FILE NAME: company.wpt (1/1/2006) (xml)
Template Number P25

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

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Interregional Research Project Number 4 (IR-4)

EPA has received pesticide petitions (**[6E7137, 6E7139**) from **[IR-4]**, **[500 College Road East, Suite 201W, Princeton, New Jersey, 08540],** 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 180.574 by establishing tolerances for residues of fluazinam in or on the following raw agricultural commodities:

PP# 6E7137

Vegetable, legume, edible podded, subgroup 6A, except pea at 0.15 part per million (ppm); Brassica, leafy greens, subgroup 5B 0.02 ppm; Brassica, head and stem, subgroup 5A at 0.01 ppm; and Turnip, tops at 0.02.

IR-4 has also requested to establish residues of fluazinam and its metabolite AMGT in or on Bushberry subgroup 13B; Berry, aronia; blueberry, Lowbush; currant, buffalo; guava, Chilean; Barberry, European; cranberry, highbush; honeysuckle; jostaberry; Juneberry; lingonberry; currant, native; salal; and buckthorn, sea at 4.5 ppm

PP# 6E7139

Ginseng at 3 ppm; Bean, dry at 0.01 ppm; and Pea and bean, succulent shelled, subgroup 6B, except pea at 0.02 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. This notice includes a summary of the petitions made by ISK Biosciences Corporation, 7470 Auburn Road, Suite A, Concord, OH 44077.

A. Residue Chemistry

1. *Plant metabolism.* The residue of concern is best defined as the parent, fluazinam in most crops and as the parent, fluazinam and its metabolite, AMGT, in fruit crops (grape and blueberry).

The metabolism of fluazinam in plants (potatoes, peanuts, apples and wine grapes) is

adequately understood for the purposes of these tolerances. The metabolism of fluazinam in peanut and potato involves initial reduction of the nitro groups, hydrolysis of the trifluoromethyl group as well as replacement of chlorine by glutathione with subsequent reactions along the glutathione pathway. Following replacement of the deactivating NO_2 and Cl groups with activating groups such as OH, NH_2 and sulfhydryl, ring cleavage occurs. Parent fluazinam is then rapidly degraded to form CO_2 and carbon fragments which are incorporated into natural products such as glucose, fructose, sucrose, oils and protein. Thus, parent fluazinam is either not found or barely detectable in peanuts and potatoes. Fluazinam parent was also the major identifiable residue in both the grape and apple metabolism studies. However, minor levels of AMGT (less than 5% of the total radioactive residue) were also formed on the surface of grapes and apples and could be expected to form on blueberry. In grape and apple metabolism studies, following reduction of the nitro groups and replacement of chlorine with a sulfur containing side-chain such as glutathione (as occurred in peanuts and potatoes), glucose is attached to the thiolactic acid conjugate of AMPA to form the metabolite known as AMGT. This metabolite was not found in
the peanut or potatoes metabolism studies. It is analogous to the cysteine conjugate of AMPA found in rats. Identifiable residues in plant metabolism studies either closely resemble fluazinam in structure or are the result of re_incorporation of the fluazinam carbon pool into natural products.

Ruminant and poultry metabolism studies demonstrated that the transmittal of residues from the feed of goats and hens through to meat, milk, and eggs was low. Total ^{14}C residues were below 1 ppm in all tissues, milk and eggs. Identifiable residues were less than 2% of the administered dose in all matrices, except for chicken fat and liver.

2. *Analytical method.* An analytical method using gas chromatography with electron capture detection (GC_ECD) for the determination of fluazinam residues on beans (snap, lima and dry), Brassica crops (broccoli, cabbage and mustard greens), ginseng and blueberry has been developed and validated. The method involves solvent extraction followed by liquid_liquid partitioning and concentration prior to a final purification using column chromatography. The method has been successfully validated by an independent laboratory using peanut nutmeat as the matrix. The limit of quantitation of the method is 0.02 ppm in snap, lima beans and blueberry and 0.01 ppm in broccoli, cabbage, mustard greens, dry beans, and ginseng. An analytical method using reversed-phase HPLC with UV absorbance detection for the determination of AMGT residues on blueberry has been developed and validated. As for fluazinam, the method involves solvent extraction followed by liquid_liquid partitioning and concentration prior to a final purification using column chromatography. The limit of quantitation of the method for AMGT is 0.04 ppm in/on blueberry. The method has been successfully validated by an independent laboratory on grapes and wine.

