NEW YORK STATE DEPARTMENT OF ENVIRONMENTAL CONSERVATION

Division of Materials Management, Bureau of Pesticides Management
625 Broadway, 9th Floor, Albany, New York 12233-7254
P: (518) 402-8768 F: (518) 402-9024
www.dec.ny.gov

August 7, 2018

Via E-Mail

Ms. Brett Steckler
Monsanto Company
800 N. Lindbergh Blvd
St. Louis, MO 63167

Dear Ms. Steckler:

Re: Registration of the New Active Ingredient Tioxazafen (Active Ingredient Code 074752) Contained in Acceleron NemaStrike ST

The New York State Department of Environmental Conservation (Department) has evaluated your application (received July 7, 2017) in support of the registration of the above-referenced pesticide product.

Acceleron NemaStrike ST (EPA Reg. No. 524-624) contains 45.9% tioxazafen. It is labeled as a seed treatment for control of nematodes on corn, cotton and soybeans. The label limits seed treatment to commercial seed treatment facilities only. The maximum application (planting) rate of the treated seed is 0.28 pounds of tioxazafen per acre per year.

The application package was deemed complete for purposes of technical review on February 6, 2018. Pursuant to the review time frame specified in Environmental Conservation Law §33-0704.2, a registration decision date of July 6, 2018 was established. A request to waive the decision date was received from Monsanto Company (Monsanto) on July 6, 2018. The Department agreed to this request to allow additional time for Monsanto and the Department to investigate and review a concern related to human health.

REGISTRATION SUMMARY

Technical reviews of the proposed uses included on the Acceleron NemaStrike ST (Acceleron) product label have been performed by the Department and the New York State Department of Health. These reviews encompassed the expected impacts of labeled use of the subject product with respect to human health, ecological effects, and environmental fate. Please see the appendix of this letter for the full technical reviews.

Neither the environmental fate review nor the ecological effects review resulted in direct objections to registration of Acceleron. Initially, the human health technical review resulted in a concern with respect to the potential for risks to applicators and other handlers. This concern was subsequently mitigated through submission of additional information. **Therefore, Acceleron NemaStrike ST (EPA Reg. No. 524-624) has been registered in New York.**

Enclosed for your record are the Certificate of Pesticide Registration and stamped “Accepted for Registration” label. Please note the classification of “RESTRICTED” under the “Restriction” column on the enclosed Certificate of Pesticide Registration and the “Classified for Restricted Use in New York State” stamp on the enclosed product label. This product is restricted in its purchase, distribution, sale, use and possession in New York State because the label limits the product’s use to “commercial seed treatment facilities using fully-automated closed transfer and application equipment ONLY.”

The New York State Department of Environmental Conservation Regulations 6 NYCRR 326.3(a) state: “It shall be unlawful for any person to distribute, sell, offer for sale, purchase for the purpose of resale, or possess for the purpose of resale, any restricted pesticide unless said person shall have applied for, and been issued a commercial permit.” Please contact the Pesticide Reporting and Certification Section, at 518-402-8748, if you require information on obtaining a commercial permit.

Please note that a proposal by Monsanto or any other registrant to register a product that contains tioxazafen, and whose labeled uses are likely to increase the potential for significant impact to humans, nontarget organisms, or the environment, would constitute a Major Change in Labeling. Such an application must be accompanied by a new application fee and meet the requirements listed in Appendix 1.B. of “New York State Pesticide Product Registration Procedures.” Such information, as well as forms, can be accessed at http://www.dec.ny.gov/chemical/8528.html.

Please contact Shaun Peterson, of the Pesticide Product Registration Section, at 518-402-8768, if you have any questions regarding this letter.

Sincerely,

Jeanine Broughel for

Scott Menrath, P.E.
Director
Bureau of Pesticides Management

Enclosures

APPENDIX

HUMAN HEALTH ASSESSMENT:

The following technical review was produced by staff within the Bureau of Toxic Substance Assessment at the New York State Department of Health (NYSDOH).

NYSDOH reviewed the application and supporting data submitted by Monsanto to register the pesticide product Acceleron NemaStrike ST (EPA Reg. No. 524-624) in New York State. This pesticide product contains the new active ingredient tioxazafen (3-phenyl-5-(2-thienyl)-1,2,4-oxadiazole) and is labeled for control of nematodes as a commercial seed treatment on corn, cotton, and soybean. Acceleron NemaStrike ST is limited for use in commercial seed treatment facilities only and cannot be used for in-field applications.

Acute Toxicity

Neither tioxazafen nor the formulated product Acceleron NemaStrike ST was very toxic in acute oral, dermal or inhalation exposure studies in laboratory animals. The active ingredient and formulated product were not eye or skin irritants (tested on rabbits). In addition, neither tioxazafen nor Acceleron was a skin sensitizer (tested on guinea pigs).

