental studies, but qualitative and/or quantitative increases in susceptibility were seen in the rat reproduction study and in the rat developmental neurotoxicity studies. Review of acceptable oncogenicity and mutagenicity studies provide no indication that flufenacet is carcinogenic or mutagenic. Acute toxicity of flufenacet is presented in Table 3. The subchronic, chronic, and other toxicity profile of flufenacet is presented in Table 4.

Table 3. Acute Toxicity of Flufenacet

Guideline No.	Study Type	MRID #(s)	Results	Toxicity Category
870.1100	Acute Oral - rat	43441104	LD_{50} = 1617 mg/kg (M) 589 mg/kg (F)	3
870.1200	Acute Dermal - rat	43441106	LD_{50} = >2000 mg/kg	3
870.1300	Acute Inhalation - rat	43441108	LC_{50} = >3.74 m/L	4
870.2400	Primary Eye Irritation - rabbits	43850017	slight eye irritant	4
870.2500	Primary Skin Irritation - rabbits	43850023	non-irritant	4
870.2600	Dermal Sensitization - Guinea pigs (Buehler test)	43850015	Not a skin sensitizer	N/A
870.2600	Dermal Sensitization - Guinea pigs (Maximization test)	43877601	Skin sensitizer	N/A

Table 4. Subchronic, Chronic and Other Toxicity Profile for Flufenacet

Guideline	MRID	Type of Study	Results	Core Grade
870.3100	43743401	90-day feeding-Rat	NOAEL(mg/kg/day)= <6.0(M); 7.2(F). LOAEL(mg/kg/day)=6.0(M) based on decreased T4; 28.8(F) based on hematology and clinical chemistry findings.	Acceptable
870.3100	4373801	90-day feeding-Mouse	NOAEL(mg/kg/day)=18.2(M);24.5(F). LOAEL(mg/kg/day)=64.2(M);91.3(F) based on systemic toxicity and histopathology of the liver, spleen, and thyroid.	Acceptable
870.3150	43619401	90-day feeding -Dog	NOAEL (mg/kg/day)=1.67(M);1.70(F). LOAEL (mg/kg/day)=7.20 (M); 6.90(F) based on increases in LDH, globulin, and spleen pigment in females, decreased T4 and ALT values in both sexes, decreased albumin in males, and decreased serum glucose in females.	Acceptable
870.3200	43850027	21-day Dermal-Rat	Dermal irritation NOAEL(mg/kg/day)=1000 (M;F). Systemic toxicity NOAEL= 20(M); 150(F). LOAEL(mg/kg/day)= 150(M);1000(F) based on decreased T4 and FT4 levels in both sexes and histopathological findings in females.	Acceptable

Guideline	MRID	Type of Study	Results	Core Grade
870.4200	43823501	Combined Chronic Toxicity/Carcinogenicity -Rat	Systemic toxicity NOAEL (mg/kg/day)=1.2(M); <1.5(F). LOAEL (mg/kg/day)=19.3(M); 24.4(F) based on methemoglobinemia and multi-organ effects in blood, kidney, spleen, heart, brain, eye, liver, and uterus. Carcinogenicity: Negative.	Acceptable
870.4300	43820701	Carcinogenicity-Mouse	NOAEL(mg/kg/day)= <7.4(M); 9.4(F) LOAEL(mg/kg/day)= 7.4(M); 38.4(F), based on increased incidence and severity of cataracts. Carcinogenicity: Negative.	Acceptable
870.4100b	43850028	Chronic oral-Dog	NOAEL(mg/kg/day)=1.29(M); 1.14(F) LOAEL(mg/kg/day)=27.75(M); 26.82(F) 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 incidences of microscopic lesions in the brain, eye, kidney, spinal cord, sciatic nerve, and liver.	Acceptable
870.3700a	43850030	Developmental-Rat	Maternal NOAEL= 25 mg/kg/day. LOAEL= 125 mg/kg/day based on decreased BWG initially. Developmental NOAEL= 25 mg/kg/day. LOAEL= 125 mg/kg/day based on decreased fetal body weight, delayed ossification in skull, vertebrae, sternebrae, and appendages, and increased extra ribs.	Acceptable
870.3700b	43850029 43850031	Developmental-Rabbit	Maternal NOAEL= 5 mg/kg/day. LOAEL= 25 mg/kg/day based on histopathological findings in liver. Developmental NOAEL= 25 mg/kg/day. LOAEL= 125 mg/kg/day based on increased skeletal variations.	Acceptable

Guideline	MRID	Type of Study	Results	Core Grade
870.3800	43850032 43850033	Two-generation Reproduction- Rat	Maternal toxicity NOAEL (mg/kg/day)= 1.4(M);1.5(F). LOAEL (mg/kg/day)= 7.4(M);8.2(F) based on increased liver weight in F1 females and hepatocytomegaly in F1 males. Reproductive NOAEL(mg/kg/day)= 1.3. LOAEL(mg/kg/day)= 6.9 based on increased pup death in early lactation (including cannibalism) for F1 litters and the same effects in F1 and F2 pups at 36 mg/kg/day.	Acceptable
870.6300	45232501	Developmental Neurotoxicity Study - Rat	**Maternal Toxicity** NOAEL = 40.8 mg/kg/day LOAEL = Not established (no adverse effects seen) **Offspring Toxicity** NOAEL = Not established LOAEL = 1.7 mg/kg/day based on decreased preweaning body weight and body weight gain. Not established for morphometric evaluations in PND72-76 female offspring, due to the failure to evaluate the caudate putamen at the low dose level.	Acceptable/ Non-guideline
84-2	43850035	Ames Assay (S. typhimurium)	Not mutagenic	Acceptable
84-2	43850034	In vivo mammalian cytogenetics -micronucleus assay (mouse)	Not mutagenic	Acceptable
84-2	43850036	In vitro mammalian cytogenetics -Chinese hamster lung fibroblasts (V79) cells	Not mutagenic	Acceptable
84-2	43850037	In vitro cytogenetics -chromosomal analysis of cultured CHO cells	Not mutagenic	Acceptable
84-2	43850038	Unscheduled DNA synthesis in rat hepatocytes in vitro	Not mutagenic	Acceptable
870.7485	43850039	Metabolism - rat	Rapidly absorbed and metabolized following oral exposure to either single or multiple doses. The urine was the major route of excretion with small amount excreted *via* feces. Significant amounts of radiolabel were eliminated as CO_2 and CH_4. A maximum of 7% of the total recovered radiolabel was found	Acceptable

Guideline	MRID	Type of Study	Results	Core Grade
			in the tissues and residual carcass. Twenty-five metabolites arising from the fluorophenyl portion of the molecule were detected in excreta, and 17 of these were identified. The total amount of radiolabel identified ranged from [Fluorophenyl-UL-^{14}C] FOE 5043 67%-86%; [Thiadiazole-2-^{14}C] FOE 5043 84%-92%; and [Thiadiazole-5-^{14}C] FOE 5043 53%-69%. All unidentified residues in excreta were characterized.	
N/A	43850041	Metabolism/Mechanism	Hypothesis of an extra thyroidal mechanism of action for FOE 5043.	Acceptable (Non-guideline)
N/A	43850042	Metabolism/Mechanism	Hypothesis of an extrathyroidal mechanism of action for FOE 5043; a supplement to MRID 43850041.	Acceptable (Non-guideline)
N/A	43695301	Metabolism/Metabolite	Evaluated a hypothesis that the neurotoxicity observed in dogs dosed with high levels of FOE 5043 was caused by metabolic limitations.	Acceptable (Non-guideline)
870.6200	43735301	Acute oral neurotoxicity-Rat	NOAEL (mg/kg)= <75 (M,F) LOAEL (mg/kg)= 75 (M,F) based on clinical signs in females (uncoordinated gait and decreased activity) and decreased motor activity in males.	Acceptable
870.6200	43819801 43850049	Subchronic neurotoxicity-Rat	NOAEL (mg/kg/day)= 7.30(M); 8.40(F) LOAEL (mg/kg/day)= 38.1(M); 42.6(F) based on microscopic lesions (including axonal swelling in brain and spinal cord).	Acceptable

3.2 FQPA Considerations

On April 23, 2003, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for flufenacet with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. In addition, the HIARC evaluated the FQPA Safety Factor in accordance with the 2002 OPP 10X guidance document. While the endpoints and uncertainty factors (UF) selected by the HIARC in 2003 remain unchanged, this current flufenacet risk assessment reflects HED's new guidance on the categorization of the FQPA Safety Factors. Specifically, in this assessment the 10X FQPA Safety Factor has been retained; attributable to the lack of a NOAEL in the DNT study (UF_L) and the lack of comparative susceptibility data for thyroid hormone levels (UF_{DB}). The new policy guidance has been adopted to help clarify the appropriate use of the FQPA Safety and Uncertainty Factors by including all safety factors typically used in HED risk assessments (except inter- and intra-species factors) under a single value identified only as the "FQPA Safety

Factor." This avoids the confusion of parsing out the uncertainty factors under "FQPA" and "Special FQPA," as was done in the previous flufenacet risk assessment.

