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Alexander B. Grannis
Commissioner

July 14, 2009

DELIVERY CONFIRMATION (Co. No. 100)

Ms. Susan Person
Syngenta Crop Protection, Inc.
P.O. Box 18300
Greensboro, NC 27419-8300

Dear Ms. Person:

Re: Registration of Alto 100 SL (EPA Reg. No. 100-1226) Which Contains the New Active Ingredient Cyproconazole (Chemical Code 128993)

The New York State Department of Environmental Conservation (Department) has reviewed your application and data package received on July 14, 2008 and additional material received October 29, 2008 for the registration of the above referenced product. Alto 100 SL is a fungicide labeled for post-emergence control of rust and other fungal diseases on soybean crops. Alto 100 SL contains 8.9% of the active ingredient cyproconazole and is formulated as a liquid. It is to be applied using broadcast, aerial or chemigation application techniques. The maximum single application rate is 5.5 fluid ounces of Alto 100 SL (0.036 pounds of cyproconazole) per acre per application. The maximum annual use rate is 11 fluid ounces of Alto 100 SL (0.071 pounds of cyproconazole) per acre per year.

The subject application package was determined to be complete for purposes of technical review on December 29, 2008. The following technical reviews were performed to evaluate the risk of the proposed use of cyproconazole on the human health, wildlife, and groundwater resources of New York State.

Human Health Risk Assessment

Neither cyproconazole nor the formulated product Alto 100 SL was very toxic in acute dermal or inhalation exposure studies in laboratory animals. Cyproconazole was moderately acutely toxic via oral exposure, whereas the formulated product was not very toxic by this route. Neither the active ingredient nor the formulated product was very irritating to skin and eyes (tested on rabbits) or sensitizing to guinea pigs.

Cyproconazole caused some toxicity at relatively low doses in chronic animal feeding studies. In a chronic feeding study in dogs, cyproconazole caused liver effects (P450 induction in females and histopathology in males) at a dose of 3.2 milligrams per kilogram body weight per day (mg/kg/day); the no-observed-effect-level (NOEL) was 1.0 mg/kg/day. A chronic feeding/oncogenicity study in rats

noted decreased body weight in females and increased fatty infiltration of the liver in males at doses of 15.6 and 21.8 mg/kg/day, respectively, with NOELs reported at 2.2 mg/kg/day in males and 2.7 mg/kg/day in females. In a chronic feeding/oncogenicity study in mice, increased liver histopathology was reported at doses of 13.2 mg/kg/day for males and 17.7 mg/kg/day for females; the NOELs were 1.8 mg/kg/day for males and 2.6 mg/kg/day for females. The U.S. EPA Office of Pesticide Programs calculated an oral reference dose (RfD) of 0.01 mg/kg/day for cyproconazole based on a NOEL of 1.0 mg/kg/day in the one year dog feeding study and an uncertainty factor of 100. This RfD has not yet been adopted by the U.S. EPA's Integrated Risk Information System (IRIS). A current search of the toxicological literature did not find any significant new information on the toxicity of cyproconazole.

Cyproconazole caused developmental effects when administered orally to pregnant rats and rabbits during organogenesis. In the rat study, an increased incidence of supernumerary ribs was reported in fetuses at maternal doses of 12 mg/kg/day; the NOEL was 6 mg/kg/day. Maternal body weight gain was marginally depressed at 12 mg/kg/day; the NOEL was 6 mg/kg/day. In rabbits, an increase in fetuses with visceral and skeletal malformations was reported at 10 mg/kg/day; the NOEL was 2 mg/kg/day. Decreased maternal body weight gain and food consumption were reported at 50 mg/kg/day; the NOEL was 10 mg/kg/day. A two-generation reproduction study in rats reported increased liver weight and lipid storage in the liver of F_0 rats at 8.3 mg/kg/day; the NOEL was 1.4 mg/kg/day. No effects were reported in F_1 or F_2 rats, nor were there treatment-related reproductive effects during this study.