3. *Magnitude of residues.* i. Ginseng. Data from 4 field trials on ginseng (4 applications at 0.8 lb a.i./A) showed that residues of fluazinam from duplicate samples at each location ranged from 0.28 to 1.4 ppm in the RAC ginseng root harvested 30 days after the last application.

ii. Brassica. A total of 8 field trials were conducted on broccoli, 10 field trials on cabbage and 11 field trials on mustard greens with application of fluazinam in transplant water at 0.055 lbs a.i./1000 plants. Crops were harvested 60 to 113 days after application for cabbage and broccoli

and 25 to 78 days after application for mustard greens. No residues of fluazinam were found in any sample of broccoli or cabbage harvested from all location (all were below the LOQ of 0.01 ppm). The maximum residue found in mustard greens was 0.01 ppm, which is the LOQ for this matrix.

iii. Beans. A total of 11 field trials were conducted on snap beans, 7 field trials on lima beans and 13 field trials on dry beans. Two applications at 0.45 lbs a.i./A were made to snap, lima and dry beans with the first application at early bloom, however the interval between applications ranged from 2 to 6 days for snap beans, 3 to 6 days for lima beans and about 14 days for dry beans. Harvest intervals were 10-21 days, 28-71 days and 31-57 days for snap, lima and dry beans, respectively. In snap beans, residues of fluazinam ranged from <0.02 ppm to 0.109 ppm with mean residues of 0.08 ppm. Residues in lima beans and dry beans were all below the LOQ's of 0.02 and 0.01 ppm, respectively.

iv. Blueberry. A total of 13 field trials were conducted with fluazinam on blueberry (6 applications at 0.65 lb a.i./A). For fruit harvested 23-32 days after the last application, residues of fluazinam in/on blueberry ranged from 0.042 to 3.0 ppm with a mean residue of 0.91 ppm. Residues of the metabolite AMGT in/on blueberry ranged from 0.025 to 0.28 ppm with a mean residue of 0.094 ppm. Maximum total residues of fluazinam plus AMGT in/on blueberry were 3.28 ppm.

v. Secondary residues. No tolerances are proposed for residues of fluazinam in meat, milk, poultry or eggs. Blueberry, Brassica crops, beans, ginseng and imported wine grapes are not animal feed items. In addition, since levels of fluazinam in dry beans, potatoes and peanut nutmeat were below detectable levels (the fluazinam label includes a peanut hay grazing restriction), no residues of concern are expected on animal feed items. Furthermore, since animal metabolism studies do not show potential for significant residue transfer, detectable secondary residues in animal tissues, milk or eggs are not expected. Therefore, tolerances are not needed for these commodities.

B. Toxicological Profile

1. *Acute toxicity.*

A battery of acute toxicity studies was conducted which placed technical fluazinam in Toxicity Category III for oral LD_{50}, dermal LD_{50}, dermal irritation, Category II for inhalation LC_{50} and Category I for eye irritation. Technical fluazinam showed potential for dermal sensitization.

In an acute neurotoxicity study, the NOEL for neurotoxicity was 2000 mg/kg bw (HDT) and the NOEL for systemic effects was 50 mg/kg bw.

2. *Genotoxicty.* A battery of tests has been conducted to assess the genotoxic potential of technical fluazinam. Assays conducted included two gene mutation tests in bacteria, a chromosomal aberration test in mammalian cells, a mouse micronucleus test and a DNA repair test in bacteria. Technical fluazinam did not elicit a genotoxic response in any of the studies conducted.

3. *Reproductive and developmental toxicity.*

In a two_generation reproductive toxicity study, the NOEL for reproductive effects was 100 ppm (10.1 mg/kg bw/day). The NOEL for parental toxicity was 20 ppm (2.1 mg/kg bw/day).

In a rat developmental study, there were no developmental effects observed at non_maternally toxic doses. The developmental NOEL was 50 mg/kg bw/day and the LOEL was 250 mg/kg bw/day, based upon statistically significant decreased mean fetal body weight and other evidence suggestive of delayed fetal development related to maternal toxicity. The maternal NOEL was shown to be 50 mg/kg bw/day.

In a rabbit developmental study, there were no developmental effects observed at non_maternally toxic doses. The developmental NOEL was 7 mg/kg bw/day and the LOEL was 12 mg/kg bw/day, based on increased incidence of total litter loss and possible slightly increased incidences of fetal findings at this dose. It was concluded that the maternal NOEL was 4 mg/kg bw/day.

