FILE NAME: 62719.doc (11/21/2006)

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

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TEMPLATE:

[Dow AgroSciences]

[Insert petition number]

EPA has received a pesticide petition **([PP]) from [Dow AgroSciences LLC, 9330 Zionsville Road, Indianapolis, IN 46268]** 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 **[fluroxypyr MHE and its metabolite fluroxypyr (expressed as combined residues of total fluroxypyr)]** in or on the raw agricultural commodity **[Pome, fruit, group 11]** at **[0.02]** parts per million (ppm); in or on **[millet, grain]** at **[0.5]** parts per million (ppm), **[millet, forage]** at **[12.0]** parts per million (ppm), and **[millet, hay]** at **[20.0]** parts per million (ppm); in or on **[millet, proso, grain]** at **[0.5]** parts per million (ppm), **[millet, proso, straw]** at **[12.0]** parts per million (ppm), **[millet, proso, forage]** at **[12.0]** parts per million (ppm); and **[millet, proso, hay]** at **[20.0]** parts per million (ppm); in or on **[millet, pearl, grain]** at **[0.5]** parts per million (ppm), **[millet, pearl, forage]** at **[12.0]** parts per million (ppm); and **[millet, pearl, hay]** at **[20.0]** parts per million (ppm).

EPA has determined that the petition contains data or information regarding the elements set forth in section 408(d)(2) of the FFDCA; 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. *Plant metabolism.* **[The nature of the residue in plants and animals is adequately understood for the purpose of this tolerance. Based on the findings from these studies, the residues of concern in plants and animal commodities are the parent, fluroxypyr 1-methylheptly ester (MHE) and its metabolite fluroxypyr, free and conjugated. Therefore, the tolerance expression is the combined residues of total fluroxypyr.]**

2. *Analytical method.* **[Adequate enforcement method for the combined**

residues of total fluroxypyr is available to enforce the tolerance expression in or on food. The analytical method uses capillary gas chromatography and mass selective detection (GC-MSD) with limits of quantitation (LOQ) of 0.01 ppm. Fluroxypyr has also been tested through the Food and Drug Administration (FDA), Multi-residue Methodology, Protocols C, D, and E. The results have been published in the FDA Pesticide Analytical Manual, Volume 1.]

3. *Magnitude of residues.* **[Geographically representative field trials on apples, pears, and wheat (representing millet) using an emulsifiable concentrate formulation of fluroxypyr were conducted according to proposed use patterns using parameters that would likely result in the highest residues. The proposed tolerance of 0.02 ppm pome, fruit, group 11; millet, grain at 0.05 ppm; millet, forage at 12.0 ppm; millet, hay at 20.0 ppm; millet, proso, grain at 0.05 ppm; millet, proso, straw at 12.0 ppm; millet, proso, forage at 12.0 ppm; millet, proso, hay at 20.0 ppm; millet, pearl, grain at 0.05 ppm; millet, pearl, forage at 12.0 ppm; and millet, pearl, hay at 20.0 ppm was based on the maximum field trial residue and therefore, would be adequate to cover the highest residues resulting from these fluroxypyr uses. Proposed millet tolerances are based on data developed on wheat due to similarity in both agronomic practices and crop development.]**

B. Toxicological Profile

1. *Acute toxicity.* **[Fluroxypyr MHE has low acute toxicity. The rat oral LD50 is >5000 mg/kg, the rabbit dermal LD50 is >2000 mg/kg, and the rat inhalation LC50 is >1.0 mg/l (1000 mg/cubic meter). In addition, fluroxypyr MHE is not a skin sensitizer in guinea pigs, has no dermal irritation in rabbits, and shows mild ocular irritation in rabbits. The end use formulation of fluroxypyr MHE has a similar low acute toxicity profile. No appropriate endpoint has been identified to quantify a single exposure.]**

2. *Genotoxicty.* **[Short term assays for genotoxicity consisting of a bacterial reverse mutation assay (Ames test), an in vitro assay for cytogenetic damage using the Chinese hamster ovary cells, an in vitro chromosomal aberration assay using rat lymphocytes, and an in vivo cytogenetic assay in the mouse bone marrow (micronucleus test) have been conducted with fluroxypyr MHE. These studies show a lack of genotoxicity. In addition, short term assays for genotoxicity consisting of an Ames metabolic activation test, possible induction of point mutations at the HGPRT-Locus of Chinese hamster ovary cells, in vivo and in vitro chromosomal aberrations in the Chinese hamster ovary cells, unscheduled DNA synthesis in human embryonic cells, and an assay in mouse lymphoma cells have been conducted with fluroxypyr. These studies also show a lack of genotoxicity.]**

3. *Reproductive and developmental toxicity.* **[Developmental studies in rats and rabbits were conducted with both fluroxypyr MHE and fluroxypyr. Studies with fluroxypyr MHE showed maternal and fetal NOELs of 300 mg/kg/day (rat) and 500 mg/kg/day (rabbit). Studies with fluroxypyr showed NOAELs in the rat of 250 mg/kg/day for maternal effects and 500 mg/kg/day for fetal effects and a NOEL in**

the rabbit of 250 mg/kg/day for both maternal and fetal effects. These studies show that fluroxypyr and fluroxypyr MHE are not teratogenic nor will they interfere with in utero development. Two multi-generation reproduction studies were conducted with fluroxypyr in rats. The first in Wistar rats showed no effect on fertility or reproductive performance and had a NOAEL of 500 mg/kg/day (highest dose tested). The second study in Sprague-Dawley rats showed a parental NOEL for systemic effects of 100 mg/kg/day in male rats and 500 mg/kg/day in female rats. The NOEL for reproductive effects was 750 mg/kg/day for males and 1000 mg/kg/day for females (highest dose tested). The NOEL for neonatal effects was 500 mg/kg/day.]

