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The Interregional Research Project #4 (IR-4)

PP# 5E6991

EPA has received a pesticide petition (PP# 5E6991) from The Interregional Research Project #4 (IR-4), 681 U.S. Highway #1 South, North Brunswick, NJ 08902-3390, 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 180.564 by establishing a tolerance for residues of the combined residues of Indoxacarb, [(S)-methyl 7-chloro-2,5-dihydro-2-[[(methoxycarbonyl)[4-(trifluoromethoxy)phenyl]amino]carbonyl]indeno[1,2e] [1,3,4]oxadiazine-4a(3H)- carboxylate] and its R-enantiomer [(R)-methyl 7-chloro-2,5-dihydro-2-[[(methoxycarbonyl)[4-(trifluoromethoxy) phenyl] amino]carbonyl]indeno [1,2-e] [1,3,4] oxadiazine-4a(3H)- carboxylate] in a 75:25 mixture (DPX-MP062), respectively, in or on the raw agricultural commodities: Vegetable, cucurbit, group 9 at 0.5 parts per million (ppm); Fruit, stone, group 12 at 1.0 ppm; and Cranberry at 1.0 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

The active ingredient in the end-use formulation, DuPont Avaunt® Insecticide, is a 75:25 mixture of two isomers, indoxacarb (DPX-KN128) and IN-KN127. Only one of the isomers, indoxacarb (DPX-KN128), has insecticidal activity. Since the insecticidal efficacy is based on the concentration of indoxacarb (DPX-KN128), the application rates have been normalized on an indoxacarb (DPX-KN128) basis. The proposed tolerance expression includes both indoxacarb (DPX-KN128) and IN-KN127 and the residue method does not distinguish between the enantiomers, therefore residues are reported as the sum of indoxacarb (DPX-KN128) combined with IN-KN127. Residues of indoxacarb (DPX-KN128) combined with IN-KN127 will be referred to as "KN128/KN127."

1. Plant metabolism. The metabolism of indoxacarb in plants is adequately understood to support these tolerances. Plant metabolism studies in cotton, lettuce, and tomatoes showed no significant metabolites. The only significant residue was parent compound.

2 Analytical method. The plant residue enforcement method detects and quantitates indoxacarb in various matrices including sweet corn, lettuce, tomato, broccoli, apple, grape, cottonseed, tomato, peanut and soybean commodity samples by HPLC UV. The limit of quantitation in the method allows monitoring of crops with indoxacarb residues at or above the levels proposed in these tolerances.

3. Magnitude of residues.

a. Cucurbits Crop Group 9: The average field residue value for all cucurbits was 0.049 ppm

and the maximum was 0.393 ppm.

i. Ten field trials were conducted on cucumber. Four applications were made at the maximum use rate of 0.11 lb. of active ingredient per acre (0.44 lb. of active ingredient maximum seasonal use rate). Harvesting was conducted 3 days after the last application (PHI- Post Harvest Interval). The median field residue value for cucumbers was 0.023 ppm and the maximum at 0.069 ppm.

ii. Twelve field trials were conducted on cantaloupe (muskmelon). Four applications were made at the maximum use rate of 0.11 lb. of active ingredient per acre (0.44 lb. of active ingredient maximum seasonal use rate). For the twelve trials, a median 0.103 ppm residue level and a 0.393 ppm maximum residue were recorded. The trials were harvested at 3, 4, and 5 days after the final application.

iii. Eleven field trials were conducted on summer squash. Four applications were made at the maximum use rate of 0.11 lb. of active ingredient per acre (0.44 lb. of active ingredient maximum seasonal use rate). For the eleven trials, harvesting was conducted giving a median 0.027 ppm residue level and a 0.120 ppm maximum residue. The trials were harvested at 2, 3 and 4 days after the final application.

b. Stone Fruit Crop Group 12: The average field residue value for all stone fruits was 0.164 ppm and the maximum was 0.640 ppm.