4. *Subchronic toxicity.*

The NOEL for the 13-week feeding study in rats was 50 ppm (4.1 mg/kg bw/day). The LOEL was 500 ppm (41 mg/kg bw/day), based on periacinar hepatocellular hypertrophy and sinusoidal chronic inflammation in males, increased liver weights in males and increased lung weights in females.

In a 13-week dog study, the NOEL was 10 mg/kg bw/day. The LOEL was 100 mg/kg bw/day, based on ocular change observed ophthalmoscopically and liver effects consisting of increased relative liver to body weight, bile duct hyperplasia with or without cholangiofibrosis and increased plasma phosphatase levels.

In a 21-day dermal study, the NOEL for systemic effects was 10 mg/kg bw/day. The LOEL was 100 mg/kg bw/day, based on hepatocelluar hypertrophy and increases in AST and cholesterol levels.

In a subchronic neurotoxicity study, no effects considered to be indicative of neurotoxicity were observed at the highest dose tested, 3000 ppm (233 mg/kg bw/day). The NOEL for systemic toxicity (body weight differences) was 1000 ppm (74 mg/kg bw/day).

In a developmental neurotoxicity study in rats, fluazinam was administered by gavage to female rats from Day 6 after mating to Day 20 of lactation and additionally to their offspring from Day 7 of age to Day 20 or 21 of age. The maternal NOEL was 2 mg/kg bw/day based on reduced body weights and lower food intake. No effects were seen on the microscopic structure of the nervous system of the dams at any dose level (maximum dose of 50 mg/kg bw/day). The NOAEL for behavior and nervous system of the dams was 50 mg/kg bw/day. No adverse effect of treatment at any dose level was seen on number of implantations, litter size or offspring survival. Signs of general toxicity in the offspring were evident based on lower Day 1 body weights and lower weight gains at 10 and 50 mg/kg bw/day through weaning. The NOEL for general toxicity to offspring was 2 mg/kg bw/day. There was no evidence of developmental neurotoxicity in the offspring. The NOAEL for the functional and morphological development of the nervous system in the offspring was 50 mg/kg bw/day. There was no increased sensitivity of the fetus or young rat pups to fluazinam as compared to the dams.

5. *Chronic toxicity.*

Fluazinam was not carcinogenic in rats. A NOEL of 10 ppm (0.43 mg/kg bw/day) of fluazinam was established based on the following effects at 1000 and/or 100 ppm: lower food

consumption and efficiency of food utilization, slight anemia, elevated cholesterol, increased liver weights, an increased number of macroscopic liver and testes lesions and an increased incidence of microscopically observed lung, liver, pancreas, lymph node and testes lesions.

An additional study was conducted to further define the NOEL for long_term effects in the rat. In the second study, a NOEL of 50 ppm (2.2 mg/kg bw/day) was established based on liver and testes effects.

Two long_term feeding studies were conducted in mice. In the first, the NOEL for all effects was 10 ppm (1.14 mg/kg bw/day) and the LOEL was 100 ppm (11.2 mg/kg bw/day) based on the treatment_related effects observed in the liver.

A second oncogenicity study in mice was conducted at 1000, 3000 and 7000 ppm to ensure that an MTD dose was studied. Findings included increased female mortality, reduced body weight gains, increased brain weights and/or liver weights. An impurity in the test material used in this study resulted in vacuolation of the white matter of the brain and cervical spinal cord in treated animals. A statistically significant higher incidence of hepatocellular adenomas was observed in the 3000 ppm dose males. Hepatocellular adenomas are common tumors in male mice. There was no dose relationship in the induction of the adenoma and no increase in hepatocellular carcinomas. It is concluded that fluazinam is not carcinogenic in the mouse.

In a chronic dog study, the NOEL was determined to be 1 mg/kg bw/day. The LOEL was 10 mg/kg bw/day based on generalized, nonspecific toxicity. No ocular effects were observed ophthalmoscopally at any dose in this study.

6. *Animal metabolism.* After an oral dose of fluazinam the median peak time for blood concentration of radiolabel activity for both sexes was 6 hours. The major route of excretion was the feces with urine contributing as a minor route. Less than 1% of the administered dose was found in the terminated animals. The highest concentration was found in the liver. There were no major differences related to sex or dose level in the findings. It was concluded that fluazinam is metabolized by both reduction and glutathione and glucuronide conjugation and further metabolism

7. *Metabolite toxicology.*

The same metabolic processes occur in plants and animals but metabolism in plants is more extensive than in animals. All of the major identified metabolites in both plants and animals retain the phenylpyridinylamine structure. Many of the metabolites resulting from fluazinam are similar in plants and animals and, therefore, have already been evaluated toxicologically.