4. *Subchronic toxicity.* **[Fluroxypyr MHE showed a NOEL of 1000 mg/kg/day in a 90-day rat dietary study and a 21-day rabbit dermal study. Ninety day feeding studies with fluroxypyr showed NOELs of 80 mg/kg/day (Wistar rats), 700 mg/kg/day (Fischer 344 rats), 1342 mg/kg/day (male mice), and 1748 mg/kg/day (female mice). In a 4-week dietary, range finding study with fluroxypyr in dogs the NOEL found was >50 mg/kg/day.]**

5. *Chronic toxicity.* **[NOAELs found in the chronic dietary studies are as follows: 150 mg/kg/day (dog), 300 mg/kg/day (mouse), 100 mg/kg/day (male Fischer 344 rats), and 500 mg/kg/day (female Fischer 344 rats). Based on the chronic/carcinogenicity study on rat, EPA has established a chronic reference dose (cRFD) of 1 mg/kg/day. The NOAEL of 100 mg/kg/day was based on increased kidney weight in both sexes and an increase in the severity of chronic progressive glomerulo-nephropathy in the kidney in both sexes at the LOAEL of 500 mg/kg/day. No additional FQPA factor was required, therefore, the chronic population adjusted dose (cPAD) is equal to cRfD. Fluroxypyr is classified as "not likely" a human carcinogen and there was no concern for its mutagenicity potential.]**

6. *Animal metabolism.* **[Both fluroxypyr and fluroxypyr MHE have been evaluated in rat metabolism studies. In summary, these studies show that fluroxypyr MHE is rapidly hydrolyzed and the fate of the hydrolysis products, fluroxypyr and 1-methylheptanol, are independent of whether they were given as the ester or the acid. Fluroxypyr, per se, was extensively absorbed and rapidly excreted principally unchanged in the urine; 1-methylheptanol also was rapidly absorbed and rapidly eliminated. Repeated administration of fluroxypyr MHE was not associated with accumulation in tissues. Also, the metabolism and pharmacokinetics of 1-methylheptanol are comparable to that of the methylheptyl portion of fluroxypyr MHE.]**

7. *Metabolite toxicology.* **[Administration of fluroxypyr, as the acid or methylheptyl ester, in a variety of toxicological studies has produced similar effects. The principal response to sufficiently high dosages, whether administered over the short-term or, in some cases, over a lifetime, was nephrosis. Fluroxypyr is an organic acid that is actively excreted into the urine by the kidney. Thus, the target organ and dose response relationship for fluroxypyr toxicity is entirely consistent with the data on the toxicokinetics of fluroxypyr. Metabolism studies have shown**

that fluroxypyr MHE is rapidly and completely hydrolyzed to fluroxypyr acid and methylheptanol.]

8. *Endocrine disruption.* **[There is no evidence to suggest that fluroxypyr and MHE have an effect on any endocrine system.]**

C. Aggregate Exposure

1. *Dietary exposure*

i. *Food.* **[Tolerances have been established (40 CFR 180.535) for the combined residues of fluroxypyr in or on a variety of raw agricultural commodities, milk, meat and meat by-products. In this petition, tolerances of 0.02 ppm in or on pome, fruit, group 11; 0.5 ppm in or on millet, grain; millet, proso, grain; and millet, pearl, grain are being proposed.**

An acute dietary exposure is not required because no adverse effect attributable to a single exposure of fluroxypyr was observed in the available toxicity studies. Therefore, EPA did not identify an acute dietary endpoint and no acute risk is expected.

In conducting the chronic dietary assessment, Dow AgroSciences used the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID, Version 2.0) which incorporates food consumption data as reported in the CSFII Survey 1994-1996 and 1998. A conservative analysis (Tier 1) was performed with the assumptions that 100% of crops with approved and proposed uses of fluroxypyr would be treated with the pesticide and that the residues would be present at the tolerance levels. Additionally, the processing factors were used in DEEM-FCID for all processed commodities. Based on these conservative assumptions and using a cPAD of 1 mg/kg/day, the exposure to fluroxypyr from food will utilize <1% of the cPAD for the U. S. population, <1% of the cPAD for all infants, and 1.4% of the cPAD for children (1-2 years old), the population subgroup with the highest potential for exposure. Adverse effects are not expected for exposures utilizing less than 100% of the RfD, therefore, chronic dietary exposure and risk for the general U.S. population and children are well within the acceptable levels.]