3.2.1 Determination of Susceptibility

There is no indication of additional susceptibility of young rats or rabbits following pre-natal exposure to flufenacet in the developmental toxicity studies. There was an indication of qualitative susceptibility in the two generation reproduction study. Effects seen in the offspring in the reproductive toxicity studies (including increased pup death in early lactation and cannibalism) were more severe than those seen in the parental animals (increased liver weight and cytomegaly), although there was no difference in the NOAELs/LOAELS between parental animals and offspring in that study. Increased susceptibility (qualitative and quantitative) was seen in the developmental neurotoxicity study in rats. Decreased body weight was seen in pups at all dose levels, and additional effects, including decreased motor activity, delayed developmental landmarks, and decreases in morphometric measurements were seen at mid and high doses. A slight decrease in body weight in mid and high dose dams during early lactation may have been due to palatability of test substance and was not considered adverse.

The selection of 1.7 mg/kg/day as a LOAEL for the developmental neurotoxicity study is considered to be a conservative recommendation, because the decrease in pup body weight at that dose is transient, and a similar decrease was not seen in the two-generation reproduction study (decreased pup body weight seen in the one generation range-finding reproduction study occurred at higher doses than those evaluated in the developmental neurotoxicity study).

3.2.2 Degree of Concern Analysis and Residual Uncertainty

A number of potential effects that raised susceptibility issues were evaluated with regard to flufenacet. With the exception of one effect, it was determined that the susceptibility issues posed diminished to low levels of concern.

It was determined that the concern is low for the qualitative susceptibility seen in the two generation reproduction study because the pup death may be attributable to maternal cannibalism, and there was a clear NOAEL for the effect.

There is diminished concern for susceptibility seen in the DNT. Decreased offspring body weights were seen at the low dose and multiple offspring effects (including brain morphometric changes) were seen at the mid- and high doses, and no adverse maternal effects were seen at any dose. The concern for the decrease in the offspring body weight was reduced since 1) it was the only effect seen at the lowest dose; 2) the effect was transient; and 3) no decrease in body weight was seen in the offspring in the reproduction study. With regard to the lack of brain morphometric data at the low dose, there is diminished concern since no treatment-related changes were seen in Day 12 male or female offspring or in Day 72 male offspring at any dose level. Morphometric findings at the mid dose were limited to a single region (caudate putamen) of the brain, in one sex (females), at one time period (Day 72), and there was no dose-response in spite of a 5-fold increase between the mid dose (8.3 mg/kg/.day; 10% decrease) and the high

dose (40.8 mg/kg/day; 9% decrease). Therefore, it is highly unlikely that either biological significance or dose response will be demonstrated for this effect at the lowest dose tested (1.7 mg/kg/day).

Finally, there is diminished concern regarding the potential for greater sensitivity of the young to neuropathologic lesions as a result of direct exposure to flufenacet. Neurobehavioral and neuropathological changes were seen in adult animals in multiple studies following direct exposure to flufenacet. Because dosing in the submitted DNT study was to dams only, via the diet, from GD6 through PND10, pups were not directly exposed to flufenacet and thus relative susceptibility to neuropathologic effects following direct exposure to young animals has not been evaluated. Although the lack of comparative data for this effect results in some uncertainty, the lowest dose at which the adverse neuropathological effects were seen in adult rats (39 mg/kg/day after one year of exposure in the chronic rat study) is many times higher than the doses used as endpoints in this risk assessment (less than 1.7 mg/kg/day).

There are, however, residual concerns, regarding the potential for greater sensitivity in the young to flufenacet's effect on thyroid hormone levels. Available data in adult animals support the possibility of decreases in thyroid hormones at dose levels similar to those used in the submitted DNT study. Because pups were not directly dosed in the DNT study, but were exposed only *in utero* and potentially via lactation during maternal dosing (from GD6 through PND10), effects on thyroid hormone levels in young animals following direct exposure to flufenacet has not been evaluated. A special comparative sensitivity study on thyroid hormone levels in neonatal and adult rats has been requested. There is a lack of comparative susceptibility data for thyroid hormone levels.

3.2.3 FQPA Safety Factor for Infants and Children

The flufenacet risk assessment team has recommended that the 10X FQPA Safety Factor be retained in the form of a database uncertainty factor. The primary reasons for retaining the 10X safety factor are the uncertainty raised by the data gap for a comparative sensitivity study on thyroid hormone levels in neonatal and adult rats, as well as the lack of a NOAEL in the Developmental Neurotoxicity Study. Also supporting this decision, but of much less significance in the weight of evidence evaluation, are (1) the fact that brain morphometric data were not evaluated at the low dose in offspring in the developmental neurotoxicity study, which resulted in not establishing an offspring NOAEL for that effect; and (2) the absence of available data to compare the relative sensitivity of young animals to neuropathological lesions following direct exposure to flufenacet. There are no additional residual uncertainties for pre- or post-natal toxicity. There was no evidence of increased susceptibility in the developmental toxicity studies (rats and rabbits), but qualitative and/or quantitative increases in susceptibility were seen in the rat reproduction study and in the rat developmental neurotoxicity studies. There are also no additional residual uncertainties with respect to exposure data:

* The dietary drinking water assessment utilizes water concentration values generated by models and associated modeling parameters which are designed to provide conservative, health protective, high-end estimates of water concentrations which will not likely be exceeded.

* The dietary food exposure assessment is based on current registrations and % CT data verified by BEAD for several existing uses. Although somewhat refined, the assessment is based on reliable data and will not underestimate exposure/risk.

* There are no residential uses for flufenacet.

3.3 Dose-Response Assessment

Acute Dietary Endpoint: A rat developmental neurotoxicity study was used to select the dose and endpoint for establishing the aRfD of 0.0017 mg/kg/day for the general U.S. population. The LOAEL of 1.7 mg/kg was based on decreased body weight/body weight gain, and missing brain morphometric measurements in caudate/putamen, in pups. This RfD is applicable to the general U.S. population, including infants and children, and is also protective of developmental effects which may occur in females of reproductive age. Application of a 1000-fold uncertainty factor has been determined to be appropriate (10X interspecies, 10X intraspecies, 10X for the lack of a NOAEL in the DNT, and the requirement of a comparative thyroid study). Although a decrease in body weight/body weight gain is not considered to be a single dose effect, decreases in morphometric measurements in PND 72-76 female offspring, which were seen at higher doses but were not evaluated at the low doses, could occur following a single dose. This endpoint would be applicable to females 13-50 years of age, as well as to infants and children, and thus is appropriate for the general population.

Chronic Dietary Endpoint: Same as for acute dietary endpoint (see above). Use of the DNT study for chronic exposures is supported by similar NOAELs in chronic rat and dog studies (1.2 and 1.1 mg/kg/day, respectively).

Carcinogenicity: Characterized as "not likely" to be a human carcinogen.

Dermal Penetration: Dermal Absorption Factor: No dermal absorption data are available. The HIARC reaffirmed the dermal absorption rate of 4% selected by the TES Committee (document dated 2/97) based on a comparison between the LOAEL of 6 mg/kg/day in the 90-day feeding study in rats (MRID 43743401) and a LOAEL of 150 mg/kg/day in the 21-day dermal study in rats (MRID 43850027) (both endpoints based on decreased thyroid hormone levels in plasma).

Short-Term (1-30 days) and Intermediate-Term (1-6 months) Dermal Endpoints: Same as for acute dietary endpoint (see above). The available 21-day dermal study cannot be used for these endpoints, since there is concern for potential changes in pup weight and in brain morphometric measures; endpoints not addressed in the dermal study. Duration of exposure in the developmental neurotoxicity study is appropriate for short-term use. Use for intermediate-term exposures is supported by similar NOAELs in chronic rat and dog studies (1.2 and 1.1 mg/kg/day, respectively). This endpoint should be corrected for 4% absorption for dermal exposure relative to oral absorption.

Long-term Dermal Endpoint: Not required for expected use pattern.

Inhalation Endpoint (all durations): Same as for acute dietary endpoint (see above). No toxicity studies conducted via inhalation are available. Duration of the developmental neurotoxicity study is appropriate for short-term endpoints. Use for intermediate-term and long-term exposures is supported by similar NOAELs in chronic rat and dog studies (1.2 and 1.1 mg/kg/day, respectively). Absorption by inhalation is assumed to be equivalent to oral.

The doses/toxicological endpoints selected for exposure scenarios are summarized in Tables 4 and 4a.

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

Exposure Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	RfD, PAD and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General population including infants and children)	LOAEL = **1.7** mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 10X (UF_L, UF_{DB})	Acute RfD = 0.0017 mg/kg/day **aPAD = 0.0017** mg/kg/day	**Developmental Neurotoxicity study in rats**. LOAEL = **1.7** mg/kg/day based on **decreased body weight/body weight gain, and missing morphometric measurements in caudate/putamen, in pups**.
Chronic Dietary (All populations)	LOAEL= **1.7** mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 10X (UF_L, UF_{DB})	Chronic RfD = 0.0017 mg/kg/day **cPAD = 0.0017** mg/kg/day	**Developmental Neurotoxicity study in rats**. LOAEL = **1.7** mg/kg/day based on **decreased body weight/body weight gain, and missing morphometric measurements in caudate/putamen, in pups**.
Short-Term (1-30 days) and Intermediate-Term (1-6 months) Incidental Oral	There are no residential uses currently registered or proposed for flufenacet. Consequently no exposure from residential uses is expected and no residential assessment was performed.			
Short-Term (1-30 days) and Intermediate-Term (1-6 months) Dermal	There are no residential uses currently registered or proposed for flufenacet. Consequently no exposure from residential uses is expected and no residential assessment was performed.			
Short-Term (1-30 days) and Intermediate-Term (1-6 months) Inhalation	There are no residential uses currently registered or proposed for flufenacet. Consequently no exposure from residential uses is expected and no residential assessment was performed.			
Long-Term Dermal and Inhalation (>6 months)	Long term dermal and inhalation exposure is not expected and there are no residential uses at the present time. Therefore, no residential risk assessment was performed.			

