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

PREVENTION, OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: BPPD Review of Data Waiver Requests Submitted by IR-4 on behalf of the Arizona Cotton and Research Council in support of the Health Effects of *Aspergillus flavus* AF36 for use on cotton food/feed commodity (No MRID No.; EPA Reg. No. 071693-R; Chemical No. 006456).

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TO: Dennis Szuhay, Acting Chief
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ACTION REQUESTED

BPPD has received requests from Interregional Research Project Number 4 (IR-4), New Jersey Agricultural Experiment Station, Technology Center of New Jersey, Technology Center of New Jersey, 681 U. S. Highway #1 South, North Brunswick, NJ 08902-3390, on behalf of the Arizona Cotton Research and Protection Council, 3721 East Weir Avenue, Phoenix, Arizona 85040-2933 to waive certain data requirements for use of *Aspergillus flavus* AF36 (active ingredient 006456) on the food/feed commodity cotton in connection with the proposed registration of the subject pesticide (EPA Reg. No. 71693-R).

SUMMARY AND RECOMMENDATIONS

The rationales provided for the following data waiver requests are acceptable:

(i) Acute Dermal Toxicity/Pathogenicity (OPPTS 885.3100)
(ii) Primary Dermal Irritation (OPPTS 870.2500)
(iii) Primary eye irritation (OPPTS 870.2400)
(iv) Intravenous, Intracerebral, Intraperitoneal injection (OPPTS 885.3200)
(v) Hypersensitivity study (40 CFR 152-36)
(vi) Immune response (40 CFR 152-38)

The bases for these data waiver requests include (a) the low acute oral and pulmonary Toxicity Categories IV and III, respectively, of the pesticide; (b) the granular nature of the pesticide which precludes spray drift, thus minimizing non-occupational and residential dermal and inhalation exposure; (c) a low rate of application with no incremental increase in exposure to the naturally-occurring *A. flavus*; (d) no reported hypersensitivity incidents during the research and experimental phases; (e) competitive displacement of the toxigenic strains may actually decrease exposure. Data in support of the guidelines are waived if the pesticide is used as labeled for aerial and ground prebloom application to the food/feed commodity cotton in Arizona and Texas.

BACKGROUND

Aspergillus flavus AF36 has been in an experimental use program (EPA Reg. No. 69224-EUP-1) on 1000 to 20,000 acres in Arizona since May 1996 and was recently extended to include 2000 acres in Texas (July 17, 2002). A temporary exemption from tolerance was granted during the experimental period to allow a non-crop-destruct program. The current EUP terminates December 30, 2004. The pesticide was assigned Toxicity Categories IV and III respectively for the acute oral and pulmonary mammalian studies evaluated by the Agency. The granular nature of the pesticide does not allow spray drift from the aerial and ground applications without cultivation. No hypersensitivity or adverse effects have been reported during the research and experimental phases.

Review of Justifications

(i) Acute Dermal Toxicity/Pathogenicity (OPPTS 885.3100)
(ii) Primary Dermal Irritation (OPPTS 870.2500)
(iii) Primary eye irritation (OPPTS 870.2400)

With regards to the dermal and eye irritation guideline tests, it was impractical to apply the End-use Product, sterilized wheat seeds inoculated with *Aspergillus flavus* AF36, as test material. Furthermore, non-occupational dermal and eye exposures, or exposures via any of the routes in (i) thru (vi) above, are not likely to be above background levels as discussed below.

1. *Aspergillus*, a saprophytic fungus, is a normal constituent of the microflora in air and soil. The naturally occurring soil and plant colonizer is also found on living and dead plant material throughout the world. Aflatoxin-producing strains of *Aspergillus flavus* are particularly prominent in hot, dry climates supplemented with irrigation and are ubiquitous components of the natural Arizona desert ecosystem. Quantities of *A. flavus* typically increase during crop production and the fungus occurs widely on crop debris left in the soil. Shortly after application, AF36 germinates, displaces the aflatoxin-producing strains from cotton and the soil, and spore levels return to normal background, without

increase of total *A. flavus*. This was demonstrated in soil and air monitoring studies submitted over multiple years of experimental usage [MRIDs 45307201, 45307202; BPPD review by Gail Tomimatsu and John Kough dated May 15, 2003, (hereinafter referred to as ("BPPD Review - May 15, 3003")] Thus exposures to AF36 are not likely to increase above those normally associated with the naturally occurring *A. flavus* background levels.

2. The application rate is low, being less than 0.01 lb active ingredient per acre, and agricultural sites are treated, thus minimizing non-occupational and residential exposure. The proposed label rate is less than 0.01 pound of active ingredient in 10 pounds End-use Product, or approximately 1.34×10^7 colony forming units (cfu) per acre. A low application rate indicates that exposure is not likely to be greater than that which occurs normally to naturally occurring *Aspergillus flavus* strains [BPPD review - May 15, 2003]

3. Spray drift is not expected during application based on the large granular nature of the pesticide (i.e. sterilized inoculated wheat seeds). In addition, since only 1 preboom application is made, and cultivation is not recommended after application, the potential for non-occupational dermal and residential exposure is unlikely.