Neurotoxicity

Both acute and subchronic oral neurotoxicity studies were conducted on tioxazafen in rats. In the acute study, this chemical caused adverse effects on total motor and ambulatory activity at a dose level of 250 milligrams per kilogram body weight (mg/kg), the lowest dose tested. Neurotoxic effects were not observed in the subchronic study, up to dose levels of 67 mg/kg/day in males and 75 mg/kg/day in females. However, systemic toxicity consisting of decreased body weight in females only was observed at 75 mg/kg/day; the no-observed-effect-level (NOEL) was 24 mg/kg/day. The U.S. Environmental Protection Agency (U.S. EPA) Office of Pesticide Programs (OPP) established an acute reference dose (aRfD) for tioxazafen for the general public of 0.25 mg/kg/day based on the lowest-observed-effect-level (LOEL) of 250 mg/kg/day from the acute neurotoxicity study in rats and an uncertainty factor of 1,000.

Chronic Toxicity

Tioxazafen caused some toxicity in chronic feeding studies in laboratory animals. In a chronic feeding study in rats, tioxazafen caused increased adrenal weights in males, as well as adrenal vacuolation in both sexes at 40 mg/kg/day in males and 48 mg/kg/day in females; the respective NOELs were 13.3 mg/kg/day and 16 mg/kg/day. In addition, there was an increased incidence of hibernomas in females at 48.1 mg/kg/day, the highest dose tested. In a chronic feeding/carcinogenicity study in mice, tioxazafen caused an increased incidence of hepatocellular hypertrophy, pigmented macrophages, and necrotic hepatocytes at 120 mg/kg/day in males and 50 mg/kg/day in females; the NOELs were 40 mg/kg/day and 10 mg/kg/day in males and females, respectively.

Developmental/Reproductive Toxicity

Tioxazafen caused some toxicity in rats, but not rabbits, exposed to this active ingredient in developmental toxicity studies. Although no developmental toxicity was observed in the rat study up to 200 mg/kg/day, maternal toxicity characterized by decreases in adrenal weights and food consumption was observed at 200 mg/kg/day; the NOEL was 50 mg/kg/day. Neither developmental nor maternal toxicity was observed in rabbits up to a dose level of 100 mg/kg/day tioxazafen, the highest dose tested. In a multi-generation reproduction study in rats, tioxazafen did not cause any reproductive toxicity, but was associated with increased adrenal gland weights in F_1 males and microscopic findings in the adrenal cortex of F_0/F_1 males at 20 mg/kg/day; the NOEL was 5 mg/kg/day. Treatment related effects were not observed in female rats at 60 mg/kg/day, the highest dose tested. The U.S. EPA OPP established a chronic oral reference dose (cRfD) for the general public of 0.05 mg/kg/day for tioxazafen based on the parental NOEL of 5 mg/kg/day from the developmental toxicity study in rats and an uncertainty factor of 100. This cRfD value has not yet been adopted by the U.S. EPA's Integrated Risk Information System (IRIS).

Carcinogenicity

Tioxazafen caused tumors in mice, but not rats, in chronic laboratory feeding studies. In male mice administered tioxazafen in the diet, there were statistically significant trends for hepatocellular carcinomas, hepatocellular adenomas and/or carcinomas combined and systemic hemangiosarcomas. In female mice, tioxazafen caused statistically significant trends for hepatocellular adenomas and hepatocellular adenomas and/or carcinomas combined. The U.S. EPA's Cancer Assessment Review Committee (CARC) concluded that the liver tumors in both sexes of mice were treatment-related based on the presence of corroborative pre-neoplastic lesions, statistically significant increases (trend and pair-wise tests) in rates of tumor incidence, and exceedances of historical control tumor incidences for this strain of mice. The systemic hemangiosarcomas observed in male mice were considered treatment-related as the tumor incidences exceeded historical control data. However, tioxazafen was negative in several genotoxicity studies. Based on these data, U.S. EPA's CARC classified tioxazafen as "likely to be carcinogenic in humans". To evaluate cancer risks, the U.S. EPA derived a cancer potency factor (CPF) of 9.63×10^{-3} $(mg/kg/day)^{-1}$, based on the combined rates of adenoma and/or carcinoma liver tumors in female mice.

Dietary Risk Assessment

The U.S. EPA established tolerances for tioxazafen residues in or on corn, cotton, soybeans and their commodities (*Federal Register* 82(82): 20,279–84; May 1, 2017). The acute (aPAD) and chronic (cPAD) population adjusted doses for tioxazafen are 0.25 mg/kg/day and 0.05 mg/kg/day, respectively and have the same basis as the aRfD and cRfD. The U.S. EPA estimated that all acute and chronic dietary exposures (food and drinking water) to this active ingredient would be less than 1 percent of the aPAD or cPAD for the general population and all population sub-groups. The U.S. EPA additionally estimated that cancer risks from lifetime dietary exposures to tioxazafen to be 5×10^{-7}. These exposure analyses are based on the assumption that 100 percent of

labeled crops are treated and contain tolerance level residues. Actual residues and resulting exposure levels are expected to be less than these assessments estimate.