Exposure Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	RfD, PAD and Level of Concern for Risk Assessment	Study and Toxicological Effects
Cancer (oral, dermal, inhalation)	Because the cancer classification is 'Not Likely' these risk assessments are not required.			

UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no-observed-adverse-effect-level, LOAEL = lowest-observed-adverse-effect-level, PAD = population-adjusted dose (a = acute, c = chronic), RfD = reference dose (a = acute, c = chronic), MOE = margin of exposure, LOC = level of concern, NA = Not Applicable/Not Required.

Table 4a Summary of Toxicological Doses and Endpoints for Flufenacet for Use in Occupational Human Health Risk Assessments

Exposure Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	RfD, PAD and Level of Concern for Risk Assessment	Study and Toxicological Effects
Short-Term Dermal (1 to 30 days)	LOAEL= **1.7** mg/kg/day (dermal absorption rate = 4%)	UF_A = 10X UF_H = 10X FQPA SF = 3X (UF_L)	**Occupational** LOC for MOE = **300**	**Developmental Neurotoxicity study in rats**. LOAEL = **1.7** mg/kg/day based on **decreased body weight/body weight gain in pups**.
Intermediate-Term Dermal (1 to 6 months)	LOAEL= **1.7** mg/kg/day (dermal absorption rate = 4%)	UF_A = 10X UF_H = 10X FQPA SF = 3X (UF_L)	**Occupational** LOC for MOE = **300**	**Developmental Neurotoxicity study in rats**. LOAEL = **1.7** mg/kg/day based on **decreased body weight/body weight gain in pups**.
Long-Term Dermal (>6 months)	Long term dermal exposure is not expected; therefore, quantification of risk was not performed.			
Short-Term Inhalation (1 to 30 days)	LOAEL= **1.7** mg/kg/day (inhalation absorption rate = 100%)	UF_A = 10X UF_H = 10X FQPA SF = 3X (UF_L)	**Occupational** LOC for MOE = **300**	**Developmental Neurotoxicity study in rats**. LOAEL = **1.7** mg/kg/day based on **decreased body weight/body weight gain in pups**.
Intermediate-Term Inhalation (1 to 6 months)	LOAEL=**1.7** mg/kg/day (inhalation absorption rate = 100%)	UF_A = 10X UF_H = 10X FQPA SF = 3X (UF_L)	**Occupational** LOC for MOE = **300**	**Developmental Neurotoxicity study in rats**. LOAEL = **1.7** mg/kg/day based on **decreased body weight/body weight gain in pups**.
Long-Term Inhalation (>6 months)	Long term inhalation exposure is not expected; therefore, quantification of risk was not performed.			
Cancer (dermal,	Because the cancer classification is 'Not Likely' these risk assessments are not required.			

Exposure Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	RfD, PAD and Level of Concern for Risk Assessment	Study and Toxicological Effects
inhalation)				

UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no-observed-adverse-effect-level, LOAEL = lowest-observed-adverse-effect-level, PAD = population-adjusted dose (a = acute, c = chronic), RfD = reference dose (a = acute, c = chronic), MOE = margin of exposure, LOC = level of concern, NA = Not Applicable/Not Required.

For occupational exposures, use of the 3X UF_L is sufficient to extrapolate from LOAEL to NOAEL since decreased offspring body weight gain in the DNT study was transient and was not reproduced in the reproductive toxicity study at similar doses.

3.4 Endocrine Disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

4.0 EXPOSURE ASSESSMENT

Reference: *Flufenacet. Registration for Use on Field Corn, Sweet Corn, Soybeans, Wheat, and Grass Grown for Seed. Summary of Analytical Chemistry and Residue Data.* Petition Number: 6F04631. (Memo, A. Acierto, 11/29/06, DP#'s: 288564 and 288565)

4.1 Summary of Established Uses

Flufenacet is a herbicide which, based on its chemical structure, is in a class of chemicals called the oxyacetamides. Like other acetamide herbicides, flufenacet inhibits root and shoot growth of germinating seeds and very small emerged seedlings. The herbicidal mechanism of action is not well-defined, but may be via disruption of fatty acid incorporation into lipid membranes. Flufenacet is currently marketed by Bayer CropScience as a dry flowable formulation under the trade names Define™ DF Herbicide, 60% flufenacet (EPA Reg. No. 264-765), Define™ SC Herbicide, 41% flufenacet (EPA Reg. No.264-819); and Axiom® DF Herbicide, 54.4% flufenacet and 13.6% metribuzin (EPA Reg. No. 264-766). The 0.78 lb ai/acre rate for sweet

corn was used in this current assessment as the maximum seasonal/single application rate for the occupational and drinking water exposure assessments.

A summary of the use profile proposed for this Section 3 registration is presented in Table 5. A more detailed description of use is presented in the residue chemistry support document (Acierto, 11/29/06, DP#: 288564) referenced above.

Table 5 Summary of Proposed Use Profile for Flufenacet.

For Control of Grasses and Broadleaf Weeds in the Following Crops	Max. Single (and Seasonal) Application Rate (lb ai/A)	Application Methods and Timing
Sweet Corn	0.78	* Preplant surface: single or sequential application(s) made up to 45 days before planting in corn. * Preplant incorporated: upper 1-2 inches of soil, up to 14 days before planting. * Preemergence: surface broadcast or banded spray after planting, but before weed or crop emergence. * Early postemergence through the 5th leaf collar growth stage. * Groundboom (Not to be applied aerially or by chemigation)
Perennial Grasses Grown for Seed	0.44	* Only one application per use season. * Allow 120 days between application and harvest of seed grass. * Works best when applied preemergence to very early postemergence (1 to 2-leaf stage). * Groundboom (Not to be applied aerially or by chemigation)
Wheat	0.34	* Most effective application from spike to 3 leaf growth stage (early postemergence). Do not use beyond the 3rd leaf growth stage. * Groundboom (Not to be applied aerially or by chemigation)

4.2 Dietary Exposure/Risk Pathway

4.2.1 Residue Profile

Nature of the Residue – Plants

The nature of flufenacet residues in plants is understood based on adequate studies using a preplant application to corn and soybeans and a postemergence application to corn and wheat. The metabolism of flufenacet was similar for the three crops and the two types of applications. Flufenacet is metabolized in plants beginning with cleavage of the trifluoromethyl thiadiazole moiety. The remaining acetamide portion of the molecule is conjugated with glutathione, and subsequent oxidation of the glutathione moiety yields a variety of metabolites containing the 4-fluoro-*N*-methylethyl benzenamine moiety, several of which are conjugated with glucose. The thiadiazole moiety from the initial cleavage reaction was either converted to conjugated compounds containing thiadone (TH) or degraded and incorporated into naturally occurring compounds. The Metabolism Assessment Review Committee concluded in a meeting on 7/16/97 that the residues of concern in plants for both tolerance expression and risk assessment are parent and the metabolites containing the 4-fluoro-*N*-methylethyl benzenamine moiety.

Nature of the Residue- Livestock

The nature of the residue in livestock is also understood, based on adequate goat and poultry metabolism studies using ^{14}C-labeled parent and plant metabolites. The metabolism of flufenacet and its plant metabolites are similar in ruminants and poultry. The main plant metabolite arising from the thiadiazole portion of flufenacet is thiadone-*N*-glycoside (THNG; 3-glycosyl-5-trifluoromethyl-1,3,4-thiadiazole-2(3*H*)-one). Flufenacet, which is not found in livestock feed items, is initially cleaved at the ether bond releasing thiadone which is then conjugated to glucuronic acid. The remaining portion of the molecule, containing the 4-fluoro-*N*-methylethyl benzenamine moiety, is then conjugated with glutathione. Further metabolism involves the mercapturic acid pathway, with additional metabolism of the cysteine or mercapturic acid conjugates of flufenacet to methylsulfonyl-containing metabolites.

In both ruminants and poultry, accumulation and metabolism of FOE oxalate, a major plant metabolite containing the 4-fluoro-*N*-methylethyl benzenamine moiety, was limited with FOE oxalate being the principal residue in eggs, milk, and tissues.

Based on these studies, the MARC (DP Barcode 241928, N. Dodd, 12/18/97) concluded that the residues of concern in ruminants and poultry for the tolerance expression are parent and the metabolites containing the 4-fluoro-*N*-methylethyl benzenamine moiety. The dietary risk assessment for livestock commodities should include the glycoside (THNG) and malonylalanine conjugates of thiadone, which may be found in some livestock feed items. Available livestock metabolism studies should be used to account for conjugate conversion to species of toxicological concern (free thiadone and thiadone glucuronide).

