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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MAY 6 1993

MEMORANDUM

SUBJECT: New Microbial Metarhizium anisopliae Strain ESF1 for Food, Feed, and Nonfood Uses Indoors, in Greenhouses, and in Poultry and Livestock Areas (EPA File Symbols 432-TAR, TAU and 64296-R, -E, -G)
- Decision Memorandum -

FROM: Lawrence E. Culleen, Acting Director
Registration Division

TO: Douglas Campt, Director
Office of Pesticide Programs

ISSUE

Should unconditional registrations be granted for the subject products containing the new active ingredient Metarhizium anisopliae strain ESF1 as the sole active ingredient under FIFRA § 3(c)(5)? Should a registration invoking both FIFRA §3(c)(5) and §3(c)(7)(A) be granted for the fly control product containing both the new active ingredient Metarhizium anisopliae and the FIFRA '88 ingredient muscalure?

BACKGROUND

Regulatory History

Both EcoScience and Roussel Bio are submitting their own as well as citing one another's data to support their pending registration applications. All scientific reviews are now complete and there are no data gaps relevant to the pending products listed above.

On October 22, 1990 Roussel Bio Corporation applied for an experimental use permit to test Metarhizium anisopliae in bait stations for cockroach control . An EUP was issued on June 6, 1991 (432-EUP-1). On 7/25/91, Roussel Bio Corporation applied for registration of Bio-Path™ Biological Roach Control System (EPA file Symbol 432-TAR). On 10/31/91, EcoScience Corporation applied for registration of

Bio-Path™ Fly, Bio-Path™ Roach and Bio-Path™ Insecticide Technical (64926-R, -E, -G). On 10/31/91, Roussel Bio applied for registration of Bio-Path™ Technical (432-TAU). On 12/31/91, EcoScience applied for a permanent exemption from the requirement of a tolerance on all Raw Agricultural Commodities, and food and feed additive regulations for Metarhizium anisopliae.

USE SITES AND APPLICATION TIMING

The Bio-Path™ Insecticide Technical and the Bio-Path™ Technical are manufacturing-use products for use in formulating end-use Metarhizium anisopliae products.

The Bio-Path™ Biological Roach Control System and Bio-Path™ Roach cockroach control chamber products are to be used indoors and in various modes of transportation in residential, commercial, industrial, and institutional areas. These areas include food handling establishments, greenhouses, aircraft, etc. A maximum of 24 bait stations may be applied per room in residential areas and a maximum of 24 bait stations may be applied each 96 square feet in all other use sites. Chambers are to be replaced every 2-3 months to maintain control.

The Bio-Path™ Fly Control Chamber is to be used in homes, barns, sheds, garages, rest rooms, dairies, stables, poultry houses, hog houses, livestock barns, kennels, food processing plants, shops, supermarkets, restaurants and refuse containers. A maximum of 1 trap may be applied per 100 to 200 ft^2 or 60 -120 traps may be applied per 12,000 ft^2. Chambers are to be replaced as necessary with label recommendations indicating replacement every 2-3 weeks. A maximum of 1 chamber per 100 square feet may be applied.

Label directions for both the fly and the roach products indicate that fungal material may fall out of the semi-enclosed products onto adjacent areas and should be cleaned up if this happens.

The fly chamber is actually a 4 component product in which the user unfolds the chamber (which looks somewhat like a half gallon milk carton with holes cut in the side) and puts a fungal garden, a feeding stimulant, and a pheromone into the chamber. The fungal garden is contained within a foil pouch which is opened prior to placement into the chamber.

The roach control chambers are stations similar to Combat® in appearance in that they are plastic stations that are broken apart from a unit containing several stations. The active ingredient is contained within the stations and roaches enter small openings to come into contact with the active ingredient. The Metarhizium anisopliae stations have not been shown to be child resistant. They are sealed in a foil pouch to maintain humidity prior to use.

TOXICOLOGY

The toxicological data considered in support of these registration applications include an acute oral toxicity/pathogenicity study in the rat, an acute pulmonary toxicity/pathogenicity in the rat, an acute intravenous toxicity/pathogenicity in the rat, a dermal toxicity study in the rabbit, and a primary eye irritation study in the rabbit as well as data indicating that Metarhizium anisopliae is unable to grow at or above 95°F.

