COMPANY FEDERAL REGISTER DOCUMENT SUBMISSION TEMPLATE (7/1/2006)

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INSTRUCTIONS: **Please utilize this outline in preparing tolerance petition documents. In cases where the outline element does not apply please insert "NA-Remove" and maintain the outline. The comment notes that appear on the left margin represent hidden typesetting codes designed to expedite the processing of the Federal Register document. Please do not remove or alter these comment notes or change the margins, font, or format in your document. Simply replace the instructions that appear in italics and brackets, i.e., "[*insert company name*]," with the information specific to your action.]**

TEMPLATE:

[Bayer CropScience]

[0F6095]

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EPA has received a pesticide petition ([0F6095]) from [Bayer CropScience], [2 T.W. Alexander Drive, Research Triangle Park, NC 27709] proposing, pursuant to section 408(d) of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a(d), to amend 40 CFR part 180.by establishing a tolerance for residues of [the herbicide 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 raw agricultural commodities: corn, sweet, forage at 0.4 ppm; corn, sweet, kernel plus cob with husks removed at 0.05 ppm; corn, sweet, stover at 0.4 ppm; wheat, forage at 10.0 ppm; wheat, grain at 1.0 ppm; wheat, hay at 2.0 ppm; wheat, straw at 0.5 ppm; seed-grass, forage at 7.0 ppm; seed-grass, forage, regrowth at 0.1 ppm; seed-grass, hay, regrowth at 0.5 ppm.

Bayer previously requested in petition 0F6095 that the section 18 tolerances listed below in 40 CFR 180.527 (b) for combined residues of the herbicide flufenacet, N-(4-fluorophenyl)-N-(1-methylethyl)-2-[[5- (trifluoromethyl)-1,3,4-thiadiazol-2-yl]oxy]acetamide and it's metabolites containing 4-fluoro-N-methylethyl benzenamine moiety] be made permanent and moved to 40 CFR 180.527 (a), cattle, fat at 0.05 ppm; cattle, kidney at 0.5 ppm; cattle, meat at 0.05 ppm; cattle, meat byproducts at 0.1 ppm; goat, fat at 0.05 ppm; goat, kidney at 0.5 ppm; goat, meat at 0.05 ppm; goat, meat byproducts at 0.1 ppm; hog, fat at 0.05 ppm; hog, kidney at 0.5 ppm; hog, meat at 0.05 ppm; hog, meat, byproducts at 0.1 ppm; horse, fat at 0.05 ppm; horse, kidney at 0.5 ppm; horse, meat at 0.05 ppm; horse, meat byproducts at 0.1 ppm; sheep, fat at 0.05 ppm; sheep, kidney at 0.5 ppm; sheep, meat at 0.05 ppm; sheep, meat byproducts at 0.1 ppm

EPA has determined that the petition contains data or information regarding the elements set forth in section 408 (d)(2) of the FDDCA; however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data supports granting of the petition. Additional data may be needed before EPA rules on the petition.

A. Residue Chemistry

1. Pl*ant metabolism.* [The nature of the residue in field corn, soybean, rotational crops and livestock is adequately understood. The residues of concern for the tolerance expression are flufenacet parent and its metabolites containing the 4-fluoro-N-methylethyl benzenamine moiety. Based on the results of animal metabolism studies, it is unlikely that secondary residues would occur in animal commodities from the use of flufenacet on sweet corn, perennial grasses grown for seed or wheat.]

2. *Analytical method.* [An adequate analytical method, gas chromatography/mass spectrometry with selected ion monitoring, is available for enforcement purposes.