Cyproconazole caused tumors in mice, but not rats, in chronic feeding studies. In mice, there was a statistically significant positive trend for liver adenomas, carcinomas and combined adenomas/carcinomas in both males and females. There were also significant increases by pair-wise comparison with controls for these tumors at the higher dose levels. There was no treatment-related increase in tumors in a chronic feeding study in rats, but the U.S. Environmental Protection Agency (U.S. EPA) determined that the highest dose utilized in this study was not adequate to determine the carcinogenic potential of cyproconazole. However, the registrant was not required to repeat a carcinogenicity study in rats because the U.S. EPA felt that the rat is not the most sensitive animal model for the conazole chemical class. Cyproconazole was also negative in a number of genotoxicity studies.

Cyproconazole was initially reviewed for carcinogenicity by the U.S. EPA in 1990 when it was classified as a "possible human carcinogen" based on liver adenomas, carcinomas and combined adenomas/carcinomas, in both male and female mice. More recently, the U.S. EPA reviewed new studies addressing the non-linear, non-genotoxic proposed mode of action for mouse liver tumors and a weight-of-evidence evaluation for that mode of action. The proposed mitogenic mode of action involves activation of the constitutive androstane receptor (CAR) in hepatocytes which subsequently leads to a cascade of key events (altered gene expression, cell proliferation, apoptosis suppression, alterations in liver function) that result in the induction of liver tumors in cyproconazole-treated mice. This mode of action for cyproconazole is also supported by the negative results in a number of genotoxicity studies and the fact that this chemical shares structural similarity to metconazole, which the U.S. EPA has recently concluded to have a mitogenic mode of action for induction of liver tumors in mice. The data for cyproconazole did not support peroxisome proliferation, mutagenesis or cytotoxicity (followed by regenerative proliferation) as alternative modes of action. Upon review of the material, the U.S. EPA re-classified cyproconazole as "not likely to be carcinogenic to humans" at doses that do not cause a mitogenic response in the liver based on the weight-of-evidence data supporting the proposed mode of

action. Although information on the specific characteristics of the CAR receptor in the human liver is lacking, the U.S. EPA noted that a CAR mode of action is plausible in humans, which could potentially cause liver toxicity. However, the U.S. EPA considered the current RfD protective of any liver effects in humans caused by cyproconazole.

The U.S. EPA established tolerances of 0.05 parts per million (ppm) and 0.10 ppm for cyproconazole residues in or on soybean seed and refined soybean oil, respectively. The chronic population adjusted dose (cPAD) for cyproconazole is 0.01 mg/kg/day and has the same basis as the RfD. The U.S. EPA estimated that the chronic dietary exposure to cyproconazole residues from all crops for which there are tolerances (soybeans, wheat, and corn), and from drinking water, would be 3.7 percent of the cPAD for the general U.S. population, 4.8 percent for all infants less than one year old and 13.0 percent for children one to two years old. These exposure analyses are based on the conservative assumption that 100 percent of the crops are treated, and assume that treated crops contain average residues as determined in field trials. Actual exposure levels are likely to be less than those determined in this assessment.

The U.S. EPA reported the results of an occupational risk assessment for short-term (1-30 days) combined dermal and inhalation exposures to cyproconazole from use on soybeans, corn and wheat. It was assumed that cyproconazole was applied via aerial equipment to a maximum of 1,200 acres per day. An 11 percent dermal absorption factor (based on a comparison of effect levels in dermal and ingestion exposure studies) and 100 percent inhalation absorption were assumed. For determining margins of exposure (MOEs), the U.S. EPA compared estimated short-term combined dermal and inhalation exposures to a NOEL of 2.0 mg/kg/day from the developmental toxicity study in the rabbit. For mixer/loaders open pouring cyproconazole to support aerial operations, the short-term combined dermal and inhalation MOE was estimated to be 740, assuming workers wore long-sleeved shirt, long pants, shoes plus socks and chemical-resistant gloves as per label requirements. The short-term combined dermal and inhalation MOE for pilots (without gloves) was estimated to be 4,500. The U.S. EPA also estimated post-application risks from weeding, scouting, or irrigation of soybeans and wheat. These estimated risks were based on an exposure duration of 8 hours per day, the same dermal absorption factor, and the labeled restricted entry interval of 12 hours. Post-application MOEs were estimated to be 17,000 and 1,100 for soybeans and wheat, respectively. The U.S. EPA considered MOEs of 100-fold or greater to provide adequate worker protection for cyproconazole.