Residue Analytical Methods

An adequate gas chromatographic/single ion mode (GC/SIM) common moiety method (Bayer Report #106406-1) for enforcement of the tolerances for flufenacet and its metabolites containing the 4-fluoro-*N*-methylethyl benzenamine moiety on plant commodities is available following its revision in compliance with the recommendations by EPA's Analytical Chemistry Laboratory (ACL) (Memorandum, 4/8/2004, Charles J. Stafford, DP Barcode 290377). The method determines flufenacet and its phenyl-ring containing metabolites as the hydrolysis product 4-fluoro-*N*-methylethyl benzenamine (fluoroaniline). A closely related method (Bayer Report #106773) for determining residues of flufenacet in livestock commodities has been adequately radiovalidated in an independent laboratory. HED has requested ACB to conduct a petition method validation (PMV) of Bayer's proposed tolerance enforcement methods for determining flufenacet and its metabolites in livestock (A. Acierto, 4/13/2006).

Multiresidue Method (MRM)

Flufenacet and selected metabolites (FOE oxalate, FOE sulfonic acid, and FOE thioglycolate sulfoxide) have also undergone Multiresidue Method Testing. Reference standards for flufenacet, FOE oxalate, and FOE sulfonic acid (sodium salt) are currently available at the EPA National Pesticide Standards Repository. However, a standard for the FOE thioglycolate sulfoxide metabolite is not available and should be submitted.

Magnitude of Residues in Plants

Based on the proposed and recommended tolerances, the maximum theoretical dietary burdens (MTDB) are 0.60 ppm for beef cattle, 0.49 ppm for dairy cattle, and 0.49 ppm for poultry and swine. An adequate cattle feeding study is available in which dairy cattle were dosed for 29 days at levels equivalent to 13.0x, 41.2x, and 137x the MTDB of beef cattle. The available residue data support a tolerance level of 0.05 ppm for kidney of cattle, goat, sheep, horse, and hog. No other tolerances for livestock commodities are needed.

Since the field trials were conducted with a DF formulation, bridging studies (side-by-side field trials) are needed to compare the SC formulation (Define™ SC, EPA Reg. No. 264-819) and the DF formulation (Define™ DF Herbicide, EPA Reg, No. 264-765) on field corn for the midseason use (i.e., broadcast early postemergence application at the 5th leaf collar stage). Three side-by-side field trials should be conducted for field corn. (Note: Bridging studies are not needed for the preplant, preemergence or crop stubble applications since data for the DF formulation can be translated to the SC formulation for these applications.)

Adequate field trail data are available to support the current and proposed uses on soybean, corn, wheat, and grass grown for seed. An adequate number of field trials were conducted at approximately the maximum proposed use rates, and the appropriate commodities were collected at the proposed preharvest intervals (PHIs). Samples were analyzed using an adequate analytical method, and the sample storage intervals are supported by the available storage stability data.

The available soybean field trial data support the existing use pattern on soybeans and the

established 0.1 ppm tolerance for soybean seeds. Although the new or amended products (Define SC Herbicide, 41% ai and Axiom DF Herbicide, 54.4% ai) are proposed for use at a lower rate of 0.59 and 0.84 lb ai/A/season, respectively, the available field trial data for corn field and sweet corn support the application of flufenacet at up to 0.9 lb ai/A as either preplant, preemergence, or early postemergence applications. These data support the established 0.05 ppm tolerance for field corn grain but indicate that the current tolerance for field corn forage should be increased to 0.45 ppm and the tolerance for field corn stover should be decreased 0.30 ppm These tolerance levels were obtained from use of the Tolerance/MRL Harmonization Spreadsheet. The Maximum Likelihood Estimation (MLE) method was also used to supplement the data set for corn forage and stover.

The submitted field trial data for wheat support a single, early season postemergence application of flufenacet to wheat at up to 0.36 lb ai/A. The residue data indicate that the proposed tolerances on wheat forage (10 ppm), hay (2.0 ppm), straw (0.5 ppm) and grain (1.0 ppm) are too high; a revised tolerance of 6.0 ppm for wheat forage, 1.2 ppm for hay, 0.35 ppm for straw and 0.60 ppm for grain should be proposed. These are also the tolerance levels obtained from use of the Tolerance/MRL Harmonization Spreadsheet. The Maximum Likelihood Estimation (MLE) method was also used to supplement the data set for wheat grain.

The available grass field trial data support a single, early season postemergence application of flufenacet to grass at up to 0.44 lb ai/A. This use would be restricted to grass grown for seed in the Pacific NW. The available grass field trial data support tolerances (with regional restriction) of 7.0 ppm for grass forage and 0.40 ppm for grass hay.

Adequate storage stability data are available to support the field trials, processing studies, rotational crop field trials, and the livestock feeding study. The available data indicate that flufenacet and its metabolites are stable in frozen wheat, corn, soybean and turnip matrices for at least 20-28 months and that FOE oxalate is stable in livestock tissues and milk for up to 13 months.

Processed Food and Feed

Adequate processing studies are available for corn, soybeans, wheat and sorghum (rotated crop). The data indicate that separate tolerances are not required on soybean, corn, sorghum, and wheat processed commodities. Based on HAFT residues of 0.35 ppm in wheat grain and a processing factor of 2.1x in wheat bran, the maximum expected residues in bran would be 0.74 ppm. A separate tolerance for wheat bran of 0.80 ppm is needed since the recommended tolerance for wheat grain is 0.60 ppm.

Rotational Crops

Adequate confined rotational crop studies using both [fluorophenyl-^{14}C] and [thiadiazole-2-^{14}C]

flufenacet are available and indicate that limited field rotational crop trials are required. Residues of concern were identified in rotational crops from a 12-month plant-back interval (PBI) at levels in excess of 0.01 ppm. The metabolism of flufenacet in rotational crops is similar to that in the primary crops.

The available limited rotational field trial data are adequate and support the label-specified 1-month PBI for potatoes and the 4-month PBI for all other root vegetables, leafy vegetables, and cotton. Rotational crop tolerances are not required for these crops.

Adequate extensive rotational field trial data are also available for cereal grain crops. The extensive field trial data on barley and sorghum (reflecting a 1-month PBI), along with limited field trial data on wheat (reflecting 1 and 4 month PBIs) will support either a 1-month PBI for cereal grain crops or the currently specified 4-month PBI. Based on the residue data on barley (hay, straw, and grain), sorghum (forage, stover, and grain), and wheat (forage, hay, grain and straw) from the 1-month PBI, the following rotational crop tolerances are appropriate: 2.0 ppm for cereal grain forage, stover, and straw (crop group 16, except rice), and 0.10 ppm for cereal grain (crop group 15, except rice); 2.0 ppm for alfalfa, forage; 2.0 ppm for alfalfa, hay; 0.10 ppm for alfalfa, seed; 2.0 ppm for clover, forage; 2.0 ppm for clover, hay; and 2.0 ppm for grass, forage, fodder, and hay group.

International Tolerance Harmonization

No maximum residue limits (MRLs) for flufenacet have been established or proposed by Codex or Canada for any agricultural commodity. In Mexico, an MRL of 0.05 mg/kg was established in corn (communication with S. Funk, 8/17/2006). However, the petitioner indicated in Section G of the petition that MRLs are established or proposed for countries of the European Communities on the following commodities: cereals at 0.5 mg/kg, corn at 0.5 mg/kg, potato at 0.1 mg/kg, sunflower at 0.05 mg/kg, soybean at 0.05 mg/kg, livestock meat at 0.05 mg/kg, livestock edible offals at 0.05 mg/kg, livestock fat at 0.05 mg/kg, milk at 0.01 mg/kg and eggs at 0.05 mg/kg.

4.2.2 Dietary (Food plus Drinking Water) Exposure/Risk Analyses

Reference: *Flufenacet: Acute and Chronic Aggregate Dietary Exposure and Risk Assessments for the Proposed Section 3 Registration on Wheat, Sweet Corn and Grass Grown for Seed.* (Memo, S. Stanton, 12/05/06, DP#: 334695)

Refined, Tier 3 acute probabilistic and chronic dietary exposure assessments were conducted for all existing and proposed new food uses of flufenacet and drinking water. Anticipated residues for many crops (field corn, soybean, sweet corn and wheat) were developed using field trial data. Anticipated residues for livestock commodities were derived using available feeding and metabolism studies in conjunction with the anticipated dietary burden to ruminants, swine and poultry. Tolerance level residues were used to assess flufenacet exposure from the remaining commodities (i.e., cereal grains). Pesticide Data Program (PDP) monitoring data are available for wheat flour (2003,2004), wheat grain (2005) and pork fat/muscle (2005). The PDP data were

not used to develop anticipated residues for wheat commodities, since they reflect the historical, regional section 18 use of flufenacet on wheat in the Pacific Northwest, rather than the proposed section 3 national use. Since wheat makes up 80% of the theoretical swine diet, the PDP data for pork commodities are also considered inappropriate for estimating anticipated residues in these commodities.

Acute and chronic exposure estimates for all commodities were further refined using %CT data, following the guidance provided in HED SOP 99.6 (*Classification of Food Forms with Respect to level of Blending*; 8/20/99). Projected %CT data were used to refine anticipated residues for the new food uses (sweet corn and wheat). Available processing data were used to refine anticipated residues for cereal grains and corn. For all other processed commodities, DEEM (ver. 7.81) default processing factors were assumed.