3. *Magnitude of residues.* [Field residue trials were conducted across the major production regions of corn (including sweet corn), wheat and perennial grasses grown for seed in the United States. In all cases, the treatment regime was selected to represent the use patterns that are most likely to result in the highest residue and used a 60% dry flowable formulation of the active ingredient. For corn (field and sweet) the test plots received a single application of the product at a rate of 0.9 lbs. of active ingredient per acre and was applied at preplant soil incorporated, preemergence broadcast and early postemergence application timings. For corn collected at the early milk stage (and sweet corn), the highest average field trial residues in corn raw agricultural commodities were 0.36 ppm in forage, 0.16 ppm in fodder, and less than 0.05 ppm in grain (K+CWHR). For wheat, a single post-emergence foliar application of flufenacet was made to wheat at 0.36 lb ai/A/season. Applications were made in the fall or 2 weeks after the beginning of spring growth using broadcast ground equipment. The highest average field trial residues in wheat raw agricultural commodities were 8.12 ppm in/on wheat forage, 0.95 ppm in/on hay, 0.35 ppm in/on grain and 0.30 ppm in/or on straw. A comparison of the residues in the raw agricultural commodity with processed fractions obtained from a wheat processing study indicate that residues of flufenacet concentrate in bran and germ only by factors of 2.1x and 1.3x, respectively, but are reduced in flour (0.4x), shorts (0.9x), and middlings (0.8x). The maximum theoretical concentration factor for wheat is 8x (860.1520, Table 1). For perennial grasses grown for seed, a single post-emergence foliar application of flufenacet was made to grass grown for seed at 0.45 lb ai/A/season. Applications were made to immature grass at the end of winter dormancy using broadcast ground equipment. The highest average field trial residues in grass forage was 6.08 ppm, grass straw was 0.2 ppm, grass forage from regrowth was 0.08 ppm and was 0.20 ppm for hay from grass regrowth.]

B. Toxicological Profile

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1. *Acute toxicity*. [Technical grade flufenacet has a low to moderate order of toxicity in rats by the oral route of exposure. The acute oral LD_{50} was 1,617 milligrams/kilogram (mg/kg) for males and 589 mg/kg for females. ii. A dermal toxicity study on technical grade flufenacet revealed low acute toxicity to rats. The dermal LD_{50} for both sexes was >2,000 mg/kg, the highest dose tested. iii. An acute inhalation study on technical grade flufenacet showed low toxicity in rats with a 4-hour liquid aerosol LC_{50} for males and females of >3,740 mg/m3 air, the highest concentration tested. iv. An eye irritation study on technical grade flufenacet in rabbits showed minimal irritation to the [[Page 13706]] conjunctiva completely reversible within 7 days. v. A dermal irritation study on technical grade flufenacet in rabbits did not produce any irritation. vi. Skin sensitization studies on technical grade flufenacet in guinea pigs have produced equivocal results. A skin sensitization potential was exhibited under the conditions of a maximization test, whereby, there was no skin sensitization potential when tested by the Buehler Topical Closed Patch Technique.]

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2. *Genotoxicty*. [Flufenacet was negative for mutagenic/genotoxic effects in a gene mutation/in vitro assay in bacteria, a gene mutation/ in vitro assay in Chinese hamster lung fibroblasts cells, a cytogenetics/in vitro assay in Chinese hamster ovary cells, a cytogenetics/in vivo mouse micronucleus assay, and an in vitro unscheduled DNA synthesis assay in primary rat hepatocytes.]

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3. *Reproductive and developmental toxicity*. [A two-generation rat reproduction study with a parental systemic no observed adverse effect level (NOAEL) of 20 ppm (1.4 mg/kg/day in males and 1.5 mg/kg/day in females) and a reproductive NOAEL of 20 ppm (1.3 mg/kg/day) and a parental systemic lowest observed adverse effect level (LOAEL) of 100 ppm (7.4 mg/kg/day in males and 8.2 mg/kg/day in females) based on increased liver weight in F_1 females and hepatocytomegaly in F_1 males and a reproductive LOAEL of 100 ppm (6.9 mg/kg/day) based on increased pup death in early lactation (including cannibalism) for F_1 litters and the same effects in both F_1 and F_2 pups at the high dose level of 500 ppm (37.2 mg/kg/ day in F_1 males and 41.5 mg/kg/day in F_1 females, respectively). A rat developmental study with a maternal NOAEL of 25 mg/kg/day and with a maternal LOAEL of 125 mg/kg/day based on decreased body weight gain initially and a developmental NOEL of 25 mg/kg/day and a developmental LOAEL of 125 mg/kg/day based on decreased fetal body weight, delayed development (mainly delays in ossification in the skull, vertebrae, sternebrae, and appendages), and an increase in the incidence of extra ribs. A rabbit developmental study with a maternal NOAEL of 5 mg/kg/ day and a maternal LOAEL of 25 mg/kg/day based on histopathological finds in the liver and a developmental NOAEL of 25 mg/kg/day and a developmental LOAEL of 125 mg/kg/day based on increased skeletal variations.]