Occupational Risk Assessment

The U.S. EPA reported the results of an occupational risk assessment for dermal and inhalation exposures to tioxazafen from the labeled use of Acceleron as a seed treatment on corn, cotton and soybeans. For determining non-cancer margins of exposure (MOEs), the U.S. EPA compared estimated short-term (1-30 days)/intermediate-term (1-6 months) inhalation exposures to human equivalency doses (HEDs) derived from the NOEL of 50 mg/m^3 observed in a 28-day inhalation toxicity study in rats. The U.S. EPA derived an HED of 1 mg/kg/day for portal-of-entry (POE) exposures based on nasal cavity effects (hyperplasia, inflammation, metaplasia and degeneration of the respiratory epithelium, and degeneration of the olfactory epithelium) and 10.59 mg/kg/day for systemic exposures based on adrenal toxicity (decreased gland weight, as well as atrophy and vacuolation of the adrenal cortex). For determining non-cancer MOEs from dermal exposures, the U.S. EPA compared estimated short-/intermediate-term exposures to the NOEL of 100 mg/kg/day in a 28-day dermal toxicity study in rats (increased incidence of cytoplasmic vacuolation of the adrenal cortex). The estimated non-cancer inhalation MOEs for seed treatment handlers (liquid loader/applicator, bagger, sewer, and multiple activities) ranged from 33 – 440 for potential POE effects and 350 – 14,000 for potential systemic effects, depending on the crop being treated. Dermal MOEs for seed treatment handlers in these occupational scenarios ranged from 2,900 – 18,000. The estimated inhalation MOEs for workers planting treated seed ranged from 420 – 1,300 and 4,400 – 14,000 for potential POE and systemic effects, respectively, and 13,000 – 41,000 for potential dermal effects. These estimates assumed all workers wore baseline personal protective equipment (long-sleeved shirt and long pants, shoes plus socks) and loaders/applicators, multiple activity workers and planters wore chemical-resistant gloves. The U.S. EPA considered inhalation MOEs of 30-fold and dermal MOEs of 100-fold or greater in these scenarios to provide adequate worker protection.

The U.S. EPA additionally estimated lifetime cancer risks for occupational handlers (liquid loader/applicator, bagger, sewer, multiple activities, and planter) from combined dermal and inhalation exposure estimates using the CPF of 9.63×10^{-3} $(mg/kg/day)^{-1}$. Cancer risks ranged from 4.6×10^{-6} – 5.6×10^{-5} depending on the worker activity and seed being treated (corn, cotton or soybeans). As mentioned previously for estimates of non-cancer risk, these estimates assumed all workers wore baseline PPE and loaders/applicators, multiple activity workers and planters wore chemical-resistant gloves. The U.S. EPA considered cancer risk estimates between 1×10^{-6} and 1×10^{-4} to be adequately protective of workers exposed to tioxazafen from use of Acceleron.

Drinking Water/Groundwater Standards

There are no chemical-specific federal or New York State drinking water/groundwater standards for tioxazafen. Based on its chemical structure, this chemical falls under the 50 micrograms per liter (µg/L) New York State drinking water standard for “unspecified organic contaminants” (10 NYCRR Part 5, Public Water

Systems). In addition, based on its toxicity data, tioxazafen meets the definition of an oncogen in 6 NYCRR Part 700.1. Using the U.S. EPA derived CPF (9.63×10^{-3} $(mg/kg/day)^{-1}$) and procedures for deriving ambient water quality standards and guidelines based on oncogenic effects (6 NYCRR Part 702.4), the value associated with a one-in-a-million increased lifetime cancer risk is 3.63 µg/L. This value could be used to derive a screening value for comparison to estimated impacts to groundwater and surface water.

Summary

The available information on tioxazafen and the formulated product Acceleron NemaStrike ST indicates that they are not very acutely toxic or irritating in laboratory animal studies. Subchronic and chronic toxicity studies in laboratory animals indicated that the adrenal gland was the primary target organ. Developmental effects were not observed in developmental and reproductive toxicity studies in laboratory animals administered tioxazafen in the diet. Tioxazafen caused liver tumors in male and female mice and hemangiosarcomas in male mice, but was negative in a number of genotoxicity studies. This active ingredient was classified by the U.S. EPA as "likely to be carcinogenic to humans" and a CPF of 9.63×10^{-3} $(mg/kg/day)^{-1}$ was derived to estimate cancer risks. The estimated cancer and non-cancer dietary and occupational risks from exposure to tioxazafen were within the ranges considered acceptable by the U.S. EPA.