The available information on cyproconazole and Alto 100 SL indicates that neither the active ingredient nor the formulated product was very acutely toxic in laboratory animal studies. Furthermore, cyproconazole was not genotoxic in rats or mice and the U.S. EPA classified cyproconazole as “not likely to be carcinogenic to humans” based on the weight of evidence supporting a non-linear, non-genotoxic, mitogenic mode of action through CAR activation. Although data from chronic, developmental and reproductive toxicity studies showed that this chemical has the potential to cause some toxicity, the estimated risks to workers from use of Alto 100 SL and from dietary exposure to cyproconazole residues in foods and drinking water are within the range that is generally considered acceptable. Direct exposure of the general public to cyproconazole should not occur given that Alto 100 SL would be used exclusively on soybeans for control of rust and other fungal diseases. As of 2008, data collected by Cornell Cooperative Extension indicate that soybean rust has not yet been detected in New York State. This further reduces expected exposure to cyproconazole from in-state use. Given the above, the New York State Department of Health does not object to registration of the Alto 100 SL product in New York State.

Environmental Fate Risk Assessment

Solubility: Cyproconazole has a solubility of 360,000 mg/L.

Hydrolysis: (MRID 46840804 acceptable) Cyproconazole was stable in pH 4, 5, 7, and 9 aqueous buffer solutions.

Aerobic Soil/Water Metabolism: (MRID 46840810 acceptable) In a river water-loam sediment from Switzerland, cyproconazole had observed half-lives of about 3 days in the water, and >>259 days in the soil, and in the total system.

In a pond water-loam sediment system from Switzerland, cyproconazole had observed half-lives of about 3 days in the water, and >>259 days in the soil, and in the total system.

Aerobic Soil Metabolism:

Soil	**pH**	**% OC**	**T ½**	**Transformation products**
Silt loam [1] (samples collected from day 3-300)	6.1	1.5	16-23 days 63-98 days 68-150 days 98-150 days 98-150 days >300 days	Not characterized
Sandy loam [2] (open system)	7.0	1.13	84-112 days	None
Sandy loam[2] (closed system)	7.0	1.13	>140 days	CO2
Sandy loam[3]	7.3	2.2	~14 weeks	CO2
Sandy loam[4]	7.6	2.3	~ 10 weeks	None
Loamy sand[4]	6.2	1.9	~ 16 weeks	
Sandy loam[4]	5.0	0.8	> 30 weeks	
Clay loam[5]			< 14 days	CO2

[1]MRID 46840805 supplemental (transformation products not addressed)
[2]MRID 46840806 supplemental
[3]MRID 46840807 provides ancillary data
[4]MRID 46840808 provides ancillary data
[5]MRID 46840809 provides ancillary data

Adsorption/Desorption: A study was provided; however, it was incomplete and the tables with the K_{OC} values were not included. In the EPA documentation for their computer modeling, they indicated that

for SCIGROW groundwater modeling and for GENEEC aquatic exposure modeling, they used a K_{OC} of 364 and a half-life of 228 days. For FIRST surface water modeling, they used a K_{OC} of 173 and a half-life of 132 days.

Terrestrial Field Dissipation: (2/11/93 summary memo) No DERs were submitted. MRID 41384101, addendum to MRID 40624301. The registrant calculated half-life is 42.5 days when applied to a sandy loam soil (1.2% OM). MRID 41384102. the registrant calculated half-life was 192 days on a turf plot in Maryland 3.2% OM). MRID 41461501, the registrant calculated half-life was 21 days in turfgrass (0.7% OM). MRID 41800701 and 42430701 in a silty clay loam with 2.1% OM the half-life was calculated to be 252 days. MRID 41800702 and 42430702, the half-life in a silty clay loam turf plot (2% OM) was160 days.