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4. *Subchronic toxicity*. [An 84-day rat feeding study with a NOAEL less than 100 ppm (6.0 mg/kg/day) for males and a NOAEL of 100 ppm (7.2 mg/kg/day) for females and with a LOAEL of 100 ppm (6.8 mg/kg/day) for males based on suppression of thyroxine (T4) level and a LOAEL of 400 ppm (28.8 mg/kg/day) for females based on hematology and clinical chemistry findings. A 13-week mouse feeding study with a

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NOAEL of 100 ppm (18.2 mg/ kg/day for males and 24.5 mg/kg/day for females) and a LOAEL of 400 ppm (64.2 mg/kg/day for males and 91.3 mg/kg/day for females) based on histopathology of the liver, spleen and thyroid. A 13-week dog dietary study with a NOAEL of 50 ppm (1.70 mg/ kg/day for males and 1.67 mg/kg/day for females) and a LOAEL of 200 ppm (6.90 mg/kg/day for males and 7.20 mg/kg/day for females) based on evidence that the bio-transformation capacity of the liver has been exceeded, (as indicated by an increase in LDH, liver weight, ALK and hepatomegaly), globulin and spleen pigment in females, decreased T4 and ALT values in both sexes, decreased albumin in males, and decreased serum glucose in females. A 21-day rabbit dermal study with the dermal irritation NOAEL of 1,000 mg/kg/day for males and females and a systemic NOAEL of 20 mg/ kg/day for males and 150 mg/kg/day for females and a systemic LOAEL of 150 mg/kg/day for males and 1,000 mg/kg/day for females based on clinical chemistry data (decreased T4 and FT4 levels in both sexes) and centrilobular hepatocytomegaly in females.]

5. *Chronic toxicity*. [A 1-year dog chronic feeding study with a NOAEL was 40 ppm (1.29 mg/kg/day in males and 1.14 mg/kg/day in females) and a LOAEL of 800 ppm (27.75 mg/kg/day in males and 26.82 mg/ kg/day in females) based on increased alkaline phosphatase, kidney, and liver weight in both sexes, increased cholesterol in males, decreased T2, T4 and ALT values in both sexes, and increased incidences of microscopic lesions in the brain, eye, kidney, spinal cord, sciatic nerve and liver. A rat chronic feeding/carcinogenicity study with a NOAEL less than 25 ppm (1.2 mg/kg/day in males and 1.5 mg/kg/day in females) and a LOAEL of 25 ppm (1.2 mg/kg/day in males and 1.5 mg/kg/day in females) based on methemoglobinemia and multi-organ effects in blood, kidney, spleen, heart, and uterus. Under experimental conditions the treatment did not alter the spontaneous tumor profile. In a mouse carcinogenicity study the NOAEL was less than 50 ppm (7.4 mg/kg/day) for males and the NOAEL was 50 ppm (9.4 mg/kg/day) for females and the LOAEL was 50 ppm (7.4 mg/kg/day) for males and the LOAEL was 200 ppm (38.4 mg/kg/day) for females based on cataract incidence and severity. There was no evidence of carcinogenicity for flufenacet in this study.]

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

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7. *Metabolite toxicology*. [A 55-day dog study with subcutaneous administration of thiadone (flufenacet metabolite) supports the hypothesis that limitations in glutathione interdependent pathways and antioxidant stress result in metabolic lesions in the brain and heart following flufenacet exposure.]

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8. *Endocrine disruption*. [EPA is required to develop a screening program to determine whether certain substances (including all pesticides and inerts) may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other effect. The Agency is currently working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists in developing a screening and testing program and a priority setting scheme to

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implement this program. EPA may require further testing of this active ingredient and end use products for endocrine disrupter effects. Based on the toxicological findings for flufenacet relating to endocrine disruption effects, flufenacet may be considered as a candidate for evaluation as an endocrine disrupter when the exact criteria are established.]