Food

Flufenacet acute and chronic dietary exposure assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 2.03), which incorporates consumption data from USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998. The 1994-96, 98 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. Foods "as consumed" (e.g., apple pie) are linked to EPA-defined food commodities (e.g. apples, peeled fruit - cooked; fresh or N/S; baked; or wheat flour - cooked; fresh or N/S, baked) using publicly available recipe translation files developed jointly by USDA/ARS and EPA. For chronic exposure assessment, consumption data are averaged for the entire U.S. population and within population subgroups, but for acute exposure assessment are retained as individual consumption events. Based on analysis of the 1994-96, 98 CSFII consumption data, which took into account dietary patterns and survey respondents, HED concluded that it is most appropriate to report risk for the following population subgroups: the general U.S. population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, adults 20-49, females 13-49, and adults 50+ years old.

For chronic dietary exposure assessments, an estimate of the residue level in each food or food-form (e.g., orange or orange juice) on the food commodity residue list is multiplied by the average daily consumption estimate for that food/food form to produce a residue intake estimate. The resulting residue intake estimate for each food/food form is summed with the residue intake estimates for all other food/food forms on the commodity residue list to arrive at the total average estimated exposure. Exposure is expressed in mg/kg body weight/day and as a percent of the cPAD. This procedure is performed for each population subgroup.

For acute exposure assessments, individual one-day food consumption data are used on an individual-by-individual basis. The reported consumption amounts of each food item can be multiplied by a residue point estimate and summed to obtain a total daily pesticide exposure for a deterministic exposure assessment, or "matched" in multiple random pairings with residue values and then summed in a probabilistic assessment. The resulting distribution of exposures is expressed as a percentage of the aPAD on both a user (i.e., only those who reported eating

relevant commodities/food forms) and a per-capita (i.e., those who reported eating the relevant commodities as well as those who did not) basis. In accordance with HED policy, per capita exposure and risk are reported for all tiers of analysis. However, for Tiers 1 and 2, any significant differences in user vs. per capita exposure and risk are specifically identified and noted in the risk assessment.

The residues of concern in plants for both tolerance expression and risk assessment are parent and the metabolites containing the 4-fluoro-*N*-methylethyl benzenamine moiety. The residues of concern in ruminants and poultry for the tolerance expression are parent and the metabolites containing the 4-fluoro-*N*-methylethyl benzenamine moiety. The dietary risk assessment for livestock commodities should also include thiadone related residues, glycoside conjugate (THNG) and the malonylalanine conjugate of thiadone.

Drinking Water

The residues of concern in drinking water include flufenacet and its degradate, thiadone. The Environmental Fate and Effects Division (EFED) provided estimated drinking water concentrations (EDWCs) of flufenacet and thiadone in surface water using the Tier II PRZM/EXAMS models. Groundwater EDWCs were provided for parent flufenacet only using the Tier I SCIGROW model. (Reference: *Revised Estimated Drinking Water Concentrations of Flufenacet and Degradate Thiadone for the Use in Human Health Risk Assessment*; Ronald Parker; DP Num: 318616, 318629; 10/04/06)

Ground Water: For ground water, the acute and chronic flufenacet EDWC from the SCIGROW model is 0.10 ppb. Ground-water monitoring information provided by the registrant supports the SCIGROW model result as a reasonable estimate of groundwater concentrations. Acute and chronic concentrations of 0.18 ppb and 0.03 ppb, respectively, were seen in a small-scale prospective groundwater study conducted by the registrant in a Nebraska aquifer that could reasonably be expected to be used for drinking water. (FOE 5043; Reregistration Eligibility Document; October,1997). The Agency has been unable to locate any other field monitoring data for flufenacet in groundwater.

Surface Water: For surface water, the combined one-in-ten-year peak (acute) and one-in-ten-year mean (chronic) estimated concentrations of flufenacet *and* thiadone are presented in Table 6 for two Midwest corn belt cropping scenarios (Ohio corn and Illinois corn). Thiadone concentrations are expected to average 11 percent of parent flufenacet concentrations at the time of year when combined concentrations are the highest. Therefore, combined concentrations of flufenacet and thiadone were derived by multiplying parent flufenacet concentrations by a factor of 1.11.

Table 6. Combined Acute and Chronic Surface Water Concentrations for Parent Chemical Flufenacet Plus Degradate Thiadone.

PRZM Scenario	Acute Parent Flufenacet (ppb)	Chronic Parent Flufenacet (ppb)	Acute Degradate Thiadone (ppb)	Chronic Degradate Thiadone (ppb)	**Sum: Acute Parent Plus Degradate (ppb)**	**Sum: Chronic Parent Plus Degradate (ppb)**

Ohio Corn	7.78	2.01	0.86	0.22	**8.64**	**2.23**
Illinois Corn	9.07	2.55	1.00	0.28	10.07	2.83

Of all the labeled crops, the highest surface water concentrations would be expected for corn and soybeans, because the application rate is higher and there is more area planted to these crops; and surface water EDWCs for these two crops should not be different. The Ohio and Illinois corn scenarios were chosen as the most appropriate national-level scenarios based on their location in the Midwestern corn belt. The modeling results for these two scenarios are similar, with the Illinois scenario returning only slightly higher values. This slight difference is not due to differences in soil vulnerability in Ohio and Illinois; rather, it is an artifact of planting date selection relative to rainfall events at these two locations. EFED selected application dates 14 days before recommended planting dates without regard to rainfall dates for the two scenarios. Since growers seek to maximize the benefit of pesticide applications, they would be expected to apply flufenacet when dry weather is forecast. Therefore, the model results for the Ohio corn scenario were selected as appropriate for use in the dietary assessment. The selection of the Ohio scenario also provides consistency with the previous 2003 dietary assessment which used drinking water estimates based on the Ohio corn scenario.

The estimated surface water concentrations of flufenacet are nearly 2 orders of magnitude higher than estimated ground water concentrations. Therefore, the PRZM/EXAMS surface water modeling results were used in the dietary assessment. For the acute assessment, the entire 30-year distribution of estimated daily concentrations from the Ohio corn scenario was used in a probabilistic analysis. For the chronic assessment, the estimated 1-in-10 year annual mean residue was used as a point estimate in a deterministic analysis.

4.2.3 Acute Dietary (Food plus Drinking Water) Analysis

Estimated acute dietary exposure is below HED's level of concern for the U.S. population and all population subgroups. Combined dietary exposure from food and drinking water at the 99.9th percentile of exposure is estimated to be 0.000514 mg/kg/day for the general U.S. population, equivalent to 30% of the acute Population Adjusted Dose (aPAD). The population subgroup with the highest estimated acute dietary exposure is infants, less than 1 year old, with an estimated exposure at the 99.9th percentile of 0.001514 mg/kg/day, equivalent to 89% of the aPAD. The acute dietary exposure results at the 99.9th percentile are compared to the results at the 95th and 99th percentiles in Table 7.

Table 7. Results of Acute Dietary (Food plus Drinking Water) Exposure Analysis Using DEEM FCID							
Population Subgroup	**aPAD (mg/kg/day)**	**95th Percentile**		**99th Percentile**		**99.9th Percentile**	
		Exposure (mg/kg/day)	**% aPAD**	**Exposure (mg/kg/day)**	**% aPAD**	**Exposure (mg/kg/day)**	**% aPAD**
General U.S. Population	0.0017	0.000115	6.8	0.000230	14	0.000514	30
All Infants (< 1 year old)		**0.000396**	**23**	**0.000790**	**46**	**0.001514**	**89**
Children 1-2 years old		0.000185	11	0.000361	21	0.000720	42
Children 3-5 years old		0.000171	10	0.000325	19	0.000635	37
Children 6-12 years old		0.000118	7.0	0.000227	13	0.000444	26
Youth 13-19 years old		0.000088	5.2	0.000178	10	0.000389	23
Adults 20-49 years old		0.000105	6.2	0.000206	12	0.000424	25
Adults 50+ years old		0.000104	6.1	0.000190	11	0.000344	20
Females 13-49 years old		0.000106	6.2	0.000207	12	0.000418	25

The major contributor to dietary exposure for all population subgroups is drinking water. Estimated acute dietary exposure from food alone is less than or equal to 13% of the aPAD for the general U.S. population and all subgroups.

4.2.4 Chronic Dietary (Food plus Drinking Water) Analysis

Chronic dietary exposure estimates for food and drinking water combined are well below HED's level of concern. Using the DEEM-FCID software, chronic dietary exposure is estimated at 0.000049 mg/kg/day for the general U.S. population (2.9% of the chronic Population Adjusted Dose (cPAD)) and 0.000156 mg/kg/day (9.2% of the cPAD) for infants <1 year old, the population subgroup with the highest estimated chronic dietary exposure to flufenacet. As with the acute assessment, the major contributor to estimated chronic dietary exposure is drinking water. Estimated chronic dietary exposure from food alone represents less than 1% of the aPAD for the general U.S. population and all subgroups. Estimated chronic exposures from food alone and drinking water alone are compared to exposures for food and water combined in Table 8, below.