Because of the rapid and complete elimination (in animals) and re_incorporation (in plants) of fluazinam, the toxicity of metabolites is expected to be similar to but lower than the toxicity of the parent compound. The residue of concern is parent fluazinam only in most crops and parent fluazinam plus its minor metabolite AMGT on/in fruit crops such as grape and blueberry.

8. *Endocrine disruption.* The toxicological profile of fluazinam shows no evidence of physiological effects characteristic of the disruption of the hormone estrogen in mammalian chronic studies or in mammalian or avian reproduction studies. It is therefore considered that there is an adequate level of safety over the reference dose for possible endocrine effects and that an additional safety factor for possible endocrine effects is not warranted.

C. Aggregate Exposure

1. *Dietary exposure*. Potential dietary exposures from food were estimated using the proposed tolerances for all crops using the Dietary Exposure Evaluation Model-Food Consumption Intake Database (DEEM-FCID^{TM}) and percent crop treated of 100% (with the exception of imported wine grapes as discussed below). The following raw agricultural commodities were included: ginseng, potato, head and stem Brassica, leafy Brassica greens, bean Groups 6A, 6B and 6C, blueberry, grape wine and sherry, and peanut. For acute dietary exposure, the acute population adjusted dose (aPAD) was based on the NOEL of 50 mg/kg bw/day from an acute rat neurotoxicity study. For chronic dietary exposure, the chronic population adjusted dose (cPAD) was based on the NOEL from the one-year dog study (1 mg/kg bw/day). An uncertainty factor of 100 was used in both cases since the results of a DNT study confirmed there was no increased sensitivity of the fetus or young rat pups to fluazinam as compared to the dams and the FQPA uncertainty factor could be reduced to one (1).

i. *Food.*

Acute Risk Tier 1 acute dietary exposure analyses were conducted for fluazinam in/on ginseng, beans (Subgroups 6A, 6B and 6C), head and stem Brassica, leafy Brassica greens, blueberry, peanuts, potatoes and imported wine grapes to determine the exposure contribution of these commodities to the diet and to ascertain the acute risk potential. The estimates were based on proposed tolerance level residues for all the crops, peanut and potato processing studies, market share assumptions of 100% crop treated (except wine grapes where it was assumed that 100% of the imported wine grapes would be treated and 23% of wine consumed in the US is imported), and consumption data from USDA's CSFII (1994 through 1996 and 1998) continuing survey of food intake.

Even using all of the worst-case exposure scenarios listed above, the Tier 1 95th percentile acute dietary exposure (per capita) for the U.S. population was estimated to be 0.001085 mg/kg bw/day or 0.22% of the aPAD. The highest acute exposure estimate (95th percentile) was observed in all infants (<1 year) subpopulation: 0.004921 mg/kg bw/day. This corresponds to only 0.98% of the aPAD.

Chronic Risk Tier 1 dietary exposure analyses were conducted for fluazinam in/on ginseng, beans (Subgroups 6A, 6B and 6C), head and stem Brassica, leafy Brassica greens, blueberry, peanuts, potatoes and imported wine grapes to determine the exposure contribution of these commodities to the diet and to ascertain the chronic risk potential. The estimates were based on proposed tolerance level residues for all the crops, peanut and potato processing studies, market share assumptions of 100% crop treated (except wine grapes where it was assumed that 100% of the imported wine grapes would be treated and 23% of wine consumed in the US is imported), and consumption data from USDA's CSFII (1994 through 1996 and 1998) continuing survey of food intake.

Even using all of the worst-case exposure scenarios listed above, the Tier 1 chronic dietary exposure estimates resulted in an estimated exposure for the U.S. population of 0.000215 mg/kg bw/day. This exposure corresponds to 2.2% of the cPAD of 0.01mg/kg bw/day. The highest exposure estimate was calculated for the children 1-2 years of age population subgroup. This exposure was determined to be 0.000373 mg/kg bw/day (3.7% of the cPAD).

