

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, apparently 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 [BPPD Review - May 15, 2003]. Thus exposures to AF36 are not likely to increase above those normally associated with the naturally occurring *A. flavus* background levels.

Second, 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.

Finally, drift is not expected during application based on the large granular nature of the pesticide (i.e., sterilized inoculated wheat seeds). In addition, only one prebloom application is made, and cultivation is not recommended after application. Thus, once again, the potential for non-occupational dermal and residential exposure is unlikely.

The acute oral toxicological study demonstrated an LD₅₀ of greater than 5,000 mg/kg with no toxicity/infectivity effects, and demonstrable clearance from organs examined *post mortem* [MRID 43972403; BPPD Review - April 23, 1996]. This rationale supported the request to waive the acute intraperitoneal study.

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 [BPPD Review - April 02, 2003d]. Nevertheless, reports of hypersensitivity incidents associated with the use of the pesticide are still required to comply with FIFRA section 6(a)(2) requirements.

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. Thus, the request to waive the immune response study was granted.

On the basis of the foregoing rationales, and there being no documented problems associated with the non-aflatoxin producing strain, *Aspergillus flavus* AF36, data waivers for the studies listed in Unit III.5.i.—vi., were granted to the applicant for the proposed use of *Aspergillus flavus* AF36 on cotton.

6. *Subchronic, chronic toxicity and oncogenicity, and residue.* Based on the data generated in accordance with the Tier I data requirements set forth in 40 CFR 158.740(c), the Tier II and Tier III data requirements were not triggered and, therefore, not required in connection with this action. In addition, because the Tier II and Tier III data requirements were not required, the residue data requirements set forth in 40 CFR 158.740(b) also were not required.

IV. Aggregate Exposures

In examining aggregate exposure, section 408 of the FFDCA directs EPA to consider available information concerning exposures from the pesticide residue in food and all other non-occupational exposures, including drinking water from ground water or surface water and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor uses).

There is a potential for aggregate exposure of adult humans, infants and children to the microbe because of the ubiquitous distribution of *Aspergillus* fungal strains in the environment. The Agency has considered the incremental exposure and risk associated with the proposed application of this strain of *Aspergillus flavus*, AF36, as summarized below, and concludes that use of AF36 is not likely to add an incremental risk above that posed by the normal exposure of adults, infants and children to *Aspergillus flavus* strains present in the environment. In fact, use of the pesticide, AF36, may decrease potential environmental aflatoxin exposure to exposed populations.

A. Dietary Exposure

1. *Food.* Based on submitted studies, the end-use product, *Aspergillus flavus* AF36, demonstrates low acute oral toxicity category IV potential [BPPD Review - April 23, 1996]. No toxicity endpoints were indicated to justify setting a numerical tolerance for the

fungal active ingredient, *Aspergillus flavus* AF36. An LD₅₀ greater than 5,000 mg/kg body weight, in the acute oral studies discussed above, indicates that consumption of food commodities treated with AF36 poses no incremental risk via dietary exposure. Indeed, the submitted data indicate no toxicity or infectivity of AF36 in the acute oral test mammalian systems.

Cotton itself is not a food commodity. Residues of *A. flavus* AF36, the microbial active ingredient, are not likely to survive the heating and pressure associated with the processing of cottonseed into cottonseed meal. Moreover, *A. flavus* AF36 will not separate into the edible fraction, cotton seed oil. Thus, potential transfer of residues of *A. flavus* AF36 to edible cotton food/feed commodities is not expected. Consequently, human dietary exposure to *A. flavus* AF36 via cottonseed oil, or by secondary transfer of *A. flavus* AF36 residues to meat and milk via cottonseed meal, is not expected. Therefore, the Agency has determined that dietary exposure to *A. flavus* AF36 is not likely to result in any undue health effects and risk.

While the Agency has concluded that AF36 is not likely to add to the dietary burden, any potential contribution by AF36 to aflatoxin contamination was also considered, for a conservative estimate of the health effects of this pesticide. This is because aflatoxin is considered a public health hazard (see Unit VII.D.) and AF36 is proposed as a biocontrol agent for aflatoxin-producing strains of *A. flavus*. Even if AF36 does not control aflatoxin levels in the treated cotton food/feed commodities, a safety net exists in the screening of cotton and its by-products for aflatoxin prior to their introduction into the channels of commerce. For instance, FDA does not allow cotton seed products containing aflatoxin above 20 parts per billion (ppb) to be used in dairy rations or above 300 ppb to be used for feeding beef cattle. As previously stated, the registrant claims that quality control and selection procedures will not allow aflatoxin production in the starter cultures for pesticide manufacture [BPPD review - March 29, 1999; BPPD review - May 14, 1999]. Any batches with aflatoxin are to be destroyed. For these reasons, the Agency has determined that use of AF36 will not add to the dietary burden of aflatoxin, but is rather more likely to ameliorate aflatoxin levels in treated cotton food/feed commodities. Therefore, dietary exposure to aflatoxin, as a result of AF36 use, is not likely to be greater, and may even be less, than that which currently exists.