The results of the toxicity/pathogenicity studies show no toxic, pathogenic, or adverse effects. These studies demonstrated that rodents can effectively clear the fungus from their bodies even after it is injected at high amounts. The results of the temperature growth study show that Metarhizium anisopliae can not grow at mammalian body temperatures and therefore would not grow in the organs or tissues of humans. No toxicity or irritation were observed in the dermal study and only grade one erythema and edema were present in most animals at the one and twenty-four hour evaluation periods in the seven day primary eye irritation study, i.e. Toxicity Category IV. The applicants have provided acceptable discussions regarding the lack of toxic components in their product for the proposed uses, as required by 40 CFR Part 158. Analysis of mycotoxins was not required for the current uses. As mentioned earlier, there are no data gaps relevant to mammalian health effects for registration of the pending products. However, prior to supporting uses entailing wider and direct exposures of the fungus to food, HED indicated that the applicants should determine if strain ESF1 does not produce detectable levels of destruxins (a type of mycotoxin) or that there is no mammalian toxicology associated with these substances.

In response to the applicants' rebuttal to required labeling modifications in the pre-acceptance letter, PM Team 18 contacted an Office of Research and Development researcher to confirm that his ongoing study of a Metarhizium anisopliae strain (distinct from the applicants' ESF1 strain) showed adverse effects to fish embryos and to obtain further details. In that verbal communication of 11/13/92, we learned that the effects were not simple pathogenicity, but the apparently teratogenic effect of gelatinous backbone formation and subsequent death. Besides being made aware of the potential fish teratogenic effects of another strain of this fungus, RD was informed of the ORD researcher's opinion that a fungus may produce different toxins in insects than in the growth media of the end-use products. The genus Metarhizium has been shown to produce mycotoxins, i.e. the destruxins. The potential for mammalian toxicity of these toxins is unknown. Due to the preliminary nature of these studies, the researcher requested that the results not be discussed outside the Agency.

On 11/18/92, RD met with HED and EFED staff to further discuss these issues. EFED supported the use site deletion of zoos and pet stores unless data demonstrating no hazards were submitted and found acceptable. HED indicated that, for the current pending uses, no further information should be necessary prior to registration. HED

based their conclusion on at least these two points; 1) the acute toxicity/pathogenicity studies adequately predict the potential for subchronic, chronic, and teratogenic effects and 2) even if the acute toxicity/pathogenicity studies did not adequately predict the potential for subchronic, chronic, and teratogenic effects, potential exposure to the fungus and any metabolites would be insignificant.

On 11/23/92, RD management and staff met with HED management and staff to further discuss the relevance of the fish embryo study, possible presence of mycotoxins, and potential exposure to mycotoxins from the pending products. Regarding the fish embryo study, HED pointed out that the study was ongoing and had not been peer reviewed. HED further indicated that the correlation of the in vitro fish embryo assay used in the subject study to human teratology predictions was poor. Therefore, even if after peer review and journal publication the fish embryo study effects remain as reported verbally to RD, the study should not be used to predict human health effects.

Regarding exposure, the pending end-use products do not involve surface dusting, space sprays, or other high exposure application methods. However, the fly product does involve dermal exposure to the fungal garden during the time that the homeowner or pest control operator constructs the fungal chamber. Further, both the fly product and the roach product may allow additional exposure due to fungal material becoming dislodged from the chambers and falling to the surrounding area. According to HED, the dislodged fungal material in these latter cases would primarily be conidia, i.e. dust fine asexual spores. HED indicated that fungal conidia do not normally contain mycotoxins and that mycotoxins are usually produced during growth of the hypha, i.e. the fungal filaments, in growth media or target insects. For the cockroach products, exposure to hyphae and thus possibly to mycotoxins may exist through contact with infected roaches or by children taking apart the non-child resistant chambers. For the fly product, contact with diseased flies and with the fungal garden during construction of the chamber would constitute the most probable exposure scenarios.

There are no known reports of destruxins causing adverse mammalian health effects, however other mycotoxins are known to adversely affect human health. As stated earlier in this memorandum, no toxic, pathogenic or toxic adverse effects were observed in any of the submitted studies. Based on these studies, the form of Metarhizium anisopliae strain ESF1 that was tested and is to be sold in commerce either do not contain destruxins or if these compounds are present that they pose no threat of causing significant adverse effects to human health. This conclusion is drawn from the assumption that mycotoxins that may adversely affect human health would show acute adverse effects in toxicity/pathogenicity studies. Since different environmental conditions may affect destruxin production, lack of acute effects in mammalian toxicity/pathogenicity studies alone could not preclude the potential for

destruxin production in the target insects. However, since the LT_{50}s (time required to kill 50% of the population) for strain ESF1 in the German cockroach and the house fly are 10 days and greater than 6 days, respectively, there is little or no chance that insects infected with strain ESF1 from the attractant stations would contain destruxins. Destruxin producing strains of Metarhizium anisopliae tend to cause faster insect mortality due to destruxin toxicity. The mode of action for strains not producing destruxins appears to be primarily from proliferation of the fungus and subsequent death of the infected insect.