i. Sixteen field trials were conducted on cherry. Four applications were made at the maximum use rate of 0.11 lb. of active ingredient per acre (0.44 lb. of active ingredient maximum seasonal use rate). The trials were harvested at 12, 13, 14, and 15 days after the final application for sixteen (16) field trials. The median field residue value for cherry was 0.0.231 ppm with a maximum residue level of 0.640 ppm.

ii. Fifteen field trials were conducted on peach. Four applications were made at the maximum use rate of 0.11 lb. of active ingredient per acre (0.44 lb. of active ingredient maximum seasonal use rate). The trials were harvested 13, 14, and 15 days after the final application for fifteen (15) field trials. The median field residue value for peach was 0.183 ppm with a maximun residue level of 0.590ppm.

iii. Twelve field trials were conducted on plum. Four applications were made at the maximum use rate of 0.11 lb. of active ingredient per acre (0.44 lb. of active ingredient maximum seasonal use rate). Twelve field trials were harvested 13, 14, 15 and 16 days after the final application. The median field residue value for peach was 0.045 ppm with a maximum residue value of 0.190 ppm.

c. Cranberries- Six trials were conducted to determine residues for cranberries. Four applications were made at the maximum use rate of 0.11 lb. of active ingredient per acre (0.44 lb. of active ingredient maximum seasonal use rate). The trials were harvested 28, 29, and 30 days following the final application. Average residues for the six trials were 0.22 ppm with a maximum residue of 0.69 ppm.

B. Toxicological Profile

1. Acute toxicity. Based on EPA criteria, indoxacarb is classified as follows for Toxicity Categories

Guideline	Title	Results	Category
870.1100			

870.1200

870.1300

870.2400

870.2500

870.2600 Acute Oral Toxicity

Acute Dermal Toxicity

Acute Inhalation Toxicity

Primary Eye Irritation

Primary Dermal Irritation

Skin Sensitization LD50: 1730 mg/kg (Male Rat)
LD50: 268 mg/kg/(Female Rat)

LD50: >5000 mg/kg (Rat)

LC50: >5.5 mg/L (Male Rat)
(70% MUP)

Effects reversed within 72 hours (Rabbit)

No irritation (Rabbit)

Sensitizer (Guinea Pig) Category II

Category IV

Category IV

Category III

Category IV

Formulated products are slightly less acutely toxic than indoxacarb.

In an acute neurotoxicity study, indoxacarb exhibited decreased forelimb grip strength, decreased foot splay, and some evidence of slightly reduced motor activity, but only at the highest doses tested. The NOAEL was 100 mg/kg for males and 12.5 mg/kg for females based on body weight effects in females 50 mg/kg.

2. Genotoxicty. Indoxacarb has shown no genotoxic activity in the following listed in vitro and in vivo tests:

Ames Negative
In vitro mammalian gene mutation (CHO/HGPRT) Negative
In vitro unscheduled DNA synthesis Negative
In vitro chromosomal aberration Negative
In vivo mouse micronucleus-Negative

3. Reproductive and developmental toxicity. The results of a series of studies indicated that there were no reproductive, developmental or teratogenic hazards associated with the use of indoxacarb. In a 2 generation rat reproduction study, the parental NOAEL was 1.5 mg/kg/day. The parental NOAEL was based on observations of reduced weight gain and food consumption for the higher concentration groups of the F0 generation and potential treatment related changes in spleen weights for the higher groups of the F1 generation. There was no effect on mating or fertility. The NOAEL for fertility and reproduction was 6.4 mg/kg/day. The offspring NOAEL was 1.5 mg/kg/day, and was based on the reduced mean pup weights noted for the F1 litters of the higher concentration groups. The effects on pup weights occurred only at a maternal effect level and may have been due to altered growth and nutrition in the dams. In studies conducted to evaluate developmental toxicity potential, indoxacarb was neither teratogenic nor uniquely toxic to the conceptus (i.e., not considered a developmental toxin). Developmental studies conducted in rats and rabbits demonstrated that the rat was more susceptible than the rabbit to the maternal and fetal effects of DPX MP062. Developmental toxicity was observed only in the presence of maternal toxicity. The NOAEL for maternal and fetal effects in rats was 2 mg/kg/day based on body weight effects and decreased food consumption at 4 mg/kg/day. The NOAEL for developmental effects in fetuses was >4 mg/kg/day. In rabbits, the maternal and fetal NOAELS were 500 mg/kg/day based on body weight effects, decreased food consumption in dams and decreased weight and delayed ossification in fetuses at 1000 mg/kg/day.