ii. *Drinking Food.* **[Since the Agency lacks sufficient monitoring data to complete a comprehensive exposure and risk assessment for fluroxypyr in drinking water, drinking water concentration estimates are made on simulation taking into account data on the physical characteristics of fluroxypyr.**

Guidance from EPA has indicated that Tier 1 screening level models, such as GENEEC and SCI-GROW, may be used to estimate upper-bound pesticide residues in surface water and ground water when assessing potential exposure through

drinking water. The main inputs and outputs into each model, as well as the resulting Estimated Environmental Concentrations (EEC) are shown in the table below. Estimated environmental concentrations (EEC) of pesticide in surface water or ground water were then inputted into DEEM model for estimation of dietary exposure from water both direct and indirect sources. The input of water residues along with food into the DEEM model provides a conservative estimate of the total exposure from food and water sources.

In a recent assessment (Federal Register Vol. 68, No. 250 December 31, 2003, FRL-7340-5), EPA used PRZM/EXAMS and SCI-GROW models to estimate the environmental concentrations (EECs) of fluroxypyr in surface water and ground water. The EECs for chronic exposures are estimated to be 3.3 ppb in surface water and 0.062 ppb in ground water. For the U.S. population and all infants, the exposures from food and water represent less than 1% of the cPAD. Additionally, for children age 1-2 years, the population with the highest exposure, the exposures represent approximately 1% of the cPAD. EPA has no concern for aggregate chronic exposure below 100% of the cPAD.]>

<2. Non-dietary exposure. [Fluroxypyr is currently registered for use on residential turfgrass and recreational sites such as golf courses and sports fields. Short- and intermediate-term exposures to fluroxypyr may occur during post-application activities for adults and children. The risk assessment was conducted using the following assumptions: Adults and children may be exposed from dermal contact with turf during post-application activities. Toddlers may experience short- and intermediate-term oral exposure from incidental non-dietary ingestion during post-application activities. Residential handlers may receive short-term dermal and inhalation exposure during mixing, loading and applying the formulations. The HED's Draft Standard Operating Procedures for Residential Exposure Assessments and Recommended Revisions (HED Policy Number 11, February 22, 2001) along with the ORETF and turf transferable residue data were used as the basis for exposure calculations.

Using the above assumptions, the aggregated food and residential exposures resulted in estimated MOEs of 31,000 for the U. S. population and 4,500 for children 1-2 years old. These MOEs are substantially greater than 100, indicating that the risk from potential non-dietary/residential exposures is well within an acceptable level.]>

D. Cumulative Effects

[The potential for cumulative effects of fluroxypyr MHE and fluroxypyr and other substances that have a common mechanism of toxicity is also considered. There is no reliable information to indicate that toxic effects produced by fluroxypyr MHE and fluroxypyr would be cumulative with those of any other pesticide chemical. Thus, it is appropriate to consider only the potential risks of fluroxypyr MHE and fluroxypyr in an aggregate exposure assessment.]

E. Safety Determination

1. *U.S. population.* **[Chronic dietary exposure for the general U.S. population to residues of fluroxypyr from current and proposed uses were estimated to occupy <1% of the cPAD. Thus, the aggregated chronic exposure to fluroxypyr resulting from current and proposed uses is well within the acceptable levels of risk.**

Use of fluroxypyr on turf results in potential short-and intermediate-term exposures. Potential food dietary and residential exposures were combined into an aggregate MOE value, which was calculated to be 31,000 for the U.S. population. The aggregate MOE is well above 100, indicating risk is well within acceptable levels.

Thus, based on the completeness and reliability of the toxicity data and the conservative exposure assessment, it is concluded that there is a reasonable certainty that no harm will result to the U.S. population from chronic, short- and intermediate-term aggregate exposures to fluroxypyr residues from current and proposed uses.]>

2. *Infants and children.* **[FFDCA Section 408 provides that EPA may apply an additional safety factor for infants and children in the case of threshold effects to account for pre- and post-natal toxicity and the completeness of the database. Based on the current toxicological data requirements, the database for fluroxypyr MHE relative to pre- and post-natal effects for children is complete. There were no indications of neurotoxicity and developmental toxicity was not observed in the absence of maternal toxicity. It is concluded that there is no indication of increased sensitivity of infants and children relative to adults and that an additional FQPA safety factor is not required.**

Chronic dietary exposure to residues of fluroxypyr from current and proposed uses was estimated to occupy only 1.4% of the chronic PAD for children 1-2 years old, the population subgroup predicted to be most highly exposed.

Potential food dietary and residential exposures to children 1-2 years old were combined into an aggregate MOE value. The aggregate MOE was estimated to be 4,500 and well above 100, indicating risk is well within acceptable levels.

Thus, based on the completeness and reliability of the toxicity data and the conservative exposure assessment, it is concluded that there is a reasonable certainty that no harm will result to infants and children from chronic, short- and intermediate-term aggregate exposures to fluroxypyr residues from current and proposed uses.]

F. International Tolerances

[There are no Codex maximum residue levels established for residues of fluroxypyr MHE and fluroxypyr on any food or feed crop.]>