NYSDOH Recommendation

While NYSDOH generally has concerns about registering pesticide products that have demonstrated oncogenic properties for use on food crops, tioxazafen is labeled for use only in commercial seed treatment facilities and exposure to the general public via dietary exposure is expected to be minimal. However, NYSDOH did have concerns for occupational handlers of Acceleron NemaStrike ST. The U.S. EPA Health Effects Division (HED) estimated cancer and non-cancer risks from exposure to tioxazafen assuming loaders/applicators, workers doing multiple activities, and planters of treated seed wore gloves, due to a lack of surrogate exposure data. The U.S. EPA required the use of gloves for these occupational scenarios based on the estimated non-cancer risks[1]. However, the product label does not contain a requirement for gloves and a waiver/rationale for this omission was not provided by the registrant.

Given the above, NYSDEOH did not support the registration of Acceleron NemaStrike ST until requirements for gloves were included in the list of personal protective equipment for applicators and other handlers on the product label or an acceptable explanation for why this requirement was waived was provided by the registrant.

[1] "Therefore, based on the occupational non-cancer handler risk estimates and surrogate unit exposure values, HED recommends that the tioxazafen labels require gloves for occupational handlers and seed planters." U.S. EPA. *Revised Human Health Risk Assessment for the First Food Uses on Corn, Cotton, and Soybean Seeds*. March 21, 2017. Page 30.

In response to this concern, the registrant cited a U.S. EPA registration decision document for tioxazafen[2] which contained the following statement: “To address any occupational cancer risk, the label mandates this product only be used in commercial seed treatment facilities, using fully automated, closed transfer and application equipment; thereby significantly reducing exposure to seed treatment workers. The functions of loading/applying tioxazafen to seed, bagging treated seed, and sewing closed bags of treated seed are performed by machinery and not by humans.” This document was not included in the original registration package for Acceleron NemaStrike ST submitted by the registrant and subsequently was not available for NYSDOH review at that time. After independently obtaining and reviewing an electronic version of this document, NYSDOH concurs with the registrant that the registration conditions set forth by the U.S. EPA mitigate concerns for occupational risks from use of tioxazafen. Therefore, NYSDOH does not object to registration of Acceleron NemaStrike ST in New York State.

ENVIRONMENTAL FATE ASSESSMENT:

Environmental chemistry staff within the Department’s Bureau of Pesticides Management evaluated the proposed use of tioxazafen as contained in Acceleron NemaStrike ST.

In each section that follows, the corresponding USEPA study guideline number, the subject matter of the study, and the EPA MRID number will be noted.

Guideline No. 835.1230, Sediment and Soil Adsorption/Desorption Batch Equilibrium, MRID 49066910

In a study that was rated as acceptable, the adsorption/desorption of tioxazafen was performed using six soils. These soils and their properties are listed in the following table and it was noted in the Data Evaluation Record (DER) that soil adsorption generally increases with organic carbon content, however the correlation was weak (r^2 = 0.43). When the Dana sandy loam soil was regarded as an outlier and excluded from the data set, the adsorption in the remaining soils is highly correlated with organic carbon (r^2 = 0.97). The pH and percent organic carbon for the Tift loamy sand corresponds with Riverhead, NY soil so those Kfoc and 1/n values will be used in subsequent LEACHP modeling. These values are listed in bold type.

Soil Type	pH	% OC	Adsorption Kfoc	Adsorption 1/n
Tift loamy sand, Georgia	**5.3**	**0.64**	**4039**	**0.80**
KD-SL-PF, sandy loam, N. Dakota	7.1	1.4	2385	0.82
Carlyle, silt loam, Illinois	7.3	1.2	2051	0.76

[2] U.S. EPA. *Final Registration Decision Document for the New Active Ingredient Tioxazafen*. April 10, 2017. Pg 11.

DU-L, clay loam, N. Dakota	5.7	3.3	2052	0.69
Dana, sandy clay loam, Iowa	6.9	2.4	5151	0.66
Madera, sandy loam, California	6.9	4.3	3714	0.79

Guideline No. 835.2120, Aqueous Hydrolysis, MRID 49066911

In a study that was rated as acceptable, tioxazafen was found to be hydrolytically stable in sterile aqueous buffer solutions at pH 4, 7, and 9, which are at environmentally relevant acidic, neutral and alkaline pH. The respective half-lives were noted to be 2.7, 6.3, and 3.1 years.

Guideline No. 835.2240, Aqueous Photolysis, MRID 49304209

In a study rated as acceptable, the phototransformation of tioxazafen in sterile pH 7 buffer solution was investigated. Duplicate irradiated samples were analyzed at 1, 2, 4, 7, 10 and 24 hours and duplicate controls that were kept in the dark were analyzed at the beginning and the end of this study.