4. Subchronic toxicity. Subchronic (90 day) feeding studies were conducted with rats, mice, and dogs. In a 90 day feeding study in rats, the NOAEL was 3.1 and 2.1 mg/kg/day for males and females, respectively. In male rats, the NOAEL was based on decreased body weight and nutritional parameters, mild hemolytic anemia and decreased total protein and globulin concentration. In female rats, the NOAEL was based on decreased body weight and food efficiency.

In a subchronic neurotoxicity study in rats, there was no evidence of neurotoxicity at 11.9 and 6.09 mg/kg/day, the highest dose tested for males and females, respectively. The subchronic NOAEL in dogs (5.0 mg/kg/day, M/F) was based on hemolytic anemia. Erythrocyte values for most dogs were within a range that would be considered normal for dogs in a clinical setting. Mice were less sensitive to indoxacarb than the rats or dogs. NOAELs (23 mg/kg/day, males, 16 mg/kg/day, females) were based on mortality (males only); increased reticulocytes and Heinz bodies and decreased body weight, weight gain, food consumption, food efficiency; and increased clinical signs (leaning to one side and/or with abnormal gait or mobility) (females only). In a 28 day repeated dose dermal study, the NOAEL was 50 mg/kg/day based on decreased body weights, body weight gains, food consumption, and food efficiency in females, and changes in hematology parameters, the spleen and clinical signs of toxicity in both sexes in rats.

5. Chronic toxicity. Chronic studies with indoxacarb were conducted on rats, mice, and dogs to determine oncogenic potential and/or chronic toxicity of the compound. Effects generally similar to those observed in the 90 day studies were seen in the chronic studies. Indoxacarb was not oncogenic in rats or mice. The chronic NOAEL in male rats was 5 mg/kg/day based on body weight and nutritional effects. In females, the NOAEL of 2.1 mg/kg/day was based on body weight and nutritional changes, as well as biologically significant hematologic changes at 3.6 mg/kg/day and above. Hemolytic effects were present only through the 6 month evaluation and only in females. The regenerative nature of indoxacarb induced hemolytic anemia was demonstrated by the absence of significant changes in indicators of circulating erythrocyte mass at later evaluations. In mice, the chronic NOAEL of 2.6 mg/kg/day for males was based on deceased body weight and weight gain effects and food efficiency at 13.8 mg/kg/day and above. The NOAEL for females was 4.0 mg/kg/day based on body weight nutritional effects, neurotoxicity, and clinical signs at 20 mg/kg/day. In dogs, the chronic NOAEL was about 2.3 and 2.4 mg/kg/day in males and females, respectively based on hemolytic effects similar to those seen in the subchronic dog study.

6. Animal metabolism. Livestock animal metabolism. Animal metabolism has been studied in the rat, hen, and cow and is well understood. In contrast to crops, indoxacarb is extensively metabolized in animals.

Poultry. In poultry, hens were fed at 10 ppm/day for 5 days, 87 88% of the total administered dose was excreted; parent comprised 51 54% of the total dose in excreta. Concentrations of residues in eggs were low, 0.3 0.4 of the total dose, as were the concentrations of residues in muscle, 0.2% of the total dose. Parent and metabolite IN JT333 were not detected in egg whites; only insecticidally inactive metabolites were identified. Parent and IN JT333 were found in egg yolks; however, their concentrations were very low 0.01 0.02 ppm. Concentrations of parent and IN JT333 in muscle were at or below the limit of quantitation, (LOQ) (0.01 ppm).