Table 8. Summary of Chronic Dietary (Food plus Drinking Water) Exposure and Risk for Flufenacet[1]

Population Subgroup	Food Only		Drinking Water Only		Total	
	Exposure (mg/kg/day)	% cPAD	Exposure (mg/kg/day)	% cPAD	Exposure (mg/kg/day)	% cPAD
	cPAD = 0.0017 mg/kg/day					
General U.S. Population	0.000002	<1	0.000047	2.8	0.000049	2.9
All Infants (< 1 year old)	**0.000002**	<1	**0.000154**	**9.1**	**0.000156**	**9.2**
Children 1-2 years old	0.000005	<1	0.000070	4.1	0.000075	4.4
Children 3-5 years old	0.000005	<1	0.000065	3.8	0.000070	4.1
Children 6-12 years old	0.000003	<1	0.000045	2.7	0.000048	2.9
Youth 13-19 years old	0.000002	<1	0.000034	2.0	0.000036	2.1
Adults 20-49 years old	0.000002	<1	0.000044	2.6	0.000046	2.7
Adults 50+ years old	0.000001	<1	0.000046	2.7	0.000048	2.8
Females 13-49 years old	0.000002	<1	0.000044	2.6	0.000045	2.7

[1]The population subgroup with the highest estimated chronic dietary (food + drinking water) exposure and risk is indicated by bold text.

4.2.5 Anticipated Residue and Percent Crop Treated (%CT) Information

BEAD recommended that a projected percent crop treated (PPCT) of 3% be used for flufenacet on sweet corn and 1% on wheat for chronic dietary risk assessment, and a PPCT of 10% be used for flufenacet on sweet corn and 3% on wheat for acute dietary risk assessment. BEAD has considered all information currently available and believes it is unlikely that the above estimates for PPCT will be exceeded during the next five years. (ref: BEAD memo from A. Grube and N. Zinn, *Projected Percent Crop Treated for Herbicide Flufenacet on Sweet Corn, Wheat and Grasses Grown for Seed,* DP#'s 320497 and 321194, 10/25/06)

Residue Data used for the Acute and Chronic Assessments

Food: Refined, Tier 3 acute probabilistic and chronic dietary exposure assessments were conducted for all existing and proposed new food uses of flufenacet and drinking water. Anticipated residues for many crops (field corn, soybean, sweet corn and wheat) were developed using field trial data. Anticipated residues for livestock commodities were derived using available feeding and metabolism studies in conjunction with the anticipated dietary burden to ruminants, swine and poultry. Tolerance level residues were used to assess flufenacet exposure from the remaining commodities (i.e., cereal grains). Pesticide Data Program (PDP) monitoring data are available for wheat flour (2003, 2004), wheat grain (2005) and pork fat/muscle (2005). The PDP data were not used to develop anticipated residues for wheat commodities, since they reflect the historical, regional section 18 use of flufenacet on wheat in the Pacific Northwest, rather than the proposed section 3 national use. Since wheat makes up 80% of the theoretical swine diet, the PDP data for pork commodities are also considered inappropriate for estimating anticipated residues in these commodities.

Acute and chronic exposure estimates for all commodities were further refined using %CT data, following the guidance provided in HED SOP 99.6 (*Classification of Food Forms with Respect to level of Blending*; 8/20/99). Projected %CT data were used to refine anticipated residues for the new food uses (sweet corn and wheat). Available processing data were used to refine anticipated residues for cereal grains and corn. For all other processed commodities, DEEM (ver. 7.81) default processing factors were assumed. Anticipated residues for ***plant*** commodities were calculated in accordance with HED guidance for Tier 3 assessments as follows:

Acute Assessment:

- Field corn, soybean and wheat (blended commodities): Average field trial residues were calculated and multiplied by the maximum %CT or projected %CT (wheat) estimates in the acute DEEM analysis. A residue value equal to ½ the Limit of Quantitation (LOQ) was assumed for all field trial samples with non-detectable (ND) residues.
- Other cereal grains (blended commodities): Flufenacet is not registered for direct application to these crops; however, inadvertent residues may occur in these crops from flufenacet's use on other crops. In the DEEM analysis, the tolerance level of 0.1 ppm for inadvertent residues was multiplied by the maximum projected %CT estimate for wheat (the field crop with the highest estimated or projected maximum %CT).
- Sweet corn (not blended or partially blended): All sweet corn field trial samples contained ND residues of flufenacet. For the acute assessment, a residue distribution file was constructed using ½ the LOQ for non-detectable residues and incorporating zeros to account for the percent of the crop not likely to be treated with flufenacet.

Chronic Assessment:

- Field corn, soybean, wheat (blended commodities) and sweet corn (not blended or partially blended): Average field trial residues were calculated and multiplied by the average %CT or projected %CT (wheat) estimates in the chronic DEEM analysis. A residue value equal to ½ the Limit of Quantitation (LOQ) was assumed for all field trial samples with non-detectable residues.
- Other cereal grains (blended commodities): Flufenacet is not registered for direct application to these crops; however, inadvertent residues may occur in these crops from flufenacet's use on other crops. In the DEEM analysis, the tolerance level of 0.1 ppm for inadvertent residues was multiplied by the average projected %CT estimate for wheat (the field crop with the highest estimated or projected average %CT).

The residue data for plant commodities used in the chronic and acute dietary assessments are summarized in the table below.

Data and Residue Estimates Used in Dietary Analyses

RAC	Food Forms	Classification[1]	Data Source	No. of Samples	No. of Detectable Residues	LOQ (ppm)	%CT		Processing Factors	Anticipated Residue Estimates/Tolerance	
							Ave.	Max.		Acute (Tol., AR, RDF)[5]	Chronic (Tol., AR)
Cereal Grains (Barley, Buckwheat, Millet, Oat, Popcorn, Rye, Sorghum)	All	B	Tolerance	N/A	N/A	N/A	1[2]	3[2]	Flour: 0.44x[3] Bran: 2.1x[3]	0.1 ppm adjusted by 3%CT	0.1 ppm adjusted by 1%CT
Corn, field	All	B	Ave. Field Trial; MRID: 45012405 & 45012407	62	0	0.05	<1[4]	<2.5[4]	All: 1x[5]	0.025 ppm adjusted by 2.5%CT	0.025 ppm adjusted by 1%CT
Corn, sweet	All	NB/PB	Field Trial; MRID: 45012405 & 45012407	18	0	0.05	3[6]	10[6]	N/A	RDF: 'Sweet Corn, using maximum projected 10%CT TOTALZ=90 TOTALLOD=10 LODRES=0.025	0.025 ppm adjusted by 3%CT
Soybean	All	B	Ave. Field Trial: MRID: 43850093	22	2	0.05	<1[4]	<2.5[4]	1x[5]	0.03 ppm adjusted by 2.5%CT	0.03 ppm adjusted by 1%CT
Wheat/Triticale	All	B	Ave. Field Trial: MRID: 45012401	38	38 (29 above LOQ)	0.05	1[6]	3[6]	Flour: 0.44x[3] Bran: 2.1x[3]	0.13 ppm adjusted by 3%CT	0.13 ppm adjusted by 1%CT

1. Classification of blended (B), partially blended (PB), not blended (NB).
2. Based on projected %CT for wheat, the field crop with the highest estimated ave. and max. %CT.
3. Based on processing data for wheat: MRID#45012408; A. Acierto; DP Num: 288564; 07/27/06.
4. Screening Level Usage Analysis; BEAD; 08/18/2005
5. N. Dodd; DP Num: 224142: 12/12/96
6. *Projected Percent Crop Treated for Herbicide Flufenacet (PC 121903) on Sweet Corn, Wheat and Grasses Grown for Seed*; N. Zinn & A Grube; DP Nums: 320497, 321194; 10/25/2006

4.3 Residential Exposure/Risk Pathway

There are no residential uses currently registered or proposed for flufenacet. Consequently no exposure from residential uses is expected and no residential assessment was performed.

4.3.1 Non-Occupational Off-Target Exposure

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from groundboom application methods. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

Short- and intermediate-term aggregate risk assessments were not performed because flufenacet is not registered or proposed for residential uses. A cancer aggregate risk assessment was not performed because flufenacet is not carcinogenic. Aggregate risk assessments for acute exposure (food + drinking water) and chronic exposure (food + drinking water) are presented in Sections 4.2.2.1 and 4.2.2.2 above.

6.0 CUMULATIVE RISK

Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

EPA does not have, at this time, available data to determine whether flufenacet has a common mechanism of toxicity with other substances. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to flufenacet and any other substances and flufenacet does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that flufenacet has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of

Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

7.0 OCCUPATIONAL EXPOSURE

Reference: *Occupational and Residential Risk Assessment for Request to Establish Permanent Tolerances for the Use of Flufenacet (Thiafluamide) on Winter Wheat, Perennial Grasses Grown for Seed and Sweet Corn*. (Memo, J. Arthur, 12/22/06, D334694)

7.1 Occupational Handler

There is a potential for occupational exposure to flufenacet during mixing, loading and applying. The Hazard Identification Assessment Review Committee (HIARC) selected dermal (short-term and intermediate-term) and inhalation (for any time period) endpoints for flufenacet. Chronic exposures are not expected for handlers or postapplication workers. Occupational exposure assessments for short-term and intermediate-term dermal and inhalation exposures were conducted. No chemical-specific handler exposure data were submitted in support of this Section 3 registration request. Therefore, data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 as presented in PHED Surrogate Exposure Guide (8/98) were used.