In the irradiated samples, the phototransformation of tioxazafen occurred rapidly declining from a mean of 99.7% at time zero to 0.3% at 24 hours. A single major transformation product was formed and was identified as 3-thienyl-tioxazafen. This photoproduct reached a maximum of 94% of the originally applied parent at 10 hours before declining slightly to 91.1% at 24 hours. At 24 hours there were five minor transformation products but none exceeded 1.8% of the originally applied amount. Tioxazafen remained intact in the dark controls.

The calculated phototransformation half-life was <2 hours. As a result, direct aqueous photolysis is expected to be a major dissipation route for tioxazafen in aquatic environments, but the use of this active ingredient as a seed treatment will limit the potential for tioxazafen to reach water bodies. Because the major degradate 3-thienyl-tioxazafen has very low absorbance at wavelengths above 290 nm, the estimated half-life would exceed 30 days even in summer at 20°N latitude. Therefore, 3-thienyl-tioxazafen is expected to be relatively stable to photolysis.

Guideline No. 835.2410, Photo-degradation in Soil, MRID 49304210

In a study rated acceptable, the photo-degradation of tioxazafen on non-sterile Hoyleton silt loam soil was studied. The soil was treated with about 4.5 times the expected field rate, which was presumed to enhance the sensitivity of the analysis and to help identify any transformation products.

The light exposure continued for 15 days and control samples were kept in the dark over this time period. Sampling was conducted at 1, 3, 7, 11, and 15 days after

application and there were no significant levels of any photo-transformation products found and only 3.0-3.6% of what was applied was transformed into 3-thienyl-tioxazafen after 15 days. The half-life calculation was not performed because the results showed virtually no photolysis or degradation, which demonstrated that tioxazafen is photolytically stable on soil surfaces.

Guideline No. 835.4100, Aerobic Soil Metabolism, MRID 49096801 and 490304211

In a study that was classified as acceptable, four U.S. soils were used to study aerobic soil degradation and the properties of these soils are listed in the following table. The soils were treated with 0.28 lbs per acre, which is equivalent to the labeled rate for the treated seeds.

Soils Type, MRID 49096801	Soil pH	Percent Organic Carbon	t½ (Days)	Major Degradate
Manning sandy loam, N. Dakota	7.5	1.4	22.1	Unextracted Residues, $^{14}CO_2$
Hoyleton silt loam, Illinois	7.5	1.2	53.9	Unextracted Residues, $^{14}CO_2$
Webster sandy clay, Iowa	7.0	2.4	147	Unextracted Residues
Barnes-Svea clay loam	5.7	3.3	270	Unextracted Residues

In the Manning sandy loam, total extractable radioactivity declined from 99.5% of the applied at time zero to 24.4% at 123 days posttreatment. Unextractable radioactivity increased to a maximum of 56.2% of the applied at 78 days posttreatment and was 54.6% at 121 days. Evolved $^{14}CO_2$ totaled a maximum of 19.8% of the applied at study termination and other volatiles were not detected.

In the Hoyleton silt loam, total extractable radioactivity declined from 99.0% of the applied at time zero to 31.2% at 123 days posttreatment. Unextractable radioactivity increased to a maximum of 47.7% of the applied at 123 days posttreatment. Evolved $^{14}CO_2$ totaled a maximum of 20.7% of the applied at study termination and other volatiles were not detected.

In the Webster sandy clay loam, total extractable radioactivity declined from 103.1% of the applied at time zero to 57.4% at 121 days posttreatment. Unextractable radioactivity increased to a maximum of 36.1% of the applied at 121 days posttreatment and was 54.6% at 121 days. Evolved $^{14}CO_2$ totaled a maximum of 5.7% of the applied at study termination and other volatiles were not detected.

In the Barnes-Svea clay loam, total extractable radioactivity declined from 96.8% of the applied at time zero to 68.2% at 121 days posttreatment. Unextractable radioactivity increased to a maximum of 28.6% of the applied at 90 days posttreatment and was 27.9% at 123 days. Evolved $^{14}CO_2$ totaled a maximum of 3.6% of the applied at study termination and other volatiles were not detected.

In another study using the same soils and classified as acceptable, a NAFTA kinetics evaluation for tioxazafen using the PestDF v.0.8.4 tool, developed by the USEPA and Canada's PMRA, different half-lives were determined. The following table lists these half-lives and it is noted in this study that the half-life values, "…were considered appropriate as input to parameterize the USEPA and PMRA surface and groundwater models." It is due to that, and the value for the Hoyleton silt loam of 70.3 days, which has the lowest organic carbon content and a larger half-life from the previous study (MRID 49096801), which is a more conservative half-life, that half-life will be used in subsequent LEACHP modeling (bold type).