Poultry Feeding study. A poultry feeding study was not conducted for the initial Section 3 registration because finite concentrations of residues would not be expected based on the low concentration of residues in the metabolism study. However, the Agency has required a poultry feeding study as a condition of registration for indoxacarb. The study was submitted on October 31, 2003. Once the Agency has determined the components of the tolerance expression, poultry meat, fat, by-products and egg tolerances will be proposed.

Cattle. For the cow study, the cattle were fed at 10 ppm/day for 5 days; approximately 20% of the total administered dose was excreted in urine and 53 60% was excreted in feces in 5 days. Four tenths to 1.2% of the total dose in urine was parent indicating extensive metabolism; parent represented 46 68% of the fecal activity. Thus, most residues were not absorbed; those residues that were absorbed were extensively metabolized. Less than 1% of the total administered dose was in milk, most of which was parent compound. The insecticidally active metabolite IN JT333 was not found in milk. Residues in muscle represented less than 0.01% of the total administered dose most of which was parent. IN JT333 was not detected in muscle. No other metabolites were seen above 10% of the dose, thus only parent and IN JT333 were monitored in the cattle feeding study.

Cattle feeding study. A cattle feeding study was conducted with indoxacarb at doses of 7.5 ppm, 22.5 and 75 ppm. The mean KN128/KN127 concentrations were proportional to the dosing level in whole milk, skim milk, cream, muscle, fat, liver and kidney. Based on final residue values for the respective commodities contributing to the cattle diet, the anticipated dietary burden in dairy cattle is 51.7 ppm and the anticipated dietary burden in beef cattle is 49.1 ppm. The proposed grape use will not increase the animal dietary burden. Based on standard curves constructed from data in the cattle feeding study, KN128/KN127 concentrations at the 51.7-ppm feeding level are 0.123 ppm for whole milk, 0.033 ppm for skim milk and 1.46 ppm for cream. The KN128/KN127 concentrations at the 49.1 ppm feeding level are 0.046 ppm for muscle, 1.37 ppm for fat, 0.012 ppm for liver and 0.026 ppm for kidney. Tolerances have been established at 1.5 ppm in fat (cattle, goat, horse, sheep and hog), 0.05 ppm in meat, 0.03 ppm in meat by products, 0.15 ppm in milk and 4.0 ppm in milk fat.

7. Metabolite toxicology. In rats, indoxacarb was readily absorbed at low dose (5 mg/kg), but saturated at the high dose (150 mg/kg). Indoxacarb was metabolized extensively, based on very low excretion of parent compound in bile and extensive excretion of metabolized dose in the urine and feces. Some parent compound remained unabsorbed and was excreted in the feces. No parent compound was excreted in the urine. The retention and elimination of the metabolite IN JT333 from fat appeared to be the overall rate determining process for elimination of radioactive residues from the body. Metabolites in urine were cleaved products (containing only one radiolabel), while the major metabolites in the feces retained both radiolabels. Major metabolic reactions included hydroxylation of the indanone ring, hydrolysis of the carboxylmethyl group from the amino nitrogen and the opening of the oxadiazine ring, which gave rise to cleaved products. Metabolites were identified by mass spectral analysis, NMR, UV and/or by comparison to standards chemically synthesized or produced by microsomal enzymes.

8. Endocrine disruption. Lifespan, and multigenerational bioassays in mammals

and acute and subchronic studies on aquatic organisms and wildlife did not reveal endocrine effects. Any endocrine related effects would have been detected in this definitive array of required tests. The probability of any such effect due to agricultural uses of indoxacarb is negligible.

C. Aggregate Exposure

Tolerances for indoxacarb are proposed to support agricultural use on leafy greens, except spinach, subgroup 4A, spinach, leaf petioles subgroup 4B, fruit, pome, except pear, group 11, vegetables, tuberous and corm, subgroup 1C, okra, pea (southern), and mint. Tolerances for indoxacarb are pending to support agricultural use on grapes and leafy brassica.

