New York State Department of Environmental Conservation
Division of Solid and Hazardous Materials
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May 17, 2005

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ms. Marie Maks
Manager, Regulatory Affairs
Nichino America, Inc.
4550 New Linden Hill Road, Suite 501
Wilmington, Delaware 19808

Dear Ms. Maks:

Re: Registration of the New Active Ingredient Pyraflufen-Ethyl, Contained in the Pesticide Product ET Herbicide/Defoliant (EPA Reg. No. 71711-7)

The New York State Department of Environmental Conservation (Department) has reviewed your application, received April 28, 2004, from Nichino America, Inc., to register the above-mentioned product in New York State. The product contains the new active ingredient pyraflufen-ethyl (chemical code 030090).

The application was deemed complete for purposes of review on December 16, 2004 and a registration decision is due by **May 20, 2005.**

ET Herbicide/Defoliant (EPA Reg. No. 71711-7) contains the new active ingredient pyraflufen-ethyl (ethyl 2-chloro-5-(4-chloro-5-difluoromethoxy-1-methyl-1H-pyrazol-3-yl)-4-fluorophenoxyacetate) and is labeled for use as a harvest aid in cotton and potatoes; as a preplant or preemergence burndown in field corn, cotton, soybeans, and wheat; post-emergence use in cotton; for weed control in non-crop land and uncultivated agricultural areas (nonfood producing) and; as a nonselective herbicide for control of broadleaf weeds in non-crop areas. ET Herbicide/Defoliant is labeled "Not for homeowner use."

HUMAN HEALTH REVIEW:

The New York State Department of Health (DOH) states that neither the active ingredient pyraflufen-ethyl nor the formulated product ET Herbicide/Defoliant was very acutely toxic to laboratory animals via the oral, dermal or inhalation routes of exposure. The active ingredient was not very irritating to the skin (tested on rabbits), whereas the formulated product was moderately irritating. Neither of them was a skin sensitizer (tested on guinea pigs). Whereas pyraflufen-ethyl caused moderate eye irritation, the ET product was corrosive, causing irreversible eye damage (tested on rabbits).

Pyraflufen-ethyl caused some toxicity in chronic feeding studies in rodents, but not dogs. In a chronic feeding/oncogenicity study in rats, pyraflufen-ethyl caused a decrease in body weight and body weight gain in male rats. This chemical also caused anemia and liver and kidney lesions at doses of 468 milligrams per kilogram body weight per day (mg/kg/day) in males and 579 mg/kg/day in females. The respective no-observed-effect levels (NOELs) were 87 and 112 mg/kg/day. In a chronic feeding/oncogenicity study in mice, liver toxicity (increase in absolute and/or relative liver weights and an increase in microscopic and gross liver lesions) was reported in both sexes at doses of 110 mg/kg/day (males) and 98 mg/kg/day (females); the respective NOELs were 21 and 20 mg/kg/day. No effects were reported in a chronic dog feeding study at doses up to 1,000 mg/kg/day (the highest dose tested). The United States Environmental Protection Agency (USEPA) Office of Pesticide Programs calculated an oral reference dose (RfD) for pyraflufen-ethyl of 0.20 mg/kg/day based on the NOEL of 20 mg/kg/day in the chronic feeding/oncogenicity study in mice and an uncertainty factor of 100. This RfD value has not yet been adopted by the USEPA's Integrated Risk Information System (IRIS).

Pyraflufen-ethyl caused some developmental toxicity in the offspring of pregnant rabbits, but not of pregnant rats, administered this chemical during organogenesis at doses that also caused maternal toxicity. In rabbits, an increased incidence of abortion was reported at a maternal dose of 150 mg/kg/day; the NOEL was 60 mg/kg/day. Maternal toxicity (increase in death rate) was reported at 60 mg/kg/day with the NOEL at 20 mg/kg/day. In rats, neither developmental nor maternal toxicity was observed at doses up to 1,000 mg/kg/day, which was the highest dose tested. In a rat multigeneration reproduction study, decreased body weights and body weight gains in rat pups were reported at doses of 721 to 844 mg/kg/day for males and 813 to 901 mg/kg/day for females; the respective NOELs were 71 to 82 mg/kg/day and 80 to 91 mg/kg/day. Parental toxicity, characterized by decreased body weights and body weight gains in both sexes, occurred at the same doses that were associated with decreased rat pup body weight gains (see above); the respective NOELs for female and male parental rats were also the same as for offspring (71 to 82 mg/kg/day for males and 80 to 91 mg/kg/day for females).