9. *Other studies*. [An acute rat neurotoxicity study with a NOAEL less than 75 mg/kg/day and a LOAEL of 75 mg/kg/day based on decreased motor activity in males. A rat subchronic neurotoxicity study with a NOAEL of 120 ppm (7.3 mg/kg/day in males and 8.4 mg/kg/day in females) and a LOAEL of 600 (38.1 mg/kg/day in males and 42.6 mg/kg/day in females) based on microscopic lesions in the cerebellum/medulla and spinal cords. A rat developmental neurotoxicity dietary study established an overall NOAEL for both dams and offspring of 17.5 ppm. A LOAEL of 80.8 ppm was established based on body weight and feed consumption declines common to both dams and offspring as well as developmental delays which were noted in the offspring (eye opening, preputial separation). No evidence of specific neurobehavioral effects in the offspring were observed at dietary concentrations of up to 404 ppm.]

C. Aggregate Exposure

1. *Dietary exposure*. [A tolerance currently exists 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 corn, field, forage; corn, field, grain; corn, field, stover; and soybean, seed; and for indirect or inadvertent residues for flufenacet and its metabolites in or on alfalfa, forage; alfalfa, hay; alfalfa, seed; clover, forage; clover, hay; grain, cereal, group 15, except rice; grain, cereal, forage, fodder and straw, group 16, except rice; and grass, forage, fodder, and hay, group 17. Section 18 emergency exemptions for use on wheat have been approved in several states. Bayer CropScience is requesting that the current time limited tolerances for meat and meat by-products also be made permanent. There are no residential uses for flufenacet; therefore aggregate exposure would consist of any potential exposure to flufenacet residues in the registered and proposed crops and in drinking water.]

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i. *Food*. [Tier 3 acute and chronic dietary assessments were conducted to evaluate the dietary exposure of the U.S. population and selected subpopulations to flufenacet residues. These analyses cover the current flufenacet registrations which include application to soybeans, pre- and early post- application to corn, and indirect or inadvertent residues on alfalfa, clover and crop groups 15, 16, and 17. In addition, proposed uses on wheat, sweet corn, popcorn and grasses grown for seed are included in this assessment. The analyses were conducted using Exponent, Inc.'s DEEM-FCID™ software. Consumption data used in this program were taken from USDA's CSFII, 1994-1996 and 1998. Acute dietary risk is expressed as a percentage of the acute Population Adjusted Dose (aPAD) of 0.0017 mg/kg bw/day based on a LOAEL of 1.7 mg/kg bw/day from a developmental neurotoxicity study in rats with an uncertainty factor of 1000 [10X uncertainty factor (UF) for interspecies extrapolation, 10X UF for intraspecies variation;

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and 10X UF due to the lack of a No-Observed-Adverse-Effect-Level]. The estimated acute exposure at the 99.9th percentile for the U. S. population was 12.2% of the aPAD. Children 1-2 years were the most highly exposed subpopulation at 22.4% of the aPAD. Beef was the main contributor to the acute exposure for all population groups. Chronic dietary risk is expressed as a percentage of the chronic Population Adjusted Dose (cPAD) of 0.0017 mg/kg bw/day based on a LOAEL of 1.7 mg/kg bw/day from a developmental neurotoxicity study in rats with an uncertainty factor of 1000 [10X uncertainty factor for interspecies extrapolation, 10X UF for intraspecies variation; and 10X UF due to the lack of a No-Observed-Adverse-Effect-Level]. The estimated chronic exposure for the U.S. population was 0.8% of the cPAD. Two subpopulations, Children 1-2 year and Children 3-5 years, were the most highly exposed groups at 1.6% of the cPAD. Commodities contributing to the over-all dietary exposure for all the population groups were beef (~80%) and cereal grains (~15%).]