1. Dietary exposure. The chronic RfD of 0.02 mg/kg bw/day is based on a NOAEL of 2.0 mg/kg bw/day from the subchronic rat feeding study, the subchronic rat neurotoxicity study, and the chronic/carcinogenicity study, using an uncertainty factor of 100. The acute RfD for the general population is 0.12 mg/kg/day, based on the NOAEL of 12.5 mg/kg in the acute neurotoxicity study and an uncertainty factor of 100. The acute RfD for females 13 50 years of age is 0.02 mg/kg/day, based on the NOAEL of 2 mg/kg/day observed in the developmental rat toxicity study and using an uncertainty factor of 100.

i. Food. Chronic dietary exposure assessment. Chronic dietary exposure resulting from the currently approved use of indoxacarb on apples, Crop group 5 (brassica vegetables), cotton, pears, peppers, sweet corn, tomatoes, eggplant, alfalfa, head and leaf lettuce, peanuts, potatoes, soybeans, and the proposed uses on grapes, leafy Brassica, leafy greens crop subgroup 4A (except spinach), spinach, leaf petioles crop subgroup 4B, tuberous and corm vegetables crop subgroup 1C, pome fruits crop group 11 (except pear), okra, pea (Southern), mint, Cucurbits (Crop Group 9), Stone Fruit (Crop Group 12), and Cranberries are well within acceptable limits for all sectors of the population. The Chronic Module of the Dietary Exposure Evaluation Model (DEEM, Exponent, Inc., formerly Novigen Sciences, Inc., Version 7.87) was used to conduct the assessment with the reference dose (RfD) of 0.02mg/kg/ day. The analysis used overall mean field trial values, processing factors and projected peak percent crop treated values. Secondary residues in milk, meat and poultry products were also included in the analysis. The chronic dietary exposure to indoxacarb is 0.000191 mg/kg/day, and utilizes 1% of the RfD for the overall U.S. population. The exposure of the most highly exposed subgroup in the population, children age 1-2 years, is 0.000362 mg/kg/day, and utilizes 2% of the RfD. The table below lists the results of this analysis, which indicate large margins of safety for each population subgroup and very low probability of effects resulting from chronic exposure to indoxacarb.

SubgroupSubgroup
Maximum Dietary Exposure (mg/kg/day) % cRfD
U.S Population
All infants
Children 1-2
Children 3-5
Children 6-12
Youth 13-19
Adults 20-49

Adults 50+ 0.000191
0.000133
0.000362
0.000329
0.000199
0.000176
0.000167
0.000192 1
1
2
2
1
1
1
1

Acute dietary exposure. Acute dietary exposure resulting from the currently approved use of indoxacarb on apples, Crop group 5 (brassica vegetables), cotton, pears, peppers, sweet corn, tomatoes, eggplant, alfalfa, head and leaf lettuce, peanuts, potatoes, soybeans, and the proposed uses on grapes, leafy Brassica, leafy greens crop subgroup 4A (except spinach), spinach, leaf petioles crop subgroup 4B, tuberous and corm vegetables crop subgroup 1C, pome fruits crop group 11 (except pear), okra, pea (Southern), mint, Cucurbits (Crop Group 9), Stone Fruit (Crop Group 12), and Cranberries are well within acceptable limits for all sectors of the population. The Dietary Exposure Evaluation Model (DEEM, Exponent, Inc., formerly Novigen Sciences, Inc., Version 7.87) was used to conduct the assessment. Margins of exposure (MOE) were calculated based on a NOAEL of 12 mg/kg/day for children and the general population (Pesticide Fact Sheet for Indoxacarb). An endpoint of concern attributable to a single dose was not identified for women of childbearing age; therefore an acute RfD was not established for this population. The Tier 3 analysis used distributions of field trial residue data adjusted for projected peak percent crop treated. Secondary residues in milk, meat and poultry products were also included in the analysis. The results of this analysis are given in the table below. The percent of the acute population adjusted dose (a PAD) for all population subgroups shows that an adequate margin of safety exists in each case. Thus, the acute dietary safety of indoxacarb for established and the follow on use clearly meets the FQPA standard of reasonable certainty of no harm and presents acceptable acute dietary risk.