For handlers, daily short- and intermediate-term dermal exposures were compared to a LOAEL = 1.7 mg/kg/day from an oral rat developmental neurotoxicity study, using a 4% dermal absorption factor for route-to-route extrapolation and a 60 kg standard female body weight. Daily inhalation exposures also were compared to the 1.7 mg/kg/day LOAEL from the oral rat developmental neurotoxicity study, using an absorption factor of 100% (for an oral equivalent dose). Dermal and inhalation exposure estimates, as described above, were then combined to obtain a total dose and compared to the 1.7 mg/kg/day LOAEL from the oral rat developmental neurotoxicity study, because the same endpoint is applicable to both routes of exposure. The level of concern (LOC) for both short- and intermediate-term dermal and inhalation exposure is for an MOE of 300 or less. **The MOEs for the combined dermal and inhalation exposures for most scenarios are not of concern when handlers are wearing baseline clothing, plus gloves**. **However, mixing/loading dry flowable to support groundboom applications on sweet corn requires gloves, coveralls and a dust/mist respirator (combined MOE = 330), or packaging of the product in water-soluble packets (combined MOE = 1000) in order to not be of concern to HED. It should be noted that the use of water-soluble packets may not be practical since formulation as a dry flowable is already considered as an engineering control.**

The minimum level of PPE for handlers is based on acute toxicity for the end-use product. The Registration Division (RD) is responsible for ensuring that PPE listed on the label is in compliance with the Worker Protection Standard (WPS).

Assumptions and estimates for occupational handler exposure are summarized below in Tables 9 and 9a.

Table 9. Exposure and Risk Estimates for Occupational Mixer/Loader and Applicators at Baseline Clothing											
PHED Scenario Selected from PSEG Version 1.1	Personal Protective Equipment	Exposure Route	Application Rate (lb ai/acre)	Acres Treated (acres/ day)	PHED Unit Exposure (mg/lb ai)	PHED Data Confidence	Absorption Factor	Body Weight (kg)	Daily Dose [1] (mg/kg/day)	Short- and Intermediate-Term NOAEL (mg/kg/day)	Short- and Intermediate Term MOE [2]
1. Mixer/loader Dry Flowable (Open Mixing) for Groundboom on **Sweet Corn**	Long Sleeves, Long Pants, Gloves [4]	Dermal	0.78	200	0.066	High	0.04	60	0.0069	1.7	**250** [3]
		Inhalation	0.78	200	0.00077	High	1.0	60	0.0020	1.7	850
Total:									0.0089	1.7	**190** [3]
2. Applicator Groundboom (Open Cab) for **Sweet Corn**	Long Sleeves, Long Pants	Dermal	0.78	200	0.014	High	0.04	60	0.0015	1.7	1100
		Inhalation	0.78	200	0.00074	High	1.0	60	0.0019	1.7	900
								Total:	0.0034	1.7	**500**
3. Mixer/loader Dry Flowable (Open Mixing) for Groundboom on **Grass Grown for Seed**	Long Sleeves, Long Pants, Gloves [4]	Dermal	0.44	200	0.066	High	0.04	60	0.0039	1.7	440
		Inhalation	0.44	200	0.00077	High	1.0	60	0.0012	1.7	1400
Total:									0.0051	1.7	**330**
4. Applicator Groundboom (Open Cab) for **Grass Grown for Seed**	Long Sleeves, Long Pants	Dermal	0.44	200	0.014	High	0.04	60	0.00082	1.7	2100
		Inhalation	0.44	200	0.00074	High	1.0	60	0.0011	1.7	1500
Total:									0.0019	1.7	**890**
3. Mixer/loader Dry Flowable (Open Mixing) for Groundboom on **Wheat**	Long Sleeves, Long Pants, Gloves [4]	Dermal	0.34	200	0.066	High	0.04	60	0.003	1.7	570
		Inhalation	0.34	200	0.00077	High	1.0	60	0.00087	1.7	2000
								Total:	0.0039	1.7	**440**
4. Applicator Groundboom (Open Cab) for **Wheat**	Long Sleeves, Long Pants	Dermal	0.34	200	0.014	High	0.04	60	0.00063	1.7	2700
		Inhalation	0.34	200	0.00074	High	1.0	60	0.00084	1.7	2000
								Total:	0.0015	1.7	**1100**

[1] Daily Dose =[Application Rate (lb ai/A) x Acres Treated (A/day) x Unit Exposure(mg/lb ai handled) x Absorption Factor]/Body Weight
[2] Short- and Intermediate Term MOE = Short- and Intermediate Term NOAEL (1.7 mg/kg/day)/Daily Dose.
[3] Does not reach MOE of 300, and therefore is of concern to HED.
[4] PHED value is the same for gloved and ungloved hand. Confidence in gloved hand data is high, and use of gloves is recommended.

Table 9a. Exposure and Risk Estimates for Occupational Mixer/Loader and Applicators with Additional Mitigation Measures											
PHED Scenario Selected from PSEG Version 1.1	Personal Protective Equipment	Exposure Route	Application Rate (lb ai/acre)	Acres Treated (acres/ day)	PHED Unit Exposure (mg/lb ai)	PHED Data Confidence	Absorption Factor	Body Weight (kg)	Daily Dose [1] (mg/kg/day)	Short- and Intermediate-Term NOAEL (mg/kg/day)	Short- and Intermediate Term MOE [2]
1. Mixer/loader Dry Flowable (Open Mixing) for Groundboom on **Sweet Corn**	Long Sleeves, Long Pants, Gloves, **plus Coveralls**	Dermal	0.78	200	0.047	High	0.04	60	0.0048	1.7	350
		Inhalation	0.78	200	0.00077	High	1.0	60	0.0020	1.7	850
Total:									0.0068	1.7	**250** [3]
2. Mixer/loader Dry Flowable (Open Mixing) for Groundboom on **Sweet Corn**	Long Sleeves, Long Pants, Gloves, **plus Coveralls and a Dust/Mist Respirator**	Dermal	0.78	200	0.047	High	0.04	60	0.0048	1.7	350
		Inhalation	0.78	200	0.00015	High	1.0	60	0.00039	1.7	4400
Total:									0.0052	1.7	**330**
3. Mixer/loader Dry Flowable (Open Mixing) for Groundboom on **Sweet Corn**	Long Sleeves, Long Pants, Gloves, **plus water-soluble packets**	Dermal	0.78	200	0.0098	High	0.04	60	0.0010	1.7	1700
		Inhalation	0.78	200	0.00024	High	1.0	60	0.00062	1.7	2700
								Total:	0.00162	1.7	**1000**

[1] Daily Dose =[Application Rate (lb ai/A) x Acres Treated (A/day) x Unit Exposure(mg/lb ai handled) x Absorption Factor]/Body Weight
[2] Short- and Intermediate Term MOE = Short- and Intermediate Term NOAEL (1.7 mg/kg/day)/Daily Dose.
[3] MOE does not reach MOE of 300, and therefore is of concern to HED.

7.2 Occupational Postapplication Exposure

Flufenacet uses subject to this action involve preplant, pre-emergence and some post-emergence applications. Potential postapplication exposures from preplant and pre-emergence applications are usually considered to be negligible. However, because the proposal does include a post-emergence use, a postapplication exposure/risk assessment has been performed. While exposure is expected to be minimal, a risk assessment was performed for potential postapplication dermal exposure to scouts, and field workers performing irrigation. Inhalation exposure is expected to be negligible. Because this herbicide is not registered for residential or public use sites, a non-occupational postapplication risk assessment for residential or recreational settings has not been performed.

There were no chemical-specific data with which to estimate postapplication exposure of agricultural workers to dislodgeable residues of flufenacet. Therefore, theoretical estimates of exposure, based on surrogate studies, have been conducted. The ExpoSAC (Policy 003.1, Rev. 7 Aug. 2000, Regarding Agricultural Transfer Coefficients; Amended ExpoSAC Meeting notes - 13 Sept 01) lists a number of possible postapplication agricultural activities relative to the subject crops that result in potential pesticide exposure to agricultural workers. Transfer coefficients (TCs) used in this assessment are derived from data in surrogate exposure studies conducted during the various activities listed. TCs expressed as cm^2/hr are identified for each of the postapplication, agricultural activities. The data from these studies are proprietary and compensation issues with ARTF may need to be addressed. It is the intention of HED's ExpoSAC that this policy will be periodically updated to incorporate additional information about agricultural practices in crops and new data on TCs. Much of this information will originate from exposure studies currently being conducted by the ARTF, from further analysis of studies already submitted to the Agency, and from studies in the published scientific literature.

Since no chemical-specific DFR data are available, postapplication worker exposure is estimated using the HED procedure that assumes 20% of the application rate is available as dislodgeable foliar residue on the day of treatment. The estimates provided are for short/intermediate-term dermal exposures (1 day-6 months), and are considered to be screening level estimates (i.e., conservative).

The short- and intermediate-term MOEs for postapplication exposure on day zero range from 460 to 4000. Since the calculated MOEs are greater than 300 on the day of application, they **DO NOT exceed HED's level of concern**, and the interim WPS REI of 12 hours is sufficient to protect workers from excessive exposure.

A summary of the postapplication exposure/risk assessment is presented in Table 10.