ii. *Drinking water*. [In EPA's HED Human Health Risk Assessment, Environmental Fate and Ecological Effects Division (EFED) provided the Estimated Environmental Concentration (EEC) for flufenacet and for thiadone, its primary degradate of concern in water. The drinking water assessment was driven by the peak concentration in surface water. The surface water estimates were calculated using the PRZM and EXAMS simulation models. For surface water, the acute (peak) value of 9.6 ppb, as well as the long-term average of 1.3 ppb, were based on application of flufenacet to corn. The simulation also showed that thiadone would not exceed three percent of the amount of the parent compound at the time of year when the parent compound concentrations are highest. Therefore, the parent plus degradate acute concentration value was estimated not to exceed 9.9 ppb. The groundwater EEC concentration of 0.21 ppb was estimated using the SCIGROW program. Both the surface and groundwater values represent upper-bound conservative estimates for concentrations that might be found in surface water and ground water due to the use of flufenacet. The peak and annual average concentrations calculated by the model are well below the calculated Drinking Water level of Comparison (DWLOC) and demonstrate that the dietary exposure to flufenacet residue with these registered and pending uses is below the Agency's level of concern.]

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2. *Non-dietary exposure*. [There are no non-food uses of flufenacet currently registered under the Federal Insecticide, Fungicide and Rodenticide Act, as amended. No non-dietary exposures are expected for the general population.]

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D. Cumulative Effects

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Flufenacet is structurally a thiadiazole. Bayer CropScience is not aware of any other pesticides with this structure. For flufenacet, EPA has not yet conducted a detailed review of common mechanisms to determine whether it is appropriate, or how to include this chemical in a cumulative risk assessment. After EPA develops a methodology to address common mechanism of toxicity issues to risk assessments, the Agency will develop a process (either as part of the periodic review of pesticides or otherwise) to reexamine

these tolerance decisions. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, flufenacet does not appear to produce a toxic metabolite produced by other substances.

E. Safety Determination

1. *U.S. population.* [Using the conservative exposure assumptions described above and based on the completeness of the toxicity data, it can be concluded that aggregate exposure to residues of flufenacet present a reasonable certainty of no harm. Exposure from residues in crops utilize 12.2% of the aPAD and 0.8% of the cPAD. EPA generally has no concerns for exposures below 100% of the Population Adjusted Doses. Drinking water levels of concern are well above the estimated drinking water concentrations as calculated by conservative models. An aggregate assessment for all uses for flufenacet demonstrated that there is a reasonable certainty that no harm will result to the US Population from uses of flufenacet.]

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2. *Infants and children.* [EPA has considered data from developmental toxicity studies in the rat and rabbit and a 2-generation reproduction study in the rat. These studies are discussed under Section B (Toxicology Profile) above. The developmental toxicity data demonstrated no increased sensitivity of rats or rabbits to in utero exposure to flufenacet. In addition, the multi-generation reproductive toxicity study did not identify any increased sensitivity of rats to in utero or post-natal exposure. Parental NOAELs were lower or equivalent to developmental or offspring NOAELs. The developmental toxicity studies are designed to evaluate adverse effects on the developing organism resulting from maternal pesticide exposure during gestation. Reproduction studies provide information relating to effects from exposure to the pesticide on the reproductive capability of mating animals and data on systemic toxicity.

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FFDCA section 408 provides that EPA shall apply an additional tenfold margin of safety for infants and children in the case of threshold effects to account for pre-and post-natal toxicity and the completeness of the data base unless EPA determines that a different margin of safety will be safe for infants and children. EPA has determined that the toxicological database is complete for FQPA purposes and that there are no residual uncertainties for pre-/post-natal toxicity for flufenacet. Based on the available toxicity data the EPA has recommended that the Special FQPA Safety Factor be reduced to 1x.

Based on the exposure assessments described above and on the completeness and reliability of the toxicity data, it can be concluded that the dietary exposure from all label and pending uses of flufenacet consumes 22.4% of the aPAD at the 99.9th percentile and 1.6% of the cPAD for the most sensitive population subgroups, children 1-2 years and children 3-5 years. Thus, it can be concluded that there is a reasonable certainty that no harm will result from aggregate exposure to flufenacet residues.]

F. International Tolerances

[[No CODEX Maximum Residue Levels (MRLs) have been established for residues of flufenacet on any crops.**]**