4. AF36 is proposed as a biocontrol agent of aflatoxin-producing strains of *A. flavus* Displacement of the aflatoxin-producing *A. flavus* by the non-toxigenic AF36 may actually reduce the environmental burden of the toxigenic strains, and consequently, aflatoxin. Thus, non-occupational dermal, inhalation, eye, and general exposure to the potent carcinogen, aflatoxin, is expected to be no greater, or may even be less, than that which normally exists. Rationales provided for these data waiver requests are acceptable.

(iv) Intravenous, Intracerebral, Intraperitoneal injection (OPPTS 885.3200)

Submitted acute oral and pulmonary toxicity/pathogenicity studies in the rodent (required for microbial pesticides) indicate that following oral and pulmonary routes of exposure, the immune system is still intact and able to process and clear the active ingredient [MRID 43972403; BPPD Review from Cindy Schaffer and Roy Sjoblad, dated April 23, 1996, (hereinafter referred to as ("BPPD Review - April 23, 1996"); and MRID 45798201; BPPD Review from Carl Etsitty and John Kough, dated April 02, 2003c, (hereinafter referred to as ("BPPD Review - April 02, 2003c")]. The acute oral toxicological study (Toxicity Category IV) demonstrated an LD_{50} of greater than 5000 mg/kg with no toxicity/infectivity effects, and demonstrable clearance from organs examined post mortem [MRID 43972403; BPPD Review - April 23, 1996].

No clinical signs that were considered to be due to the test organism were observed in the test rats following intratracheal instillation of AF36 in physiological saline solution. Organs were examined post mortem. *Aspergillus flavus* AF36 was detected in the lungs with clearance by day 8 after dosing. No test organism, *A. flavus* AF36, was detected in any samples from the shelf control or inactivated test organism treated rats. AF36 was classified Toxicity Category III on the basis of this acceptable pulmonary study [BPPD Review - April 02, 2003c]. Results from these studies support waiving the data requirement for the acute intravenous, intracerebral, intraperitoneal injection study, (OPPTS 885.3200).

(v) Hypersensitivity study (Guideline 152-36)

A hypersensitivity study was waived since hypersensitivity incidents were not reported from maximally exposed workers and researchers during the research and experimental phases associated with the use of the active ingredient, *A. flavus* AF36 [MRID 45739104; BPPD Review from Carl Etsitty and John Kough, dated April 02, 2003d, (hereinafter referred to as ("BPPD Review - April 02, 2003d")]. Nevertheless, hypersensitivity incidents associated with the use of the pesticide must be reported by the company to comply with FIFRA 6(a)(2) requirements.

(vi) Immune response (Guideline 152-38)

Submitted toxicity/pathogenicity studies in the rodent (required for microbial pesticides) also indicate that following oral and pulmonary routes of exposure [BPPD Review - April 23, 1996; BPPD Review - April 02, 2003c], the immune system is still intact and able to process and clear the active ingredient (see discussion above for **(iv) Intravenous, Intracerebral, Intraperitoneal injection**). The data waiver request for immune response is granted for the proposed use of AF36 on cotton.

CONCLUSION

On the basis of the foregoing rationales, and there being no documented problems associated with the non-aflatoxin producing strain, *Aspergillus flavus* AF36, granting these data waivers for the following studies is recommended for the proposed use of *Aspergillus flavus* AF36 on the food/feed commodity, cotton, in Arizona and Texas: **(i) Acute Dermal Toxicity/Pathogenicity; (ii) Primary Dermal Irritation; (iii) Primary eye irritation; (iv) Intravenous, Intracerebral, Intraperitoneal Injection (OPPTS 885.3200); (v) Hypersensitivity study (40 CFR 152-36); (vi) Immune response (40 CFR 152-38)**. Nevertheless, hypersensitivity incidents associated with the use of the pesticide must be reported by the company to comply with FIFRA 6(a)(2) requirements. These conclusions may be revisited if other application methods, uses, or sites are requested for *Aspergillus flavus* AF36, or adverse effects are reported in connection with the use of AF36.

References

1. MRIDs 45307201, 45307202; BPPD review of Soil and Air Monitoring data by Gail Tomimatsu and John Kough, dated May 15, 2003.

2. MRID 43972403; BPPD Review of acute oral test in rats, from Cindy Schaffer and Roy Sjoblad, dated April 23, 1996.

3. MRID 45798201; BPPD Review of Acute Pulmonary studies in rats, from Carl Etsitty and John Kough, dated April 02, 2003c.

4. MRID 45739104; BPPD Review of Acute Pulmonary studies in rats, from Carl Etsitty and John Kough, dated April 02, 2003d.

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Chemical:	**Aspergillus flavus 36 colonized wheat seed**
	PC Code:
	006456
HED File Code:	**41500 BPPD Tox/Chem**
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File ID:	**00000000**
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