Pyraflufen-ethyl caused oncogenic effects in the liver of mice administered this chemical in chronic feeding studies. In male mice, there was a significant increase by pair-wise comparisons with the controls for hepatocellular adenomas and combined adenomas/carcinomas and/or hepatoblastomas at 110 and 547 mg/kg/day. In female mice, there was a significant increase by pair-wise comparison with the controls for hepatocellular adenomas and combined adenomas/carcinomas at 524 mg/kg/day, which was the highest dose tested. In addition, in both male and female mice there was a significant dose-related positive trend for these liver tumors. In rats chronically fed pyraflufen-ethyl, there was no significant treatment-related increase in any tumors. Pyraflufen-ethyl gave negative results in all reported genotoxicity studies. Based on the above data, the USEPA's Health Effects Division Cancer Assessment Review Committee classified this chemical as "likely to be carcinogenic to humans" due to the occurrence of liver tumors in male and female mice. The USEPA Office of Pesticide Programs calculated a cancer potency slope factor for pyraflufen-ethyl of 0.0332 $(mg/kg/day)^{-1}$ using the data on male mouse liver tumors.

The USEPA established a tolerance for pyraflufen-ethyl residues in or on field corn at 0.01 parts per million (ppm); potato (0.02 ppm); soybean (0.01 ppm); and wheat forage, grain, hay and straw (0.10, 0.01, 0.10 and 0.01 ppm, respectively). The chronic population adjusted dose

(cPAD) for pyraflufen-ethyl is 0.2 mg/kg/day and has the same basis as the RfD. The USEPA estimated that chronic dietary exposure to pyraflufen-ethyl would be less than one percent of the cPAD for each of the following population subgroups: general U.S. population, children one to six years old and all infants of less than one year of age. This chronic exposure analysis is based on the conservative assumptions that 100% of the crops are treated and contain tolerance level residues of pyraflufen-ethyl. Based on the cancer potency slope factor of 0.0332 $(mg/kg/day)^{-1}$, an increased lifetime cancer risk of 1.4×10^{-6} can be calculated for the general U.S. population. The USEPA generally considers an increased lifetime cancer risk level of 1×10^{-6} or lower to be acceptable for the general population.

The USEPA conducted a risk assessment for workers to pyraflufen-ethyl as well as for incidental residential exposures of children and adults to pyraflufen-ethyl residues. For workers, it was assumed that they wore long pants, long-sleeved shirt, and shoes (the ET Herbicide label also requires the use of chemical-resistant gloves and protective eyewear). Both dermal and inhalation absorption was assumed to be 100%. The NOEL used for estimating the inhalation MOEs was 20 mg/kg/day from the rabbit developmental toxicity study. The margins of exposure (MOE) for short/intermediate-term inhalation exposures were 68,000 and above. Generally, the USEPA considers MOEs of 100-fold or greater to provide adequate protection. As no systemic effects were observed in a 28-day dermal toxicity study on pyraflufen-ethyl at doses up to 1,000 mg/kg/day (the highest dose tested), the USEPA did not conduct a noncancer risk assessment for dermal exposure to this active ingredient. However, the USEPA estimated increased cancer risks of no greater than 4.2×10^{-5} for workers handling pyraflufen-ethyl for the labeled applications. These values are within what USEPA generally considers to be acceptable (1×10^{-4} or less) for occupational exposures. For post-application occupational dermal exposures, the estimated increased cancer risks were 3.1×10^{-6} or less. The USEPA also conducted a risk assessment for non-dietary exposure to pyraflufen-ethyl by children and adults. In regard to children's incidental oral exposures resulting from various activities on lawns treated with pyraflufen-ethyl, the MOEs ranged from 300,000 to 89,000,000. The estimated increase in cancer risk to adults from dermal contact with treated lawns was 1.7×10^{-7}.