In the unlikely event that insects exposed to strain ESF1 in attractant stations contain destruxins, and such insects before death contaminate foods or feeds processed or stored in a food or feed handling establishment, such foods may be considered adulterated under provisions of 21 U.S.C. 342(a)(3) and be subject to regulatory sanctions by the Food and Drug Administration (FDA). To avoid potential FDA enforcement action, all food handling facilities using pesticides, including those that use Metarhizium anisopliae strain ESF1 for insect control, should make every effort to protect foods and feeds from contamination with insects or insect fragments.

Questions regarding the potential for human skin infections with Metarhizium anisopliae were discussed with HED. Apparently, the majority of human skin, nail and hair fungal infections are caused by fungi within the genera Microsporum, Trichophyton, and Epidermophyton. Metarhizium anisopliae is not in these genera.

Reference Dose (RfD) and maximum permissible intake (MPI) considerations are not relevant to this application because the data submitted demonstrate that this biological control agent is not toxic to humans.

TOLERANCE EXEMPTION AND FOOD AND FEED ADDITIVE REGULATION

Food and feed additive regulations as well as an exemption from the requirement of a pesticide tolerance on all raw agricultural commodities permitting the use of the microbial pest control agent Metarhizium anisopliae Strain ESF1 in food handling establishments, greenhouses, and enclosed and semi-enclosed poultry and livestock areas according to the following prescribed conditions listed below is attached for signature. The conditions of the regulations include: (a) Application shall be limited solely to attractant station placement and (b) To assure safe use of the microbial pest control agent, its label and labeling shall conform to that registered by the U.S. Environmental Protection Agency, and it shall be used in accordance with such label and labeling.

The request for a tolerance regulation was submitted by EcoScience Corporation of Worcester, MA. Both Health Effects Division and the Office of General Counsel have concurred with comment and their comments have been incorporated.

FDA Interaction

We requested the Food and Drug Administration to provide comments on the tolerance rule, mainly due to the filth standard language involving 21 U.S.C. 342(a)(3). FDA comments were mostly incorporated. John Jones of FDA indicated via personal communication on 2/5/93 with Michael Mendelsohn of PM Team 18 that FDA's major concern was the draft rule's discussion of potential destruxin presence. He suggested language in the draft rule regarding the potential for mycotoxin presence to be modified by "little of no." This was done. Further, Dr. Jones indicated that FDA does not need for EPA to contact them again on this issue.

ECOLOGICAL EFFECTS

All ecological effect data for Metarhizium anisopliae strain ESF1 pertaining to the pending products have been waived due to the indoor use. However, due to the potential of affecting the beneficial muscid fly in poultry house,
the following environmental hazards statement must be added to the fly control product's label.

This product is pathogenic to muscid flies (Ophyra aenescens), a biocontrol agent for house fly larvae in poultry houses.

Further, a statement must be added to the directions for use section of the label that instructs the user that when muscid flies are used as biocontrol agents that the chambers should be placed high up, away from the manure surface to minimize harmful effects on these flies.

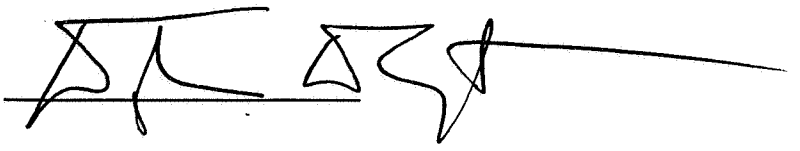
EFFICACY

Submitted efficacy data show that the roach control and fly control products perform their desired function.

CONGRESSIONAL INQUIRY

On 8/11/92, Mr. B.J. Wynne (Regional Administrator for EPA Region 6) received a letter from Senator Lloyd Bensten regarding a concern that his constituent, Ms. Jennifer Bellamy, had regarding the safety of the roach control product. Apparently, a magazine article about research on this fungus stated "It won't hurt pets, or any warm-blooded creature, because the substance can't live over 98° F." Assistant Administrator Linda Fisher responded to Senator Bensten's office explaining that Metarhizium anisopliae cannot grow over 95°F and that rodent studies investigating toxicity and pathogenicity showed no potential for human pathogenicity.

The Registration Division recommends that the subject products containing Metarhizium anisopliae strain ESF1 as the sole active ingredient be registered under FIFRA § 3(c)(5) and that the fly product containing strain ESF1 along with the FIFRA '88 List D pesticide muscalure be registered under both FIFRA § 3(c)(5) and 3(c)(7)(A)[1].

Concur: 

Nonconcur: _____

Comments: _____

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Date: MAY 7 19__

Attachments:

Fact Sheet
Tolerance Document
FDA Communication
Concurrences
OPPTS Congressional Response
OGC Note

[1]OGC recommended either issuing one registration under both § 3(c)(5) and § 3(c)(7)(A) or issuing two registrations for the same product under each of these sections respectively. Both options would take care of FIFRA '88 concerns regarding muscalure.