Soils Type, MRID 49304211	Soil pH	Percent Organic Carbon	t½ (Days)	Major Degradate
Manning sandy loam, N. Dakota	7.5	1.4	48.1	Unextracted Residues, $^{14}CO_2$
Hoyleton silt loam, Illinois	**7.5**	**1.2**	**70.3**	**Unextracted Residues, $^{14}CO_2$**
Webster sandy clay, Iowa	7.0	2.4	167	Unextracted Residues
Barnes-Svea clay loam	5.7	3.3	303	Unextracted Residues

Guideline No. 835.4400, Anaerobic Aquatic Metabolism, MRID 49304215

Because tioxazafen is intended for use as a seed treatment, its potential to reach water bodies is limited so a detailed review of the aerobic aquatic metabolism study is not included in this environmental fate technical review but an Excel table listing the various recoveries of the two radio-labels and their degradation products in the various layers of the systems over time are available.

Tioxazafen degraded rapidly in anaerobic water/sediment systems and represented <50% of the applied after two weeks of incubation and declining to below detection limits after one month. Tioxazafen-iminoamide was the major transformation product early in the study and represented up to an average of 29.6% of the applied parent in ^{14}C-labeled and ^{14}C-TH-labeled samples by day 7 and subsequently declining to below detection limits by the end of the study. In ^{14}C-PH-labeled samples, benzamidine was the main transformation product observed in water layers and sediment extracts and represented up to a maximum average of 55.7% of the applied. Its decline was observed in both test systems by the end of the incubation period. In the ^{14}C-TH-labeled samples, the degradate 2-thiophenecarboxylic acid was found and it represented up to an average of 19.8% of the applied by day 62.

Bound residues represented up to 68.1% of the applied in ^{14}C-PH-labeled samples and up to 23.9% in the 14C-TH-labeled samples. Fractionation of the bound residues into fulvic acid and humic acid fractions showed that most of the radiocarbon

was associated with the unextracted humins for both labeled samples. Fulvic acid fractions contained an average of 19.6% and 3.8% of the applied in the ^{14}C-PH-labeled and ^{14}C-TH-labeled samples respectively, and the humic acid fractions contained <4% of the applied.

Guideline No. 835.4300, Aerobic Aquatic Metabolism, MRID 49304214

Because tioxazafen is intended for use as a seed treatment, its potential to reach water bodies is limited so a detailed review of the aerobic aquatic metabolism study is not included in this environmental fate technical review but an Excel table listing the various recoveries of the two radio-labels and their degradation products in the various layers of the systems over time are available.

Tioxazafen degraded rapidly in aerobic sediment/water systems and represented <10% of the applied after two weeks of incubation, declining to <1.1% of the applied by the end of the aerobic incubation period. Tioxazafen-iminoamide was formed early in the study, and represented up to 35.7% of the applied in the ^{14}C-TH-labeled samples and ^{14}C-PH-labeled samples by Day 7, subsequently declining to <0.3% of the applied by the end of the incubation period. In the ^{14}C-PH samples, benzamidine was the main transformation product observed in water layers and sediment extracts and represented up to a maximum average of 63.0% of the applied. Its decline was also observed in both test systems during the incubation period. In ^{14}C-TH samples, 2-thiophenecarboxylic acid represented up to an average of 20.8% of the applied, and declined to below detection limits by Day 59.

Bound residues represented up to 69.0% of the applied in ^{14}C-PH-labeled samples and up to 23.4% of the applied in the ^{14}C-TH-labeled samples. Fractionation of the bound residues into fulvic acid and humic acid fractions showed that most of the radiocarbon was associated with the unextractable humins for both the ^{14}C-PH-labeled and the ^{14}C-TH-labeled samples. Fulvic acid fractions contained up to 14.4% and 5.5% of the applied in the ^{14}C-PH- and ^{14}C-TH-labeled samples, respectively, and the humic acid fractions averaged <3.0% of the applied in both labels and both systems.

By the end of the incubation period $^{14}CO_2$ represented up to 78.5% of the applied in the ^{14}C-TH-labeled samples, and up to 23.3% in the ^{14}C-PH-labeled samples.

Dissipation of tioxazafen in the total system and the water layer was rapid. The DT50 for tioxazafen in the total system ranged from 4.37 to 5.94 days, while the DT50 for tioxazafen in the water layer ranged from 4.0 to 4.87 days. In the sediment, the DT50 for tioxazafen was 1.61 days in the Golden Lake system and 10.61 days in the Goose River system. The dissipation of tioxazafen-iminoamide was rapid, with DT50 values ranging from 2.94 to 5.09 days. Dissipation of 2-thiophenecarboxylic acid was slightly slower with DT50 values ranging from 10.6 to 13.1 days. The dissipation of benzamidine was slower, with DT50 values ranging from 55.2 to 78.7 days.

Guideline No. 835-6100, Terrestrial Field Dissipation, MRID 49304217

In a study rated as acceptable, the dissipation of tioxazafen and the degradate benzamidine in soil when applied as a pre-coated soybean seed treatment under field conditions is described. The tests were done in four different North American sites: Tift County, Georgia; York County, Nebraska; Champaign County, Illinois; and Grey Rural Municipality, Manitoba.