DOH briefly reviewed the environmental fate data on pyraflufen-ethyl. These data indicate that one of the major degradates of this chemical, denoted as E-1, may have the ability to leach through certain soil types and contaminate groundwater. The adsorption coefficients (K_{oc}), depending on soil type, ranged from 81.5 to 196.8 for this degradate of pyraflufen-ethyl.

There are no chemical-specific federal or New York State drinking water/groundwater standards for pyraflufen-ethyl or its E-1 degradate. Based on their chemical structures, these compounds fall under the 50 microgram per liter (_g/L) New York State drinking water standard for "unspecified organic contaminants" (10 NYCRR Part 5, Public Water Systems). The NewYork State drinking water standard for the sum of "unspecified organic contaminants" and "principal organic contaminants" is 100 _g/L. Using the USEPA cancer potency slope factor of 0.0332 $(mg/kg/day)^{-1}$ and 6 NYCRR Part 702.4 procedures for deriving ambient water quality standards and guidelines based on oncogenic effects, the ambient water quality value associated with a one in one million increased lifetime cancer risk is 1.1 _g/L for pyraflufen-ethyl. This value could be used to derive a screening value for comparison to estimate impacts to groundwater and surface water.

The available information indicates that neither pyraflufen-ethyl nor ET Herbicide/Defoliant were very toxic by the oral, dermal or inhalation routes of exposure. The formulated product is corrosive to the eyes, but the label requires the use of protective eyewear (goggles or face shield) to mitigate this concern. Pyraflufen-ethyl also caused some other effects in laboratory animal studies, but the primary concern for this pesticide product is that pyraflufen-ethyl produced liver tumors in mice and is classified by the USEPA as "likely to be carcinogenic to humans." While the estimated dietary and occupational risks posed by the ET Herbicide/Defoliant product are within or close to the USEPA acceptable range, the Department has general concerns for registering pesticide products that have carcinogenic potential unless the need for the product is significant or it replaces products that pose greater risks. The information submitted by the registrant indicates that the various alternative chemicals for crop use also have some toxicity concerns, though not necessarily for oncogenic effects. Information on the relative need for this product has not been submitted.

Given the relatively low estimated exposure from ET use and that the alternatives also pose some toxicity concerns, DOH would not object to the use of ET Herbicide/Defoliant on labeled crops providing there is a need for this product and that the parent compound or its degradates do not pose a significant risk of groundwater/drinking water contamination. However, the ET label is not clear in regard to non-crop use areas. Specifically, the label does not indicate whether the product can be applied to use sites where there is significant exposure potential such as residential lawns or public turf areas. Use on such sites may pose a concern for the general public, and children in particular, given the carcinogenic potential of pyraflufen-ethyl. Consequently, the Department recommends that the registrant be required to specify on the label which non-crop use sites they intend on including for the ET product. If it is labeled for use where the general public and children are likely to be exposed (e.g., residential lawns or turf sites at parks, schools, daycare facilities), the Department may need to revisit the risks posed by the ET Herbicide/Defoliant product in the settings specified. Such an evaluation would require that the registrant submit information that compares the toxicological properties and exposure potential of the ET Herbicide/Defoliant product to those of the other products registered in New York State for the same use.

In response to these concerns, a revised label for ET Herbicide/Defoliant was submitted by the registrant. This revised label also submitted to the USEPA on March 16, 2005, permits use of the ET product on uncultivated agricultural areas (nonfood producing) and no longer lists "non-crop" use sites which could include residential lawns or turf areas where the general public including children could become exposed to pyraflufen-ethyl residues. With this product label revision, the DOH have no objection to the registration of ET Herbicide/Defoliant in New York State providing there is a need for this product and that pyraflufen-ethyl or its degradates do not pose a significant risk of groundwater/drinking water contamination.