Table 10. Exposure and Risk Assessment for Occupational Postapplication Activities

Crops	Application Rate (lb ai/A)	Post-application Day (t)	Fraction of ai Retained on the Foliage	Fraction of Residue That Dissipates Daily	Dislodgeable Foliar Residue (ug/cm^2) [1]	Dermal Transfer Coefficient [2] (cm^2/hr)	Exposure Time (hrs/day)	Dermal Absorption Factor [3]	Body Wt (kg)	Daily Dose [4] (mg/kg/day)	Short-/ Intermed. Term Dermal MOE [5]
Corn	0.78	0	0.2	0.1	1.75	scout: 400[6]	8	0.04	60	0.0037	460
						irrigate: 100[7]				0.0009	1800
Grasses Grown for Seed	0.44	0	0.2	0.1	0.987	scout: 400[6]	8	0.04	60	0.0021	800
						irrigate: 100[7]				0.0005	3000
Wheat	0.34	0	0.2	0.1	0.763	scout: 400 [6]	8	0.04	60	0.0016	1000
						irrigate: 100[7]				0.0004	4000

[1] Dislodgeable Foliar Residue $_{\text{Postapplication day}}$ (ug/cm^2) = Application rate (lb ai/A) x Fraction of ai Retained on the Foliage x (1- Fraction of Residue that Dissipates Daily) $^{\text{postapplication day}}$ x 4.54E+8 ug/lb x 24.7E-9 A/cm^2

[2] Harvesting corn, soybeans and wheat by mechanical means is assumed to result in negligible dermal exposure.

[3] For short- and intermediate-term dermal risk assessment, the dermal absorption factor of 4% was applied because the endpoint chosen for this risk assessment was derived from an oral toxicity study.

[4] Daily Dose = (Dislodgeable Foliar Residue x Absorption Factor x 0.001 mg/ug x Dermal Transfer Coefficient x Exposure Time)/Body weight

[5] MOE = NOAEL/Daily Dose Short-/Intermediate-Term Dermal NOAEL = 1.7 mg/kg/day

[6] Low end value from ARF009

[7] Central value from MRID 426891 [Note that there was no value for irrigation of low crop height, minimal foliage plants under Field/row crop, tall. Therefore the value for irrigating crops with this profile was obtained from the Field/row crop, low/medium as a best fit for the post-emergence use pattern proposed for flufenacet.]

7.3 Incidents

The OPP Incidents Database includes 39 entries for flufenacet. Most entries describe adverse reactions of unknown origin, such as rash, hives and headache.

8.0 DATA NEEDS/LABEL REQUIREMENTS

8.1 Chemistry

1. Successful agency Petition Method Validation (PMV) of the livestock analytical enforcement method is needed. HED has requested ACB to perform this PMV.

2. Bridging studies (side-by-side field trials) are needed to compare the SC formulation (Define ^{TM} SC, EPA Reg. No. 264-819) and the DF formulation (Define ^{TM} DF Herbicide EPA Reg. No. 264-765) on field corn for the midseason use (i.e., broadcast early postemergence application at the 5th leaf collar stage). Three side-by-side field trials should be conducted for field corn.

3a. A revised Section F is needed to specify kidney tolerances of 0.05 ppm for cattle, goat, horse, hog, and sheep.

3b. A revised Section F is needed to specify tolerances for corn, sweet, forage (0.45 ppm); corn, sweet, stover (0.30 ppm); corn, field, forage (0.45 ppm); corn, field stover (0.30 ppm); wheat, forage (6.0 ppm); wheat, hay (1.2 ppm); wheat, straw (0.35 ppm); wheat, grain (0.60 ppm); wheat, bran (0.80 ppm); grass, forage (7.0 ppm); and grass, hay (0.40 ppm).

3c. Based on the available field trial data, tolerances for indirect or inadvertent residue in rotational crops under §180.527(d) should be revised. The correct tolerance levels and commodity definitions are as follows: 0.10 ppm for cereal, grain, crop group 15, except rice; 2.0 ppm for cereal, grain, forage, fodder and straw, crop group 16, except rice; 2.0 ppm for alfalfa, forage; 2.0 for alfalfa, hay; 0.10 ppm for alfalfa, seed; 2.0 ppm for clover, forage; 2.0 ppm for clover, hay; and 2.0 ppm for grass, forage, fodder and hay, crop group 17.

4. Reference standards for flufenacet, FOE oxalate, and FOE sulfonic acid (sodium salt) are currently available at the EPA National Pesticide Standards Repository. However, a standard for the FOE thioglycolate sulfoxide metabolite is not available and should be submitted to the National Pesticide Standards Repository/Analytical Chemistry Branch/OPP, 701 Mapes Road, Fort George G. Meade, MD 20755-5350.

8.2 Toxicology

The HIARC determined that a special comparative sensitivity study on thyroid hormone levels in neonatal and adult rats should be **required** (see above), based on the changes seen in thyroid hormones in multiple species in adult toxicity studies. The HIARC also noted that neuropathology evaluations (morphometric measurements) could be included in the protocol for the comparative sensitivity study. The registrant should consult with the Agency in developing the protocol for that study. A request for a waiver to the requirement for this study has been submitted to the Agency by the registrant, Bayer CropScience (MRID# 46575701, May 25, 2005). A preliminary review of this submission indicates that support for a study waiver is not sufficient and that the requirement for a special comparative sensitivity study on thyroid levels remains. Formal completion of the waiver review is forthcoming and will be presented in a separate HED memorandum.

A 28-day inhalation toxicity study in rats is needed. A request for a waiver to the requirement for this study has been submitted to the Agency. HED has reviewed the submission and has determined that the rationale proposed does not support granting this waiver (J. Arthur, DP# 318557 et al., 09/01/06).

cc RAB3 Reading File.

ATTACHMENT 1 – Optional Endpoint Selection Table for CFR

Summary of Toxicological Dose and Endpoints for Flufenacet

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General population including infants and children)	LOAEL = **1.7** mg/kg/day UF = **1000**X	FQPA SF = 10X **aPAD = 0.0017** mg/kg/day **aRfD = 0.0017**	**Developmental Neurotoxicity study in rats**. LOAEL = **1.7** mg/kg/day based on **decreased body weight/body weight gain, and missing morphometric measurements in caudate/putamen, in pups**.
Chronic Dietary (All populations)	LOAEL= **1.7** mg/kg/day UF = **1000**	FQPA SF = **1X** **cPAD = 0.0017** mg/kg/day **cRfD = 0.0017**	**Developmental Neurotoxicity study in rats**. LOAEL = **1.7** mg/kg/day based on **decreased body weight/body weight gain in pups**.
Short-Term Incidental Oral (1-30 days)	LOAEL= **1.7** mg/kg/day	**Residential** LOC for MOE =**NA** **Occupational** = NA	**Developmental Neurotoxicity study in rats**. LOAEL = **1.7** mg/kg/day based on **decreased body weight/body weight gain in pups**.
Intermediate-Term Incidental Oral (1- 6 months)	NOAEL= **1.7** mg/kg/day	**Residential** LOC for MOE =**NA** **Occupational** = NA	**Developmental Neurotoxicity study in rats**. LOAEL = **1.7** mg/kg/day based on **decreased body weight/body weight gain in pups.**
Short-Term Dermal (1 to 30 days)	Oral study LOAEL= **1.7** mg/kg/day (dermal absorption rate = **4**%)	**Occupational** LOC for MOE = **300** **Residential** LOC for MOE = **NA**	**Developmental Neurotoxicity study in rats**. LOAEL = **1.7** mg/kg/day based on **decreased body weight/body weight gain in pups**.
Intermediate-Term Dermal (1 to 6 months)	Oral study LOAEL= **1.7** mg/kg/day (dermal absorption rate = **4**%)	**Occupational** LOC for MOE = **300** **Residential** LOC for MOE = **NA**	**Developmental Neurotoxicity study in rats**. LOAEL = **1.7** mg/kg/day based on **decreased body weight/body weight gain in pups**.
Long-Term Dermal (>6 months)	Long term dermal exposure is not expected and there are no residential uses at the present time. Therefore, quantification of risk is not required.		
Short-Term Inhalation (1 to 30 days)	Inhalation (or oral) study LOAEL= **1.7** mg/kg/day (inhalation absorption rate =	**Occupational** LOC for MOE = **300** **Residential** LOC for MOE = **NA**	**Developmental Neurotoxicity study in rats**. LOAEL = **1.7** mg/kg/day based on **decreased body weight/body weight gain in pups**.

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
	100%)		
Intermediate-Term Inhalation (1 to 6 months)	Inhalation (or oral) study LOAEL = **1.7** mg/kg/day (inhalation absorption rate = 100%)	**Occupational** LOC for MOE = **300** **Residential** LOC for MOE = **NA**	**Developmental Neurotoxicity study in rats**. LOAEL = **1.7** mg/kg/day based on **decreased body weight/body weight gain in pups**.
Long-Term Inhalation (>6 months)	Long term inhalation exposure is not expected and there are no residential uses at the present time. Therefore, quantification of risk is not required.		
Cancer (oral, dermal, inhalation)	Because the cancer classification is 'Not Likely' these risk assessments are not required.		

UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no-observed-adverse-effect-level, LOAEL = lowest-observed-adverse-effect-level, PAD = population-adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable/Not Required.