At each site there were three test plots: one treated seed plot, one treated in-furrow plot, and one control plot. Residues of tioxazafen remained primarily in the 0-6 inch soil layer in both, treated seed and in-furrow plots at all four locations and there were no benzamidine residues found at or above the limit of quantitation (LOQ, 5.0 ppb) below the 0-3 inch depth.

After the soil plots were treated, moisture was input into the ground at a rate of 120% of normal rainfall and was adequate to evaluate the leaching potential of tioxazafen and although the wetting front had reached 24-36 inches in depth, no significant downward movement of tioxazafen or benzamidine was observed in any of the treated plots.

The dissipation of tioxazafen was assessed using first order (SFO) and biphasic (FOMC/IORE, DFOP) kinetic models and the total mass of tioxazafen in the 0-12 inch sampled soil profile (deepest depth with residues detected above the LOQ) was used in the kinetic calculations.

Residues of tioxazafen remained primarily in the 0-6 inch soil layer in both treated plots at all four sites. Only the Manitoba site had tioxazafen being detected above the LOQ at the 6-12 inch depth at 6.9 and 5.6 ppb. There were no tioxazafen residues found at or above the LOQ in any sample below the 6-12 inch depth.

There were no residues of benzamidine found at or above the LOQ in any samples below the 0-3 inch depth in both treated plots at all four locations. Benzamidine residues were found sporadically at low levels in the 0-3 inch depth at all four sites ranging from 1.4 to 24.3 ppb. The following table lists the half-lives of the treated seed and in-furrow plots at all four sites:

Site	Plot	DT50 (Days)
Georgia	Treated Seed	94.3
	In-Furrow	40.1
Nebraska	Treated Seed	14.7
	In-Furrow	101
Illinois	Treated Seed	44.7
	In-Furrow	90.5
Manitoba	Treated Seed	258
	In-Furrow	87.3

LEACHP Modeling of Tioxazafen

As was noted in the previous relevant sections, the following inputs were used for the LEACHP modeling. There were no major degradates in the aforementioned sections so only the parent tioxazafen was LEACHP modelled.

New Active	Water Solubility (mg/L)	Maximum Seasonal Application Rate (lbs ai/acre/yr)	Aerobic Soil Half-Life (Days)	Adsorption Kfoc (ml/g)	Kfoc 1/n
Tioxazafen	1.24	0.28	70.3	4039	0.80

Using the Riverhead soil series LEACHP input file, the maximum leaching concentration is at 0.00 µg/L (ppb).

Based on the LEACHP profile that shows no leaching of tioxazafen, which is consistent with the terrestrial field dissipation findings, environmental fate staff does not object to the registration of tioxazafen as a seed treatment in New York State.

ECOLOGICAL EFFECTS ASSESSMENT:

The Department's Bureau of Ecosystem Health (BEH) evaluated the proposed use of tioxazafen as contained in the subject products.

I. CHEMICAL BACKGROUND

Tioxazafen, 3-phenyl-5-(2-thienyl)-1,2,4-oxadiazole, is a new nematicidal active ingredient labeled for use as a seed treatment on corn and soybean seed. Acceleron NemaStrike ST (Acceleron) is 45.9% Tioxazafen, equaling 4.51 lbs per gallon.

Use profile

The Acceleron label allows application to seeds in commercial treatment facilities only. On corn, 2.5-5.0 fluid ounces of formulation is applied per 80,000 seeds equaling 0.5-1.0 mg active ingredient, ai, per seed. On soybean, 2.2-4.4 fluid ounces of formulation are applied per 140,000 seeds which equals 0.25-0.5 mg ai per seed. At a maximum planting rate of 40,250 seeds/acre for corn the Acceleron application rate is a maximum of 0.089 pounds ai per acre, lbs. ai/A. The maximum planting rate for soybeans is given as 250,000 seeds/acre which equals an application rate of 0.28 lbs. ai/acre.

The Environmental Hazards section of the label instructs the user "Do not plant treated seeds by broadcasting to the soil surface. Ensure that all seeds are thoroughly covered with soil. Treated seed exposed on soil surface may be hazardous to wildlife.

Cover or collect treated seeds spilled during loading." The Seed Labeling section of the label again states that any treated seed spilled during loading or planting must be covered or cleaned up. Also, treated corn and soybean seeds must be planted at a minimum depth of 1 inch.

Mode of action

The tioxazafen mode of action is ill-defined. It appears to disrupt ribosomal activity in nematodes. No other information is available.

Physical/chemical properties

Tioxazafen is slightly soluble in water and is classified as slightly mobile. Reported values are given in Table 1.