Subgroup 99.9th Percentile Of Exposure
Exposure (mg/kg/day) % Acute population adjusted dose (aPAD)
U.S. Population
All infants
Children 1-2
Children 3-5
Children 6-12
Youth 13-19
Adults 20-49

Adults 50+ 0.020408
0.018959
0.027676
0.036348
0.018096
0.022845
0.019081
0.019863 17
16
23
30
15
19
16
17

ii. Drinking water. Indoxacarb is highly unlikely to contaminate groundwater resources due to its immobility in soil, low water solubility, high soil sorption, and moderate soil half life. Based on the PRZM/EXAMS and SCI GROW models the estimated environmental concentrations (EECs) of indoxacarb and its R enantiomer for acute exposures are estimated to be 6.84 parts per billion (ppb) for surface water and 0.0025 ppb for ground water. The EECs for chronic exposures are estimated to be 0.316 ppb for surface water and 0.0025 ppb for ground water. Drinking water levels of comparison (DWLOCs), theoretical upper allowable limits on the pesticide's concentration in drinking water, were calculated to be much higher than the EECs. The chronic DWLOCs ranged from 198 to 697 ppb. The acute DWLOCs ranged from 440 to 3890 ppb. Thus, exposure via drinking water is acceptable.

2. Non-dietary exposure. Indoxacarb product registrations for residential non food uses have been approved. Non occupational, non dietary exposure for DPX MP062 has been estimated to be extremely small. Therefore, the potential for non dietary exposure is insignificant.

D. Cumulative Effects

EPA's consideration of a common mechanism of toxicity is not necessary at this time because there is no indication that toxic effects of indoxacarb would be cumulative with those of any other chemical compounds. Oxadiazine chemistry is new, and indoxacarb has a novel mode of action compared to currently registered active ingredients.

E. Safety Determination

1. U.S. population. Dietary and occupational exposure will be the major routes of exposure to the U.S. population, and ample margins of safety have been demonstrated for both situations. The chronic dietary exposure to indoxacarb is 0.000191 mg/kg/day, which utilizes 1% of the RfD for the overall U.S. population, using mean field trial values, processing factors and projected peak percent crop treated values. The percent of the acute population adjusted dose (17% aPAD) for the overall U.S. population shows that an adequate margin of safety exists.

Using only PHED data levels A and B (those with a high level of confidence), MOEs for occupational exposure are 650 for mixer/loaders and 1351 for air-blast applicators (worst case). Based on the completeness and reliability of the toxicity data and the conservative exposure assessments, there is a reasonable certainty that no harm will result from the aggregate exposure of residues of indoxacarb including all anticipated dietary exposure and all other non occupational exposures.

2. Infants and children. Chronic dietary exposure of the most highly exposed subgroup in the population, children age 1 2 years, is 0.000362 mg/kg/day or 2% of the RfD. For all infants, the exposure accounts for 1% of the RfD. For acute exposure at the 99.9th percentile (based on a Tier 3 assessment) the exposure was 0.036348 mg/kg/day (30% aPAD) for children 3 5 and 0.018959 mg/kg/day (16% aPAD) for all infants. Residential uses of indoxacarb have been approved and exposure is calculated to be extremely minimal. The estimated levels of indoxacarb in drinking water are well below the below the DWLOC. Based on the completeness and reliability of the toxicity data, the lack of toxicological endpoints of special concern, the lack of any indication that children are more sensitive than adults to indoxacarb, and the conservative exposure assessment, there is a reasonable certainty that no harm will result to infants and children from the aggregate exposure of residues of indoxacarb, including all anticipated dietary exposure and all other non occupational exposures. Accordingly, there is no need to apply an additional safety factor for infants and children.

F. International Tolerances

To date, numerous tolerances exist for indoxacarb residues in various food and feed crops and foods of animal origin in at least 25 countries.