It can be concluded that acute or long_term dietary exposure to fluazinam through residues on

treated ginseng, beans, Brassica crops, blueberry, peanuts, potatoes and imported wine grapes should not be of cause for concern.

ii. *Drinking water.* Since fluazinam is intended for application outdoors to field grown ginseng, bean Groups 6A, 6B and 6C, all Brassica crops, blueberry, peanuts, potatoes and imported wine grapes, the potential exists for parent and or metabolites to reach ground or surface water that may be used for drinking water. The calculated drinking water levels of comparison (DWLOC) for chronic exposure for adult males, adult females and toddlers were estimated to be 342 ppb, 293 ppb, and 96 ppb, respectively. The calculated drinking water levels of comparison (DWLOCs) for acute exposure for all adults, adult females and toddlers were estimated to be 17,462 ppb, 14,968 ppb, and 4,987 ppb, respectively. The chronic and acute DWLOC values are well above the modeled maximum chronic and acute drinking water estimated concentrations (DWECs) of 2.2 ppb (annual average FIRST and SCI-GROW) from use on blueberry and 71 ppb (peak day concentration FIRST and SCI-GROW) from use on blueberry or ginseng, respectively. Therefore, there is comfortable certainty that no harm will result from combined dietary (food and water) exposure due to the use of fluazinam on ginseng, beans, Brassica crops, blueberry, peanuts, potatoes and imported wine grapes.

2. *Non-dietary exposure.* No petition for registration of fluazinam is being made for either indoor or outdoor residential use. Non_occupational exposure of fluazinam to the general population is therefore not expected and is not considered in aggregate exposure estimates.

D. Cumulative Effects

Fluazinam is a phenylpyridinylamine fungicide. Since there are no other members of this class of fungicides, it is considered unlikely that fluazinam would have a common mechanism of toxicity with any other pesticide in use at this time.

E. Safety Determination

1. *U.S. population.* Based on a NOEL of 1 mg/kg bw/day from a one year feeding study in dogs, and using an uncertainty factor of 100, a reference dose (RfD) of 0.01 mg/kg bw/day is proposed for assessment of long_term risk. Since the results of a DNT study confirmed there was no increased sensitivity of the fetus or young rat pups to fluazinam as compared to the dams and the FQPA uncertainty factor could be reduced to one (1) and the cPAD is equivalent to the RfD. The estimate of dietary intake was based on proposed tolerance level residues for ginseng, beans (snap, lima and dry), Brassica crops, blueberry, peanuts, potatoes and imported wine grapes, and peanut and potato processing studies, market share assumptions of 100% crop treated and consumption data. Even using those conservative intake estimates, the proposed tolerances will utilize only 2.2% of the RfD or cPAD for the U.S. population. The estimated exposure of fluazinam from drinking water, 2.2 ppb is one to two orders of magnitude below the calculated chronic drinking water level of comparison, 293 to 342 ppb. Using these same conservative exposure assumptions, the acute dietary exposure estimates are well below the aPAD of 0.5 mg/kg bw/day and the acute DWEC of 71 ppb is well below the acute DWLOC of 14,968 to 17,462 for adult males and females, respectively. Based on this information, it can be concluded that there is reasonable certainty that no harm will result from acute or chronic exposure to fluazinam. 2. *Infants and children.*

Data from developmental toxicity studies in the rat and rabbit, a 2_generation reproduction study and a developmental neurotoxicity study were considered. These studies, which were described earlier, demonstrated no increased sensitivity of rats or rabbits to *in utero* or gavage exposure of pups to fluazinam. In addition, the multigeneration reproductive toxicity study did not identify any increased sensitivity of rats to *in utero* or postnatal exposure. For all four studies, parental NOELs were lower than or equivalent to the developmental or offspring NOELs. It is concluded that the standard margin of safety will protect the safety of infants and children and that an additional FQPA safety factor is not warranted.

The dietary exposure of fluazinam to infants and children is estimated to be low. The proposed tolerances will utilize only 0.98% of the aPAD for the most highly exposed subgroup all infants (<1 year) and only 3.7% of the cPAD for the most highly exposed subgroup children (1-2 years). The estimated exposure of fluazinam from drinking water, 2.2 ppb (chronic) and 71 ppb (acute) is well below the calculated drinking water levels of comparison of 96 and 4,987 ppb for the chronic and acute DWLOCs, respectively. Thus, it can be concluded that there is reasonable certainty that no harm will result to infants and children from acute or chronic exposure to fluazinam.

F. International Tolerances

There are presently no Codex maximum residue levels established for residues of fluazinam on any crop. The Canadian MRL for potatoes and the Mexican MRL's for beans are similar to the tolerances established or requested for these crops in the USA.