Table 1. Tioxazafen physical and chemical properties

Parameter	Value
Water solubility	1.24 mg/L
Octanol/water partitioning coefficient	log K_{OW} = 4.13
Soil partitioning coefficient	Mean K_{OC} = 4,473
Vapor pressure	$5.82x10^{-7}$ mmHg
Mass	228.27 g/mole

II. TOXICITY

Tioxazafen is classified as practically nontoxic to birds and mammals on an acute basis, and slightly toxic to birds in dietary studies. Chronic exposures can result in toxic effects in terrestrial vertebrates but only at levels that are unlikely to occur in the field. It is highly to very highly toxic to aquatic organisms. Tioxazafen was practically nontoxic to adult honey bees in acute oral and contact studies. Reported tioxazafen toxicity values used in modeling or otherwise used in this review are given in Table 2. This is a subset of the submitted data package.

Table 2. Reported tioxazafen toxicity values

Terrestrial

Study type	Results	Study classification	EPA MRID No.	Comments
Rat acute	>5000 mg/kg bw	acceptable	49304273	bw = body weight
Rat 2 generation reproduction	LOAEL=200ppm diet NOAEL= 20ppm diet	acceptable	49304292	also lowest dietary based mammal study

Bobwhite quail acute	LD_{50} = 4,500 mg/kg bw NOAEL < 580 mg/kg bw	acceptable	49066901	
Canary acute	LD_{50} = 315 mg/kg bw LOAEL = 270 mg/kg bw NOAEL = 162 mg/kg bw	acceptable	49066902	
Mallard dietary toxicity	LC_{50} = 4,085ppm diet NOAEC < 516 ppm diet	acceptable	49066904	
Mallard reproduction	LOAEC = 491 ppm diet NOAEC = 243 ppm diet	acceptable	49304231	Most sensitive endpoints- almost all reproductive measures
Honey bee acute contact	LD_{50} > 100µg/bee NOAEC = 100 µg/bee	acceptable	49066909	Practically nontoxic
Honey bee acute oral	LD_{50} >0.41 µg/bee NOAEC = 0.41 µg/bee	acceptable	49304243	
Aquatic (mg/L)				
Bluegill acute	LC_{50} = 0.51 NOAEC =0.071	acceptable	49066905	
Rainbow trout acute	LC_{50} = 0.091 NOAEC = 0.014	acceptable	49066906	
Fathead minnow ELS*	LOAEC = 0.024 NOAEC = 0.0094	supplemental	49304225	
Daphnia magna acute	EC_{50} > 1.2 NOAEC = 0.42	acceptable	49066908	
Daphnia magna L-C*	LOAEC = 0.014 NOAEC = 0.006	acceptable	49304223	
Sheepshead minnow acute	LC_{50} > 0.084 NOAEC = 0.042	supplemental	49066907	
Mysid shrimp acute	LC_{50} = 0.337 NOAEC = 0.11	acceptable	49304221	
Oyster	IC_{50} > 0.183 NOAEC < 0.019	acceptable	49304220	

Mysid shrimp L-C	LOAEC > 0.044 NOAEC = 0.044	acceptable	49304224	

ELS- early life-stage, L-C - full life cycle.

III. EXPOSURE

Tioxazafen can be persistent in some soils post application. Half-lives, $T_{1/2}$s, in submitted treated seed terrestrial field dissipation trials range from 45 days in Illinois to 220 days in Manitoba, Canada with a geometric mean of 97 days. Aquatic dissipation, via microbial metabolism, is more rapid with $T_{1/2}$s generally less than 1 week in both aerobic and anaerobic sediment/water study systems.

Tioxazafen is stable to hydrolysis. The molecule stays intact but isomerizes, $T_{1/2}$ = 2.3 hours, in aqueous photolysis studies to 3-thionyl parent and is then stable. 3-thionyl tioxazafen has similar toxicity to the original form and is considered as parent for purposes of this review. It is stable to soil surface photolysis. Mean aerobic and anaerobic soil metabolism $T_{1/2}$s in multiple soils are 83 days and 272 days respectively.

Total system $T_{1/2}$s in both aerobic and anaerobic sediment/water dissipation trials are 4.4 days.

Tioxazafen is, at most, slightly mobile in soil post application.

IV. EXPOSURE MODELING

Standard BEH screening aquatic runoff modeling was conducted in which the annual maximum application rate was made available for runoff. The standard terrestrial food item modeling was not conducted for this seed treatment use pattern.

V. MODELING RESULTS & RISK ASSESSMENT

When the highest label application rate is modeled as though it were applied to the soil surface and runoff is maximized, there are a small number of aquatic toxicity thresholds exceeded. Under the same conditions but lower runoff rates, more likely for a compound with similar partitioning coefficients, few if any toxicity thresholds were exceeded. These highly conservative conditions should not occur with legal use.

If spilled seed is not covered or cleaned up as the label directs there is the possibility that smaller birds can consume a toxic dose if they feed on the spillage.

Acceleron NemaStrike ST, when used as labeled, is not likely to result in adverse impacts to nontarget resources. Therefore, the Bureau of Ecosystem Health has no objection to its registration.