ENVIRONMENTAL FATE REVIEW:

ET Herbicide/Defoliant contains 2.5% by weight or 0.208 lb/gallon active ingredient. The maximum labeled application rate is 11 oz product per year, or 0.0179 lb ai/a/yr on potatoes; 2 oz product per year or 0.0032 lb ai/a/yr on field corn, soybeans and wheat; and 5.5 oz product per year on cotton and non-crop areas or 0.0089 lb ai/a/yr. While one of the inerts is a petroleum solvent, the amount of product used per acre is minimal and should not have an impact on groundwater.

Ms. Marie Maks 5.

Technical Review

Degradate names:

E1 = 2-chloro-5-(4-chloro-5-difluoromethoxy-1-methylpyrazole-3-yl)-4-fluorophenoxy acetic acid
E2 = (2-chloro-5-(4-chloro-5-difluoromethoxy-1-methyl-1-methylpyrazol-3-yl)-4-fluorophenol)
E3 = 4-chloro-5-(4-chloro-2-fluoror-5-methoxyphenyl)-5-difluoromethoxy)-1-methylpyrazole
E11 = 4-chloro-5-(4-chloro-2-fluoror-5-methoxyphenyl)-5-difluoromethoxy)-1-*H*-pyrazole
PD1 = ethyl 2-hydroxy-5-(4-chloro-5-difluoromethoxy-1-methylpyrazol-3-yl)-4-fluorophenoxyacetate
U1 = (2-(fluoro-5-hydroxy-5-(N-methylcarbamoyl)-4-oxo-pent-2-enoic acid)

Solubility: Pyraflufen-ethyl has a solubility of 0.082 ppm.

Hydrolysis: USEPA found this study acceptable. Pyraflufen-ethyl had a half-life of 267 days, 10.8 days and 6.2 hours in pH 5, 7 and 9, respectively. E1, which is stable to hydrolysis, was the only major transformation product.

Aqueous Photolysis: USEPA did not accept this study; however, it was not clear if it has to be repeated. In the lab, the half-life was 29.8 hours based on continuous irradiation. One major transformation product was found, E1 at 32.2%.

Soil Photolysis: Pyraflufen-ethyl had a half-life on loamy sand of 1.85 to 2.2 days with E1, E2 and U1 major transformation products.

Aerobic Aquatic Metabolism: Pyraflufen-ethyl degraded with a half-life of <6 hours in a clay loam/water system, with E1 at 96.54% and E2 at 70.5%. Pyraflufen-ethyl degraded with a half-life of <6 hours in a sand/water system with E1 at 99.75% and E2 at 14.09.

Anaerobic Aquatic Metabolism: [Pyrazole-5-^{14}C] pyraflufen-ethyl degraded with a half-life of <4 hours in a clay/water system, with E1 at 92.8% and E2 at 95.3%. [Phenol-U-^{14}C] pyraflufen-ethyl degraded with a half-life of <4 hours in a clay/water system, with E1 at 97.9% and E2 at 93.1%.

In a California loamy sand, the half-life was <6 hours with major transformation products E1, E2, E3, E11, and U1.

Leaching: In four column leaching studies, less than 0.4% of the radio labeled material was observed below 10cm soil depth. Leachate contained predominantly E-1.

Terrestrial Field Dissipation:

Soil Type	% OC	Soil pH	Parent	Deg.	Degradates
sandy loam	0.8	7.5	<1 hour	E1 161 days	E1, E3 Degradation via hydrolysis
loamy sand	2.2	6.7	<1 hour	E1 10.5 days	E1, E3 and U2 Degradation via hydrolysis

Ms. Marie Maks 6.

Adsorption/Desorption:

Soil Type	% OC	Soil pH	Ads/Des Koc Parent	Ads/Des Koc E1	Ads/Des Koc E2	Ads/Des Koc E3
sandy loam[1]	1.2	5.2		196/1082	2179/3429	4354/5054
sandy loam[1]	2.2	6.7		100/368	2145/3051	4173/4803
clay loam[1]	3.7	7.6		81/244	1424/1777	3098/4344
sandy loam	2.2		2000			
				126/565	1916/2752	109/4734

[1] Supplemental

Aerobic Soil Metabolism:

Soil Type Parent	% OM	Soil pH	Aerobic Half-life	Major Degradates
sandy silt loam[3]	2.4	6.34	<1	E1 83.66%, E2 38.63%, E3 38.36%
sandy loam[3]	1.9	4.94	<1	E1 74.56%, E2 35.98%, E3 23.78%
clay loam[3]	5.9	7.81	<1	E1 84.34%, E3 54.68%
loamy sand[2]	0.6	6.7	<6 hours	E1 95.2%, E2 15.6%, E3 51.4%, E11 11.1%, U1 26.2%
loamy sand[2]	0.6	6.7	<7 days	E1 59.8%, E2 10.1%, E3 50.7%
sandy silt loam[2]	2.4	6.34	<1 day	E1 88.65%, E2 17.22%
Metabolite E1				
sandy silt loam[3]	2.4	6.34	14.8	
sandy loam[3]	1.9	4.94	10.7	
clay loam[3]	5.9	7.81	22.1	
Metabolite E2				
silt loam[3]	3.6	5.8	8.76	E3 91.46%
sandy loam[3]	2.1	5.2	10.33	E3 84.57%
clay loam[3]	6.4	7.6	7.75	E3 85.77%
Metabolite E3				
silt loam[3]	3.6	5.8	330.7	None
sandy loam[3]	2.1	5.2	495.11	None
clay loam[3]	6.4	7.6	154.03	None

[2]EPA found this study invalid; additional data needed.
[3] Supplemental, additional information needed.

Modeling: With a half-life of <1 day, there would be no leaching from the parent. In the aerobic metabolism study, there were several degradates, but only E3 had a half-life long enough to cause leaching. Therefore, staff modeled the entire application rate of 0.0179 lb ai/a/yr as degradate E3, using the K_{oc} of 4354 from the sandy loam soil with a 1.2 % OC and soil pH of 5.2, similar to Long Island soils. The half-life for that soil was 495 days. The model projected breakthrough in four years, with increasing levels of degradate, reaching 0.003 ppt at the end of ten years.

Summary: This active ingredient has a half-life of <1 day and a very low application rate (0.0179 lb ai/a/yr), but several major degradates. Of the degradates, only E3 has a half-life that would indicate the potential to accumulate in groundwater. Therefore, staff modeled 100% of the application rate as the degradate, and the model projected no impact to groundwater. Therefore, staff have no objections to the registration of this product in New York State.

The Bureau of Habitat have reviewed the materials submitted in support of ET Herbicide/Defoliant (EPA Reg. No. 71711-7) and have no objection to its registration.

Upon review of this product, the Department noticed that on the final product label, as well as the EPA Notice of Registration, the “contains petroleum distillates” statement directly under the ingredients statement is missing. This is required for products that contain more than 10% petroleum distillates. After speaking to the USEPA product manager for this product, Joanne Miller, it was agreed that this statement needs to be added to the label immediately below the active ingredient statement. She also stated that this change could be done by notification from the registrant. Nichino agreed and an updated label was submitted with the “contains petroleum distillates” statement added.

The Department concludes that ET Herbicide/Defoliant should not have an adverse effect on the health of workers or the general public, the fish and wildlife resources, or the ground and surface water of New York State when used as labeled.

Therefore, the Department hereby **accepts for general use registration in New York State** ET Herbicide (EPA Reg. No. 71711-7) which contains the new active ingredient pyraflufen-ethyl.

Enclosed is your Certificate of Pesticide Registration and New York State stamped "ACCEPTED" label.

Nichino America, Inc., is reminded that if New York State registration is requested for this product or for any other product which contains pyraflufen-ethyl with an increased application rate and/or expanded use sites, the product will be considered **a Major Change in Labeling and the Department will require an extensive review.**

If you have any questions, please contact Samuel Jackling, Chief of our Pesticide Product Registration Section, at (518) 402-8768.

Sincerely,

Maureen P. Serafini
Director

Enclosures Bureau of Pesticides Management

cc: w/enc. - N. Kim/D. Luttinger - NYS Dept. of Health
R. Zimmerman/R. Mungari - NYS Dept. of Ag. & Markets
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