Label statements: "This chemical demonstrates the properties and characteristics associated with chemicals detected in groundwater. The use of this chemical in areas where soils are permeable, particularly where the water table is shallow, may result in ground-water contamination."

Computer Modeling: Running LEACHP on Riverhead soil using a K_{OC} of 173, a half-life of 132 days, and an application rate of 0.072 lb ai/a/yr, the model predicted cyclic peaks ranging from 0.2 to 0.55 ppb

Environmental Fate Summary: There were deficiencies in the data package, specifically the adsorption desorption study. However, utilizing the data values used by the EPA in their computer modeling, and the very low application rate, it does not appear as if this product will negatively impact groundwater when used as labeled. Therefore, Engineering Geology staff do not object to the registration of this product as labeled.

Ecological Effects Risk Assessment:

Exposure Modeling & Risk Assessment: Aquatic and terrestrial non-target organism exposure estimates were constructed for several Alto 100 application scenarios/rates. Initial worst-case screening level exposure estimates resulted in several toxicity thresholds being exceeded. Subsequent modeling iterations adjusted to more accurately reflect actual field use conditions show a lower likelihood of impacts to non-target organisms.

Avian toxicity modeling shows that at the highest possible residue levels following an application at the highest allowed Alto 100 SL single application rate there is no concern that avian acute toxicity will occur. At these residue levels, however, the avian chronic feeding NOEC (No Observed Effect Concentration) is exceeded on the four highest residue food categories. For the more probable "Typical" residues expected from such an application, the chronic NOEC thresholds are barely exceeded on the highest 2 food categories.

Mammal toxicity modeling describes a set of results for mammals very similar to the results for birds, with thresholds being exceeded to a lesser degree.

The aquatic toxicity modeling results suggest an even lower level of threat to aquatic resources. The results show that it would take an application of the highest single Alto 100 SL rate, directly to the surface of a water body (illegal/applicator error) only 6 inches deep to result in a cyproconazole concentration lethal to the most sensitive test species, the green algae *S. capricornutum*.

Aquatic toxicity modeling for post application runoff at the highest allowed single application rate and the maximum label allowed seasonal rate, the worst-case values to maximize the amount of simulated runoff, showed that only 1 NOEC, for *S. capricornutum* in the shallowest water depth, is exceeded.

Legal labeled use of Alto 100 is not likely to result in toxicity to not-target resources. The terrestrial food item modeling assumes that an animal feeds exclusively on treated food items, which is not likely to be the case in the field. Even in the event that that should occur, the predicted residue levels are unlikely to result in more than minimal effects, if any.

The only scenario that could result in adverse impacts to aquatic resources is an illegal application directly to shallow surface waters, which is a law enforcement issue. Therefore, the Bureau of Habitat does not object to registration of the Alto 100 SL product in New York State.

Summary:

The Department hereby accepts the registration of Alto 100 SL (EPA Reg. No. 100-1226) in New York State. Enclosed for your files is a copy of the stamped "Accepted for Registration" label and the New York State Certificate of Pesticide Registration for Alto 100 SL.

Please be reminded that this application was reviewed only for the particular use pattern and use sites presented on the Alto 100 SL label. Any future application containing cyproconazole that is likely to increase the potential for significant impact on humans, non-target organisms, or the environment, would constitute a major change in labeled use pattern. Such an application must be accompanied by a new fee and meet the application requirements specified in 6 NYCRR Part 326.17.

Please contact Michael Sears, of my staff, at (518) 402-8768 if you have any questions regarding this letter.

Sincerely,

Maureen P. Serafini

Maureen P. Serafini
Director
Bureau of Pesticides Management

Enclosures

ecc: w/enc. - R. Mungari - NYS Dept. of Ag. & Markets
- A. Grey/E. Horn - NYS Dept. of Health
- W. Smith - Cornell University, PSUR